MODERN METHODS OF DIAGNOSING DISEASES

Collective monograph

Technology Center

2023

UDC [616-07+616-71]:[616.3/.8/.89]
M78

Published in 2022
by PC TECHNOLOGY CENTER
Shatylova dacha str., 4, Kharkiv, Ukraine, 61165

M78 **Authors:**
Ivan Mamontov, Kostyantin Kramarenko, Tamara Tamm, Valentin Nepomniashchyi, Olena Shakalova, Dmytro Rjabushhenko, Olha Yuryk, Lukyan Anatychuk, Roman Kobylianskyi, Nadiia Yuryk, Liliia Yukhymenko, Sergii Khomenko, Lidiia Iliukha, Dmytro Maltsev, Lyudmyla Yuryeva, Andrii Shornikov
Modern methods of diagnosing diseases: collective monograph. – Kharkiv: PC TECHNOLOGY CENTER, 2022. – 176 p.

Collective monograph is dedicated to the research of diagnostic methods that can be significant for medical practice. The use of endoscopic retrograde cholangiopancreatography in the examination of the bile ducts and ductal system of the pancreas is described. The development of a thermoelectric device for diagnosing inflammatory processes and pain syndrome in degenerative-dystrophic diseases of the lumbosacral spine is presented. Evaluation scales of neurodynamic and sensorimotor functions are proposed for use in the medical field, which can be used to optimize diagnosis and improve the effectiveness of monitoring neurological morbidity, including in people with special needs. The problems of children's neuropsychiatric diseases were studied. The development of a new psychodiagnostic screening tool based on the proposed paradigm of cyber addiction, the YSCAS scale, is presented. The monograph is intended for doctors and practitioners who are engaged in the search and implementation of effective diagnostic methods to overcome the problems associated with the detection and treatment of certain pathologies. The monograph can also be useful to postgraduate and master's students of universities in the relevant educational and scientific profile.
Figures 48, Tables 26, References 289 items.

DOI: 10.15587/978-617-7319-65-7
ISBN 978-617-7319-65-7 (on-line)

AUTHORS

CHAPTER 1

IVAN MAMONTOV
Doctor of Medical Science, Associate Professor
Department of Surgery No. 6
Kharkiv National Medical University
ORCID ID: https://orcid.org/0000-0003-0059-2715

KOSTYANTIN KRAMARENKO
PhD, Associate Professor
Department of Surgery No. 6
Kharkiv National Medical University
ORCID ID: https://orcid.org/0000-0002-1997-8928

TAMARA TAMM
Doctor of Medical Sciences, Professor
Department of Surgery No. 6
Kharkiv National Medical University
ORCID ID: https://orcid.org/0000-0001-6372-2092

VALENTIN NEPOMNIASHCHYI
Doctor of Medical Science, Associate Professor
Department of Surgery No. 6
Kharkiv National Medical University
ORCID ID: https://orcid.org/0000-0001-6262-6795

OLENA SHAKALOVA
PhD, Associate Professor
Department of Surgery No. 6
Kharkiv National Medical University
ORCID ID: https://orcid.org/0000-0003-3401-4278

DMYTRO RJABUSHHENKO
Postgraduate Student
Department of Surgery No. 6
Kharkiv National Medical University
ORCID ID: https://orcid.org/0000-0002-0655-1466

CHAPTER 2

OLHA YURYK
Doctor of Medical Science, Professor, Head of Laboratory
Laboratory of Neuroorthopedics and pain problems
State Institution «Institute of Traumatology and Orthopedics of the National Academy of Medical Science of Ukraine»
ORCID: https://orcid.org/0000-0003-2245-9333

LUKYAN ANATYCHUK
Doctor of Physical and Mathematical Sciences, Professor
[1] Director of Institute
Institute of Thermoelectricity of National Academy of Sciences and Ministry of Education and Science of Ukraine
[2] Head of Department
Department of Thermoelectricity
Yuriy Fedkovych Chernivtsi National University
ORCID: https://orcid.org/0000-0002-2521-7666

ROMAN KOBYLIANSKYI
PhD, Senior Researcher
[1] Institute of Thermoelectricity of National Academy of Sciences and Ministry of Education and Science of Ukraine
[2] Department of Thermoelectricity
Yuriy Fedkovych Chernivtsi National University
ORCID: https://orcid.org/0000-0002-4664-3162

NADIIA YURYK
Doctor
State Institution «Institute of Traumatology and Orthopedics of the National Academy of Medical Science of Ukraine»

CHAPTER 3

LILIIA YUKHYMENKO
Doctor of Biological Sciences, Associate Professor
Department of Anatomy, Physiology and Physical Rehabilitation
Bohdan Khmelnytsky National University of Cherkasy
ORCID ID: https://orcid.org/0000-0002-4455-6233

SERGII KHOMENKO
PhD, Associate Professor
Department of Anatomy, Physiology and Physical Rehabilitation
Bohdan Khmelnytsky National University of Cherkasy
ORCID ID: https://orcid.org/0000-0003-0918-8735

LIDIIA ILIUKHA
PhD, Associate Professor
Department of Anatomy, Physiology and Physical Rehabilitation
Bohdan Khmelnytsky National University of Cherkasy
ORCID ID: https://orcid.org/0000-0001-9650-805X

CHAPTER 4

DMYTRO MALTSEV
PhD, Head of the Laboratory
Laboratory of Immunology and Molecular Biology
Research Institute of Experimental and Clinical Medicine
Bogomolets National Medical University
ORCID ID: https://orcid.org/0000-0002-6615-3072

CHAPTER 5

LYUDMYLA YURYEVA
Doctor of Medical Science, Professor
Department of Psychiatry, Narcology, Medical Psychology
Dnipro State Medical University
ORCID: https://orcid.org/0000-0002-1713-1037

ANDRII SHORNIKOV
Assistant
Department of Psychiatry, Narcology, Medical Psychology
Dnipro State Medical University
ORCID: https://orcid.org/0000-0001-8196-9128

ABSTRACT

Collective monograph contains the results of scientific research devoted to new views and proposals for the diagnosis of certain diseases. The proposed solutions are important for clinical practice and inspire optimism in obtaining encouraging results in overcoming some pathologies.

Chapter 1 is dedicated to endoscopic retrograde cholangiopancreatography – a contrast study of the bile ducts and ductal system of the pancreas, which is achieved by their cannulation with the help of a flexible endoscope and their visualization by X-ray (fluoroscopy). Thanks to this, it becomes possible to diagnose and perform medical interventions for choledocholithiasis, benign and malignant obstruction of the bile ducts, chronic pancreatitis accompanied by obstruction of the pancreatic ducts.

Chapter 2 presents the results of the development of a thermoelectric device for diagnosing inflammatory processes and pain syndrome in degenerative-dystrophic diseases of the lumbosacral spine. Such a device makes it possible to save, process and visualize measurement results on the display of the device and on a personal computer in real time. The results of clinical studies of thermometric indicators in the lumbosacral region of the spine in persons with chronic pain syndrome against the background of degenerative-dystrophic pathology of the spine in the presence of hernias and protrusions of intervertebral discs are given. The effectiveness of the proposed thermoelectric device in medical practice has been confirmed.

Chapter 3 presents the results of the examination of various contingents of the population: students, athletes, mobile operators, people with hearing loss, post-Covid syndrome and psychophysiological lability developed under martial law. The features of information processing by examinees with different degrees of functional mobility of nervous processes are highlighted. It was found that the deprivation of auditory function, post-conviction syndrome, psychophysiological lability developed in the conditions of martial law significantly reduce the level of neural processes and the ability to process information.

The evaluation scales of neurodynamic and sensorimotor functions proposed for use in the medical field can be used to optimize diagnosis and increase the effectiveness of monitoring neurological morbidity, including in people with special needs.

Chapter 4 is devoted to the problems of children's neuropsychiatric diseases, in particular brain damage in children with ASD. Restrained optimism is expressed for the prospect of overcoming this severe psychiatric pathology in the foreseeable future due to the introduction of genetic, biochemical and immunodiagnostic approaches, as well as metabolic and immunotherapeutic interventions with neuroprotective effects. Arguments are presented in favor of the fact that the successful testing in clinical practice of evidence-based personalized multidisciplinary strategies of diagnosis and treatment will allow a breakthrough in the clinical management of children with severe mental disorders in the near future. This will provide not only the possibility of recovery

from a prognostically unfavorable and currently incurable neuropsychiatric disorder, but will also contribute to stopping the large-scale threatening epidemic of neuropsychiatric syndromes in the modern child population.

Chapter 5 presents the evolution of views on the problem of Internet addiction, provides information on its prevalence, comorbidity with mental disorders, and provides an overview of modern clinical classifications and psychometric tools for its diagnosis. A single definition of "cyber addiction" is singled out, based on the fact that the object of addiction is interaction with various information resources and technical means.

The proposed clinical diagnostic criteria, which are based on the criteria for the diagnosis of mental and behavioral disorders due to the use of psychoactive substances ICD-11, and the characteristics of the boundary with normative behavior when using various information resources and technical means are provided. The development and validation of a new psychodiagnostic screening tool based on the proposed cyber addiction paradigm, the YSCAS scale, is presented.

KEYWORDS

Endoscopic retrograde cholangiopancreatography, endoscopic lithoextraction, osteochondrosis of the spine, thermoelectric device, individual-typological properties, functional mobility, sensorimotor reactivity, autism spectrum disorders, attention deficit hyperactivity disorder, obsessive-compulsive syndrome, immunodiagnostics, internet addiction, cyberaddiction, YSCAS scale.

CIRCLE OF READERS AND SCOPE OF APPLICATION

The monograph is intended for doctors and practitioners who are engaged in the search and implementation of effective diagnostic methods to overcome the problems associated with the detection and treatment of certain pathologies.

The monograph can also be useful to postgraduate and master's students of universities in the relevant educational and scientific profile.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

The use of modern technologies is an integral part of medical diagnosis today, so new views and concepts regarding tools, approaches, methods and models for diagnosing diseases are important for medical practice. This collective monograph is dedicated to such views regarding some pathologies.

Endoscopic retrograde cholangiopancreatography (ERCP) is proposed for diagnosing and choosing treatment options for choledocholithiasis, benign and malignant biliary tract obstruction, chronic pancreatitis accompanied by pancreatic duct obstruction, and a number of other conditions and pathologies. This is a contrast study of the bile ducts and duct system of the pancreas, achieved by their cannulation with the help of a flexible endoscope and their visualization by X-ray (fluoroscopy). At the same time, ERCP implies not only diagnostic manipulations, but also a number of medical procedures, which makes the use of ERCP relevant in a practical sense.

Of practical interest is the question of the tactics of choosing a method of treatment for osteochondrosis of the lumbar spine and its neurological manifestations, which are still debatable. In this context, the development of a thermoelectric device for diagnosing inflammatory processes and pain syndrome in degenerative-dystrophic diseases of the lumbosacral spine is proposed. Such a device makes it possible to save, process and visualize measurement results on the display of the device and on a personal computer in real time. The results that can be obtained using a thermoelectric device are definitely relevant for medical practice.

For the diagnosis and monitoring of the nervous system of young people, the research of the main nervous processes and their typological combinations is important. This makes it possible to deepen general ideas about the states of the body, as well as the possibilities of using their indicators in diagnostics. When examining different contingents of the population, the manifestation of individual-typological properties that determine the current psycho-emotional background, the speed and efficiency of sensorimotor reactivity, and the effectiveness of mental capacity during the performance of real activities can be clarified. The proposed rating scales of neurodynamic and sensorimotor functions can be used to optimize diagnosis and improve the effectiveness of monitoring neurological morbidity, including in people with special needs.

It is also relevant to solve the problems of children's neuropsychiatric diseases using the latest scientific achievements in the field of genetics, molecular biology and immunology, which demonstrate biochemical and immune-dependent ways of formation of human neuropsychiatric disorders and allow to determine the mechanisms of brain damage in children with ASD. Currently, the folate-centric concept of polygenic inheritance of predisposition to the development of neuropsychiatric syndromes in children with multisystem damage has been established. Therefore, the discussion of biochemical and immune-dependent ways of formation of microbe-induced autoimmune inflammatory encephalopathy with neuropsychiatric clinical manifestations in the context of the folate-centric concept and diagnostic possibilities is of interest. These questions are reflected in the presented monographs.

Another problem that has become obvious for modern times and poses a real threat to the development of young people is the problem of Internet addiction. Studies of the evolution of views on this problem make it possible to identify dangerous trends and generate important data on the prevalence of relevant conditions, comorbidity with mental disorders, and to determine modern clinical classifications and psychometric diagnostic tools. Based on the results of modern scientific research, conceptual development and the I-PACE model, it is relevant to define a separate definition of "cyber addiction", which can combine all variants of Internet addiction. The corresponding views are reflected in this monograph, which states that there are well-founded reasons for the selection of such a definition, based on the fact that the object of dependence is understood as interaction with various information resources and technical means. For the phenomenon of cyber addiction, clinical diagnostic criteria are proposed, which are based on the criteria for diagnosing mental and behavioral disorders due to the use of psychoactive substances of ICD-11. Characteristics of the boundary with normative behavior when using various information resources and technical means are provided, as well as a new psychodiagnostic screening tool based on the proposed paradigm of cyber addiction – the YSCAS scale – has been developed and validated.

All these views and proposals make this collective monograph relevant for medical practice.

DOI: 10.15587/978-617-7319-65-7.CH1

Ivan Mamontov, Kostyantin Kramarenko, Tamara Tamm,
Valentin Nepomniashchyi, Olena Shakalova, Dmytro Rjabushhenko

CHAPTER 1

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

ABSTRACT

Endoscopic retrograde cholangiopancreatography (ERCP) is a contrast study of the bile ducts and the ductal system of the pancreas (P), achieved by cannulating them with a flexible endoscope and visualizing them with fluoroscopy. The technique also includes a visual assessment of the major duodenal papilla (MDP).

ERCP involves not only diagnostic manipulations, but also therapeutic procedures on the MDP, bile and pancreatic ducts.

ERCP and its accompanying endoscopic interventions make it possible to diagnose and perform therapeutic interventions in choledocholithiasis, benign and malignant obstruction of the biliary tract, chronic pancreatitis accompanied by obstruction of the pancreatic ducts, and in a number of other conditions and pathologies.

KEYWORDS

ERCP, endoscopic lithoextraction, biliary obstruction, biliary decompression, choledocholithiasis, Mirizzi syndrome, tumor obstruction, chronic pancreatitis.

Endoscopic MDP cannulation was first described in 1968 [1].

Subsequently, at the turn of the 60s and 70s, several groups of Japanese researchers coworking with manufacturers of endoscopic equipment and instruments widely introduced retrograde contrast examination of the bile ducts and pancreatic ducts under direct visual control using a duodenoscope.

The technique, later called ERCP, quickly spread throughout the world. However, with the accumulation of primary experience, the possibility of serious complications soon became apparent [2].

In 1974, endoscopic sphincterotomy was performed independently in Germany and Japan [3, 4]. After that, the possibility of removing stones from the common bile duct became obvious.

In 1980, there were reports of endoscopic drainage of the bile ducts, including those with malignant obstruction [2, 5].

The introduction of treatment options has given a powerful impetus to the development and use of ERCP. Endoscopes were improved, tools and techniques were developed – both for diagnostic and therapeutic ERCP.

At the turn of the 70s and 80s, ERCP, in fact, was the only method that allows to look "inside" the bile ducts and pancreatic ducts [2].

In addition to the pathology of the bile ducts, ERCP made it possible to diagnose the dilatation of the main pancreatic duct (MPD), virsungolithiasis, and to identify the relationship between pancreatic cysts and MPD [6]. However, initially high hopes for the use of therapeutic endoscopic interventions in chronic pancreatitis subsequently did not come true [2].

The period of a decade and a half since the mid-1970s has become a "golden age" for ERCP. Despite the risk of complications, it became obvious to everyone that ERCP treatment of common bile stones and correction of tumor biliary obstruction is simpler, cheaper and safer than available surgical interventions [2].

Since the 1990s, the situation has begun to change. On the one hand, non-invasive methods of visual diagnostics were improved – ultrasound, CT, MRI, endo-ultrasound, which somewhat reduced the diagnostic contribution of ERCP. On the other hand, percutaneous interventions on the biliary tract were developed, also allowing significant progress in the correction of biliary tract obstruction – in Klatskin tumors and tumors of other localization [2]. The introduction of minimally invasive surgery – laparoscopy, in some centers, has also become an alternative to a number of endoscopic interventions performed with ERCP [7].

Nevertheless, despite the development of other minimally invasive methods, today ERCP and its associated interventions are the main ones in the diagnosis and treatment of choledocholithiasis, correction of tumor obstruction of the extrahepatic biliary tract, and MPD pathology. And the improvement of equipment, tools and skills contribute to the development of new techniques, which include, for example, endoultrasound in combination with ERCP [2, 8].

1.1 SCOPE AND INDICATIONS

ERCP is mainly used for obstructive conditions of the bile ducts. As mentioned above, with the development of other diagnostic methods, especially CT and MRI, the diagnostic value of ERCP has receded into the background, but the therapeutic potential of ERCP is difficult to overestimate. In this regard, indications for the use of ERCP can vary widely. This variability may be due to the availability of the method in a particular institution, the qualifications of the specialist performing this intervention, the availability and accessibility of an interventional radiology service, the availability and accessibility of CT, MRI, preferences and traditions developed in different centers, and a number of other factors.

The main points of application of ERCP are choledocholithiasis and other complications of cholelithiasis (for example, Mirizzi syndrome), tumor obstruction of the bile ducts, strictures of the

bile ducts, chronic pancreatitis, postoperative bile leakage, suspicion of an anomaly of the pancreatic duct system and the biliary tree, dysfunction of the sphincter of Oddi, etc. In most of these conditions, not only diagnostic but also therapeutic interventions are performed [2, 8].

An analysis of 53,394 cases published in 2017 [9] showed significant variability in indications for ERCP among different investigators:

– clinical indications: pain in the upper abdomen with or without jaundice;
– biochemical – an increase in the activity of liver tests with or without hyperbilirubinemia;
– cholangitis;
– acute biliary pancreatitis;
– history of pancreatitis;
– confirmed choledocholithiasis;
– suspicion of choledocholithiasis;
– malignant obstruction of the bile ducts;
– suspicion of malignant obstruction of the bile ducts;
– biliary fistulas and bile leakage after operations;
– strictures of the biliary tract;
– jaundice of unknown etiology;
– primary sclerosing cholangitis;
– suspicion of dysfunction of the sphincter of Oddi, etc.

In case of pathology of the bile ducts (excluding bile leakage), we consider that ERCP is indicated, first of all, when the fact of biliary obstruction is confirmed, according to the results of non-invasive imaging methods – ultrasound, CT, MRI. In rare cases, ERCP is performed by us when it is impossible to exclude choledocholithiasis in other ways.

In our opinion, in case of pathology of the pancreas, the diagnostic value of ERCP can be useful in suspicion of an anomaly of the ductal system (pancreas divisium), identification of the relation of MPD with pancreatic cysts, confirmation of a pancreatic fistula, and rarely – in assessing the possibility of endoscopic removal of MPD stones.

In some cases, there is a need for urgent ERCP – in cholangitis, in impacted MDP stone. The necessity of ERCP in acute biliary pancreatitis is also being discussed.

We have developed a scale (**Table 1.1**) to determine the urgency of ERCP [11], which is used for patients with confirmed obstruction (dilatation of common bile duct ≥8 mm). Scoring is carried out by summing up the indicators: clinical sign – hyperthermia ≥37.3 °C; one of the three hematological parameters – white blood cell count $\geq 9 \times 10^9$/L or stab neutrophils ≥7 %, or the ratio of the number of segmented and stab neutrophils < 10; two biochemical criteria – bilirubin ≥70 μmol/L and hyperamylasemia; signs identified according to the visualizing methods – gallbladder wall ≥4 mm or the presence of a shrunken gallbladder; the dilatation of the MPD, which can be both a sign of a impacted in MDP stone, or the result of chronic pancreatitis, tumor of the periampullary zone. Since, with obstruction of the extrahepatic biliary tract due to tumor or chronic pancreatitis, for which cholangitis is not typical, if there is evidence of chronic pancreatitis or a tumor, one point is subtracted.

● **Table 1.1** Indication scale for emergency ERCP in extrahepatic bile ducts obstruction

Clinical sign	
Hyperthermia ≥37.3°C	1 point
Hematological signs	
White blood cell count $\geq 9 \times 10^9$/L or stab neutrophils ≥7 % or the ratio of the number of segmented and stab neutrophils <10	1 point
Biochemical signs	
Bilirubin ≥70 μmol/L	1 point
Hyperamylosemia (Amylase > 32 g×year/L)	1 point
Data from imaging research methods	
Gallbladder wall ≥4 mm or Shrunken gallbladder	1 point
Dilatation of the main pancreatic duct	1 point
Presence of a tumor in the periampullary zone/biliary tract or signs of chronic pancreatitis	–1 point

The developed scale was tested in 171 patients with obstruction of various etiology. Of these, in 28 cases the obstruction was of a tumor nature, in 112 cases it was caused by choledocholithiasis, in 29 cases by MDP stenosis, and in 2 cases by chronic pancreatitis.

It was found that the threshold value of this scale is 3 points ($p < 0.001$), upon reaching which the patients are indicated for emergency ERCP followed by endoscopic interventions. In contrast, at ≤2 points, emergency ERCP is not indicated ($p < 0.001$).

Given the diagnostic potential of the developed scale for cholangitis and/or acute biliary pancreatitis and/or fixed MPD stone, it was found that it has a high specificity (97.1 %) and sensitivity (70.6 %). In addition, it was found that the number of points correlates with the severity of complications (cholangitis, acute biliary pancreatitis). According to the developed scale, 3 points indicate a mild form of cholangitis and/or acute biliary pancreatitis ($p < 0.01$). In these cases, urgent ERCP is indicated – in 24 hours. The presence of ≥4 points indicates a moderate or severe form of cholangitis and/or acute biliary pancreatitis ($p < 0.01$), requiring urgent correction of cholestasis – as soon as possible.

With regard to contraindications, in our opinion, the only absolute contraindication for ERCP is allergic reactions to iodine-containing contrast media. For all other conditions, the potential benefit of ERCP and the risk of its use in each case should be evaluated.

1.2 EQUIPMENT AND INSTRUMENTS FOR ERCP [2, 8]

ERCP and endoscopic interventions on the MDP are performed in a special X-ray endoscopic operating room. This should be a spacious room that meets sanitary standards and regulations, equipped with a modern X-ray machine (C-arch type) – the quality of the X-ray image is one of the most important conditions for the success of endoscopic transpapillary interventions. The operating table must be radiolucent and movable. It is necessary that the X-ray and endoscopic monitor be in the field of direct vision of the operator, and the assistants have free access to the head and right hand of the patient (**Fig. 1.1**).

Fig. 1.1 ERCP procedure

Necessary equipment is video endoscopes, both with lateral and end position of the optical window, preferably with instrumental channels of different diameters. Duodenoscopes with lateral optics (**Fig. 1.2**) are used for performing ERCP, they should have a wide instrumental channel (preferably 3.2–4.2 mm), which is very important when performing therapeutic procedures, using the full variety of necessary instruments, especially when stent placement is needed. Endoscopes with end optics (gastroscopes) may be useful in manipulating the MDP in patients who have previously undergone a Billroth-II partial gastrectomy, in whom access to the MDP may be significantly difficult. The video system should give a good image on the monitor, have a recording device for documenting and processing endoscopic data. Mandatory additional equipment for performing manipulations and operations on the MDP is a modern high-frequency electrosurgical unit and suction.

Contrast agents. When performing ERCP, preference should be given to non-ionic low-osmolar water-soluble agents (Ultravist, Omnipak, Vizipak), which cause fewer negative reactions and

complications. Generally, 20–50 ml of radiopaque substance is required for the study. It is also possible to use ionic water-soluble agents at a concentration of 20–35 % (Urographina, Triombrast).

Fig. 1.2 Distal end of the duodenoscope

Instrumentation for performing ERCP and therapeutic procedures is very diverse and occupies at least 1/3 of the total volume of endoscopic instruments produced according to the catalogs of leading manufacturers (Olympus, Cook). All tools can be conditionally divided into certain groups, depending on their purpose.

ERCP catheters (cannulas) are synthetic tubes with an outer diameter of 1.6–2.3 mm and radiopaque markers at its distal end. At the proximal end of the standard catheter there may be two inputs – for the guide wire and for connecting the syringe. Various design options for catheters differ in size, tip configuration, diameter, and number of channels (**Fig. 1.3**). The advantage of dual-channel catheters is the possibility of using two channels in parallel: the injection of a contrast media through one channel and for a guidewire through another channel. Guidewires are used to facilitate cannulation of the orifice of the MDP, going through of tortuous strictures and are usually passed through the lumen of a standard catheter, cannula or papillotome. With their help, the catheter instrument is changed to papillotome to basket, etc. The guidewire are 260–480 cm long and 0.021–0.038 inches in diameter.

Papillotomes are diathermic knives of various designs, differing in the place, direction, length, and shape of the metal electrode-string exiting the catheter. In a typical Demling-Klassen pull-type papillotome, the wire exits 4–2 cm from the tip of the catheter and reenters it a few millimeters from the tip. When using the "wire pulling" technique, the distal end of the papillotome takes the form of a bow, and the pulling string takes the form of a bowstring (**Fig. 1.4**). The cutting wire can vary in length (1–3 cm) and is a single string or several threads twisted into a bundle.

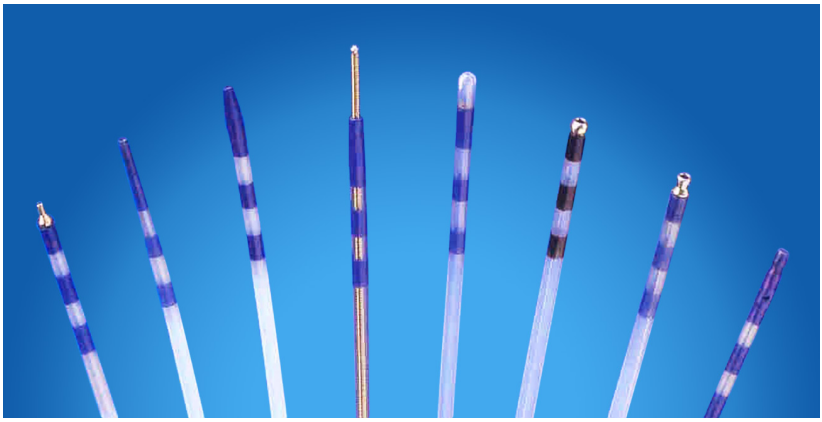
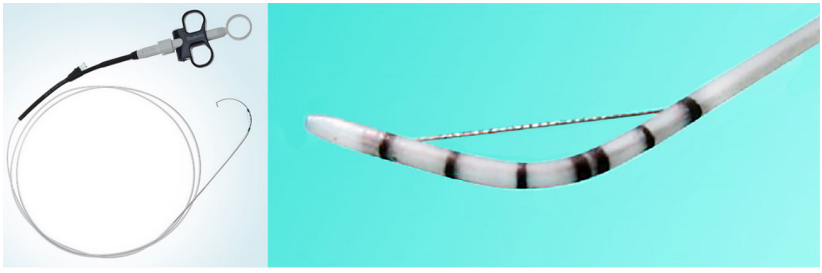


Fig. 1.3 ERCP cannulas



a *b*

Fig. 1.4 Papillotome: *a* – general view of the papillotome; *b* – distal end of the papillotome

Another type of papillotome, which is used for a non-cannulation variant of the MDP papillotomy, is a needle knife with an end exit of the knife (**Fig. 1.5**). Such a papillotome is mainly used for the pre-cut technique of papillotomy and in case of impacted stone in the MDP ampoule.

There are also rare models of papillotomes (push-type and "shark fin" type, for case after the Billroth-II partial gastrectomy and some other situations that are used very limitedly.

Currently, most papillotomes have two or three channels for injection of a contrast and for a guidewire. Such instruments (cannulatomes) are the most convenient, they provide ability of ERCP and papillotomy during one cannulation of the duct system (**Fig. 1.6**).

To perform MDP dilatation, balloon catheters with X-ray contrast marks, a maximum expansion diameter of 6–10 mm, and a balloon length of 2–4 cm are used. They are inserted with a guide-

wire through the papilla (**Fig. 1.7**). This alternative to papillotomy preserves the integrity of the MDP sphincter apparatus, but this type of access to the ducts has a greater risk of post-ERCP pancreatitis. Balloon dilatation of the MDP is advisable in patients with a high risk of hemorrhagic complications, in young patients with single small calculi without dilatation of the common bile duct, and when the stone migrates into the common bile duct during laparoscopic cholecystectomy. Balloon dilators are also used to dilate strictures of the bile and pancreatic ducts of various etiologies under X-ray control.

Fig. 1.5 Needle knife papillotome

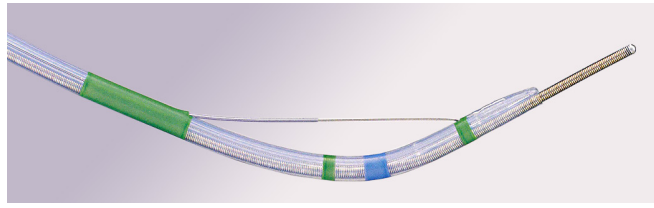


Fig. 1.6 Double lumen papillotome with guidewire

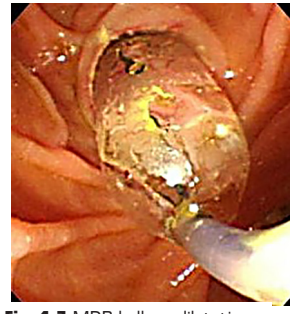


Fig. 1.7 MDP balloon dilatation

Extraction of stones (lithoextraction) is performed using Fogarty-type balloon catheters or Dormia-type baskets. The diameter of the balloon for extraction is 8–20 mm, the catheter of such an extractor contains one or two additional channels for the guidewire and the injection of contrast (two- and three-channel balloon extractors) (**Fig. 1.8**).

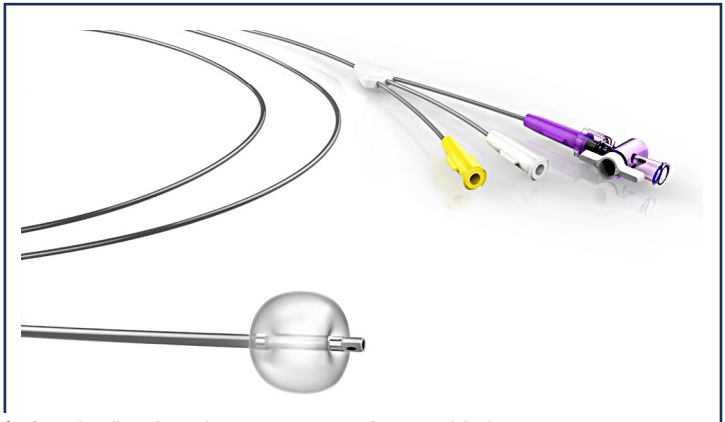


Fig. 1.8 Balloon for endoscopic extraction of common bile duct stones

Metal wire baskets have four strings (most often) in the shape of a rhombus, baskets differ in length and opening size (**Fig. 1.9**). Spiral baskets and baskets with or more than 4 strings are less commonly used.

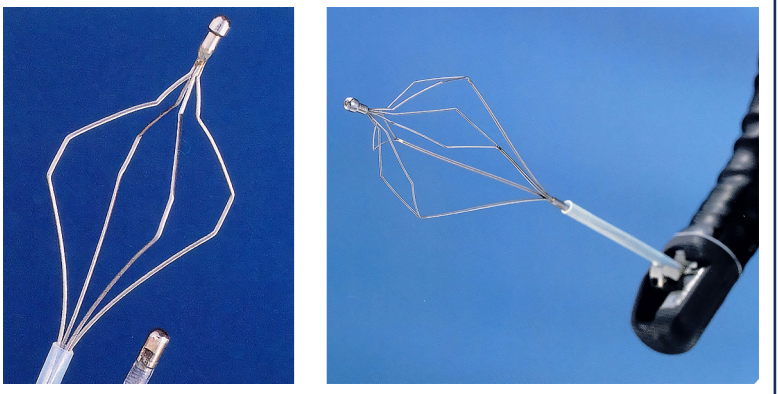


Fig. 1.9 Baskets for endoscopic extraction of common bile duct stones

To crush stones, mechanical lithotripters are used, which, in fact, are different versions of the reinforced Dormia-type basket. The lithotripter has a metal outer shell and is equipped with a special handle, which allows to create a significant force when closing the basket, sufficient to destroy the stone. The most common are lithotripters from Olympus, Cook, Boston Sientific (**Fig. 1.10**).

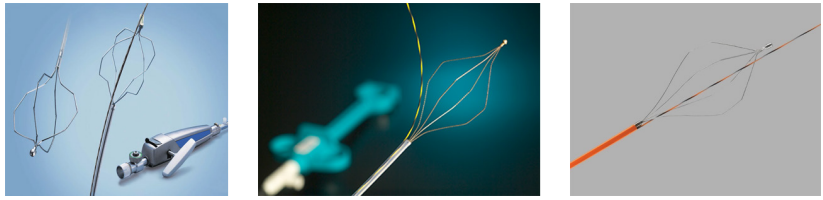


Fig. 1.10 Mechanical lithotriptors

In some cases – with benign and malignant obstruction, difficult stones, cholangitis, biliary fistulas, it becomes necessary to decompress the biliary tree, which can be achieved by installing a nasobiliary drainage or stenting of the bile ducts.

Transpapillary nasobiliary drainage (NBD) can be performed not only for decompression, but also for lavage of the biliary tract. Nasobiliary dranages are tubes that are longer than twice the length of the endoscope (250 cm) and have a diameter of 1.6–3.0 mm (5–8 Fr). The distal end of the drain has several lateral holes. Different types of drains differ in shape, diameter and angle of the fixing bend (**Fig. 1.11**).

Fig. 1.11 Nasobiliary drainage

Endoprosthesis replacement (stenting) is used to restore the natural outflow of bile in patients with tumor biliary obstruction, Vater papilla tumor, benign strictures, sometimes in case when it

is impossible to extrect common bile duct stone. Pancreatic duct stenting is performed to prevent pancreatitis after ERCP, as well as in some cases of chronic pancreatitis and pancreatic fistulas.

For endoprosthetics, plastic and metal stents are used.

Standard plastic stents have a slightly curved shape and "antennae" at both ends, which are to fix the stent (**Fig. 1.12**). Their length varies from 3 to 15 cm, and their diameter varies from 1.5 to 4.0 mm (5–12 Fr). Pigtail type stents are mainly used for stones that cannot be removed in order to restore the outflow of bile (**Fig. 1.12**). The set for stent placement includes a guidewire and a pusher tube.

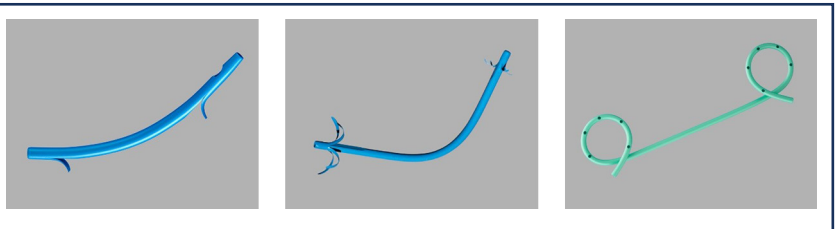


Fig. 1.12 Plastic stents of various designs

Another type of stent is metal stents, which are placed using stent and guidewire systems. They are installed in the stricture zone in the folded state, and then they expand either selfexpandeable or with the help of a balloon (**Fig. 1.13**). Metal stents can be covered or uncovered.

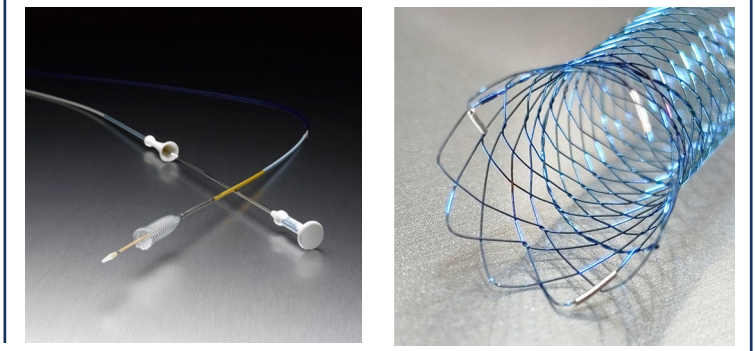


Fig. 1.13 Metal self-expanding stent system

In addition to the basic instruments described above, there are others for rare retrograde interventions (endoscopic sphincteromanometry, retrograde choledochoscopy, endosonography,

papilectomy), and there are also a lot of additional accessories and devices that facilitate the work of an endoscopist.

1.3 CHANGES DETECTED BY ERCP [2, 8]

ERCP begins with an examination of the MDP, which allows to assess its size, shape, the presence of a parapapillary diverticulum, the presence of edema and hyperemia, density – by "instrumental palpation", the state of the orifice, the presence of neoplasms, etc., as well as the outflow of the flow of bile from it.

Normally, the MDP has a round, oval or proboscis shape, its size does not exceed 1 cm, the mucosa does not visually differ from the duodenal mucosa. Above the MDP, like a hood, is framed by a fold, and from below there is most often a vertical fold – a frenulum. The extence of these folds is highly variable.

The absence of bile in the duodenum may indicate an obstruction of the biliary tract. The flow of purulent bile from the orifice of the MDP is an undoubted sign of purulent cholangitis.

When a parapapillary diverticulum is present, attention is paid to the location of the papilla, its deformation is assessed, as well as passage of bile from it. Parapapillary diverticulum presents in 7–11 % of patients, its size varies from 1.0 to 5.0 cm. MDP can be located at the bottom of the diverticulum, on one of the walls, or at the edge of the diverticulum; sometimes two diverticula are located on both sides of the MDP.

When examining the MDP zone, the following pathological changes can be detected: edema and hyperemia, an increase in size, a impacted stone with visualization of a stone at the orifice, MDP tumors, and pathological fistulas.

Edema and hyperemia of the MDP can be in case of cholangitis, a impacted stone of the MDP, biliary obstruction at the level of the MDP due to papillitis.

Enlarged papilla is also observed in case of papillitis, with impacted stone, or in case of tumor of the MDP.

MDP neoplasms (adenomas, adenocarcinomas) develop from the mucosa covering the MDP from the side of the duodenum or, more often, from the mucosal ampulla of the MDP ampulla (**Fig. 1.14**). Accordingly, the endoscopic picture will be different. Small tumors of the MDP ampulla will not have other endoscopic signs but its enlargement.

In case of the papilla cancer , there is always obstruction of the biliary tract and obstructive jaundice. A cancerous lesion of the MDP may look like a polypoid or infiltrative-ulcerative tumor of various shapes from 1.0 to 5.0 cm, which almost always bleeds upon contact with it. Bleeding from tumors is rarely severe, usually it is weak – capillary even when taking a biopsy or papillotomy. With adenocarcinoma larger than 2.0 cm, it is usually not difficult to made the correct diagnosis visually, in cases with small tumors of 1.0–2.0 cm, the final diagnosis is most often established after the biopsy.

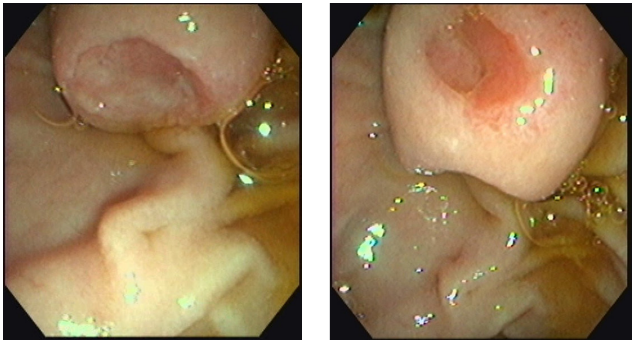


Fig. 1.14 MDP adenocarcinoma

Fistulas in the MDP area may be the result of a long-termimpacted stone in the distal common bile duct or in the ampulla. In addition, in severe destructive pancreatitis, fistulas with purulent cavities can form in the region of the pancreatic head.

After examining the MDP, as a rule, its cannulation is performed. ERCP can be performed with shallow cannulation, but in bile duct pathology, selective cannulation of the common bile duct followed by cholangiography is preferable, since cannulation of the MPD and pancteaticografy are risk factors of postERCP pancreatitis. If indicated, a contrast study of the pancreatic ducts is performed. Normally, the diameter of common bile duct does not exceed 8 mm (after cholecystectomy 10 mm), and MPD – 2 mm (**Fig. 1.15**).

Fig. 1.15 Normal ERCP

In general, changes of the ducts revealed by ERCP can be – dilatation, obstruction, narrowing, deformation of the contours, the presence of filling defects (usually stones), extravasation of the contrast (biliary or pancreatic fistulas, etc.).

Obstruction of the ductal system is characterized by narrowing of the lumen at the site of obstruction and proximal dilatation (**Fig. 1.16**). Deformation of the contour can be the result of intraluminal lesion (tumor), compression from the outside (tumor, chronic pancreatitis) or, less commonly, structuring, including postoperative changes (**Fig. 1.17**).

Fig. 1.16 Obstruction of common bile duct with proximal dilatation. The distal duct is not dilated

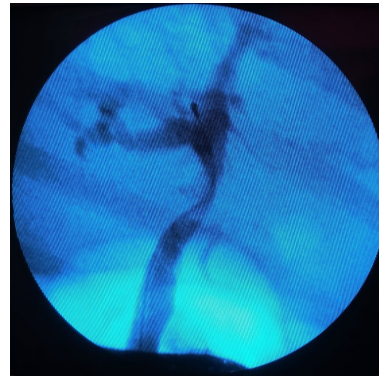


Fig. 1.17 Deformation and narrowing of the common hepatic duct

Stones in the lumen of the bile ducts or pancreatic duct are defined as filling defects (**Fig. 1.18**). Gallstones, as a rule, are moveable.

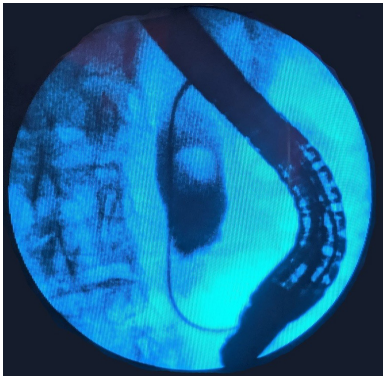


Fig. 1.18 Large stone in the common bile duct

For a correct interpretation, the data obtained by ERCP must be compared with the clinic, anamnesis, and, especially, with the data of other imaging methods (ultrasound, CT, MRI).

1.4 ERCP COMPLICATIONS

In general, being a safe procedure, in some cases ERCP can lead to complications. The complication incidence varies greatly depending on patient selection, operator experience, the nature of concomitant endoscopic interventions, and a number of other factors. According to various data, it ranges from 0.5 to 15 % [12, 13].

Complications associated with ERCP and endoscopic procedures include: acute pancreatitis, cholangitis, perforation, bleeding, and acute cholecystitis.

According to many researchers, the incidence of post-ERCP pancreatitis (PEP) is within 1–40 % of cases and depends on many factors: the nature of the disease, the type of endoscopic intervention, and the age of the patient. For example, young age, sphincter of Oddi dysfunction, absence of jaundice, history of acute pancreatitis, prior history of post-ERCP pancreatitis are factors that increase the risk of acute pancreatitis after ERCP [12–14].

Understanding the risk factors for PEP is essential to reduce the risk and improve the safety of the procedure. It is also important to identify high-risk patients prior to the procedure so that the procedure can be avoided if possible or the procedure time reduced to a minimum.

The exact pathogenesis of post-ERCP pancreatitis is not clear. Several mechanisms have been proposed in the literature. One of them is direct mechanical trauma, as a result of prolonged or complex manipulations with the instrument, for example, manipulations with the guidewire, cause swelling of the duct, leading to pancreatic outflow disorders. Another proposed mechanism is chemical damage due to contrast injection. Hydrostatic injury can also be caused by increased pressure in the pancreatic duct as measured by manometry. Infection resulting from bacteria from an endoscope or a contrast agent entering the pancreatic duct may also be another mechanism of injury. In addition, thermal injury may also result from the use of electrocautery during sphincterotomy [15, 16].

Criteria for the diagnosis of acute pancreatitis after ERCP and endoscopic interventions do not differ from those for the diagnosis of acute pancreatitis in general and include:

– abdominal pain;

– blood amylase / lipase level increase more than 3 times;

– data characteristic of acute pancreatitis according to imaging research methods (ultrasound, CT, MRI).

The presence of at least two of these signs within 24 hours after ERCP is indicative of acute pancreatitis [15, 16].

When acute pancreatitis after ERCP confirmed, the severity of the disease should be assessed immediately, as this affects the treatment and determines the prognosis [16].

With regard to acute pancreatitis after ERCP, preventive measures can be tactical, medical and technical.

Tactical measures include the selection of patients who are indeed indicated for ERCP after using other, non-invasive imaging methods [17].

A large number of different agents have been proposed as drug prophylaxis. A proven tool that significantly reduces the incidence of acute pancreatitis after ERCP is the use of nonsteroidal anti-inflammatory drugs (diclofenac, indomethacin) per rectum [17, 18].

Bleeding is another serious complication associated with ERCP. The frequency of bleeding after ERCP is estimated at 0.3–2 %.

Bleeding can be further classified as insignificant or clinically significant based on a change in hemoglobin and the absence/presence of overt gastrointestinal bleeding.

The most common reported causes of the ERCP bleeding is endoscopic sphincterotomy. Patient-related risk factors for post-sphincterotomy bleeding include coagulopathy, use of anticoagulants within 3 days of ERCP, and active cholangitis [12, 14, 19].

Cholangitis is well-known complications of ERCP, with an incidence of 0.5 % to 3 %. Clinical presentation includes fever, jaundice, and abdominal pain, and occasionally hypotension and altered mental status in severe cases [12, 14].

Risk factors are old age, previous ERCP history, and hilar obstruction. Patients with incomplete biliary drainage or prior history of liver transplantation have the highest risk of post-ERCP cholangitis [20, 21].

The risk of cholangitis can be up to 10 % in patients who have retained stone fragments following mechanical lithotripsy. Previously placed stents may also become obstructed (due to stone fragments, bacterial biofilm, sludge, tumor or tissue growth) and block the lumen of the stent, resulting in delayed infection. Furthermore, in patients with an obstructed bile duct, stent migration may occur and result in cholangitis. Of note, metal stents are associated with fewer risks.

To reduce the risk of post-ERCP cholangitis antibiotics before ERCP are recommended for patient with a history of liver transplantation or in case of suspected biliary obstruction that may be incompletely drained. However, routine use of antibiotics before ERCP is not recommended [21, 22].

Post-ERCP **cholecystitis** is not common complication and has been reported with an incidence of 0.5 %. Though not common, early recognition of Post-ERCP cholecystitis is vital as it can lead to significant morbidity such as purulent cholecystitis requiring emergent cholecystectomy. The pathogenesis involves contamination of the gallbladder by nonsterile contrast [12, 14, 23].

The risk factors for post-ERCP **cholecystitis** occurrence within 2 weeks include a history of acute pancreatitis, history of chronic cholecystitis, gallbladder opacification, biliary duct metallic stent placement, high leukocyte counts before ERCP, presence of stones in the gallbladder and having contrast fill the gallbladder during the procedure [23, 24].

The most crucial measure for prophylactic acute cholecystitis is endoscopic gallbladder drainage, which has proven to be effective and safe. Prophylactic antibiotics also may be useful.

Treatment of post-ERCP cholecystitis typically involves surgery or percutaneous cholecystostomy, and in nonsurgical candidates, transpapillary and EUS-guided gallbladder drainage may additionally be considered as treatment options.

1.5 COMMON BILE DUCT STONE

For more than 30 years, ERCP has been the "gold standard" in the diagnosis and treatment of choledocholithiasis. In most centers where ERCP is performed, treatment of common bile duct stones is routine. It includes cholangiography, in which the size, number and location of stones are assessed. Access to the common bile duct is provided by endoscopic sphincterotomy and/or balloon dilatation of the MDP. Extraction of the stone is carried out with a basket or balloon. When the size of the stone exceeds the size of the papillotomy hole, mechanical lithotripsy can be used. In case of multiple or "difficult" stones, several sessions are sometimes required for complete removal of stones [25].

In cases of "difficult stones", in addition to standard mechanical lithotripsy, balloon dilatation, peroral cholangioscopy with laser lithotripsy, electrohydraulic lithotripsy, stenting, or surgical treatment can be used [26, 27].

In general, the efficiency of endoscopic stone removal is more than 90–95 % [25–27]. One of the most difficult forms of choledocholithiasis for endoscopic treatment are patients with Mirizzi

syndrome – with cholecystobiliary fistula [8, 25, 28]. The features of ERCP in Mirizzi syndrome will be described in more detail below.

Our own experience also shows high efficiency in the treatment of choledocholithiasis. Retrospective analysis of the treatment of 302 patients with choledocholithiasis. Of these, acute cholangitis was in 29 (9.6 %), acute biliary pancreatitis in 15 (5 %), in 4 (1.3 %) cholangitis was combined with biliary pancreatitis. There were 106 men (35.1 %), women – 196 (64.9 %). The age of the patients was from 21 to 91 years (64.2 ± 14.7).

In general, restoration of bile outflow was achieved in 300 (99.4 %) patients, complete removal of stones was carried out in 290 (96 %) patients. In case of Mirizzi syndrome (MS) with cholecystobiliary fistula – stone removal was achived only in 4 out of 12 patients. Among 290 patients with choledocholithiasis (excluding MS), lithoextration was not performed in 8 (2.8 %) cases: due to the size and location of the stones (7) and because of the paraparillar diverticulum (1).

Complications after endoscopic interventions were: pancreatitis – 5 (1.7 %) patients, bleeding – 6 (2 %), perforation – 2 (0.7 %), acute cholecystitis – 3 (1 %). Of the 302 patients, 4 (1.3 %) died – from complications of biliary pancreatitis (1), cholangitis (1), cardial felure (1), as a result of perforation followed papillotomy (1).

Thus, our results showed that ERCP and endoscopic interventions allow complete removal of common bile duct stones in 96 % of patients with choledocholithiasis. The most difficult form of choledocholithiasis for endoscopic treatment is MS. Mortality is associated with complications of endoscopic interventions 0.3 %.

1.6 MIRIZZI SYNDROME

Mirizzi syndrome is severe complication of cholelithiasis and is due to developed inflammatory and degenerative changes between the wall of the gallbladder and common bile duct. Among patients with cholelithiasis, MS occurs in 0.2–5.0 % of cases [29].

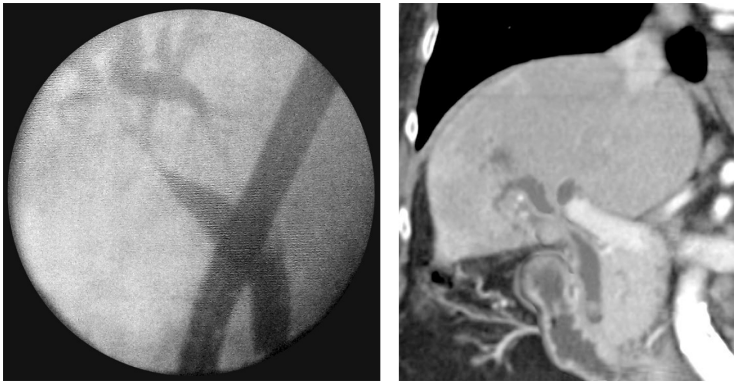
In 1948, Pablo Luis Mirizzi first described the common bile duct obstruction as a result of its compression by a stone impacted in the neck of the gallbladder [30]. Subsequently, not only this condition, but also the formation of a fistula between the lumen of the gallbladder and common bile duct with stones migration and cholestasis began to be called by the name of this surgeon.

The pathophysiological aspects of the development of MS are not completely clear. It is indisputable that it develops as a result of chronic inflammation of the gallbladder with symptoms of pericholecystitis, involvement in the inflammatory process of the hepatoduodenal ligament, which results in compression of the hepaticocholedochus at first, and then, as a result of a bedsore, the formation of a fistula between the lumen of the gallbladder and hepaticocholedochus [29]. However, the predisposing factors contributing to this are not entirely clear.

Diagnosis of MS is based on the detection of compression of the common bile duct by the gallbladder or its duct, the presence of a fistula between the gallbladder and common bile duct with stones, mainly using ERCP, MRI, CT and evaluation of intraoperative data [8, 29]. Preoperative diagnosis of MS is extremely important in terms of choosing the method of treatment and prevention of intraoperative damage to the bile ductsr and vascular structures.

There are several classifications of Mirizzi syndrome: McSherry, C. (1982), Csendes, A. (1989, 2007), Nagakawa, T. (1997), Nechitailo, M. (2005), Khvorostov, E. (2020) [31, 32]. The main factor underlying them is the presence or absence of a fistula between the gallbladder and bile ducts. This was the principle in creating the first, most common and practically convenient McSherry classification (1982): Type I – compression of the common bile duct by a stone located in the bladder itself, its neck or cystic duct; Type II – formation of a fistula between the gallbladder and common bile duct with its obstruction by a calculus [31].

With Type I MS, compression of hepaticocholedochus is most often localised in its middle third – in the area adjacent to the gallbladder. However, compression can be legalized both high, up to the hilum of the liver (**Fig. 1.19**), and low – in case of low confluence of the cystic duct. In addition, compression of the common bile duct can also be after cholecystectomy – by a stone in the stump of the cystic duct or by the stump itself.



a *b*

Fig. 1.19 Mirizzi syndrome Type I with compression of the confluence of the hepatic ducts: *a* – ERCP; *b* – CT reconstruction

Therapeutic endoscopic procedures in case of Type I MS can be nasobiliary drainage, stenting, or dilatation of the obstruction.

In order to exclude the tumor nature of the obstruction and clarify the anatomical features, it is advisable for patients with Type I MS to perform CT scan.

In most cases, Type II MS, the fistula between the gallbladder and common bile duct is located on the level of the proximal and middle third (**Fig. 1.20**). But the localization of the fistula can be detected both high (**Fig. 1.21**) and low (**Fig. 1.22**).

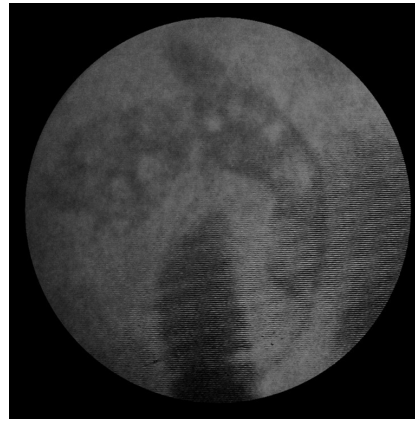


Fig. 1.20 Type II MS with multiple stones and fistula at the level of the proximal and middle third of the common bile duct

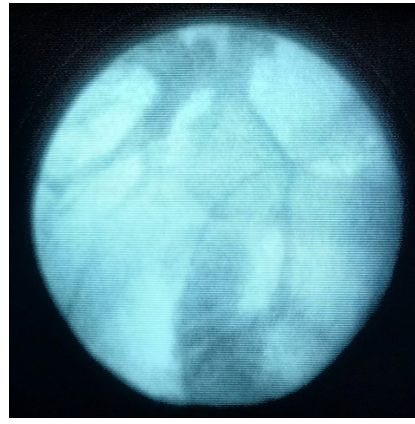


Fig. 1.21 Type II MS with a fistula and a large stone at the level of the proximal and middle third of the common bile duct with involvement of confluence

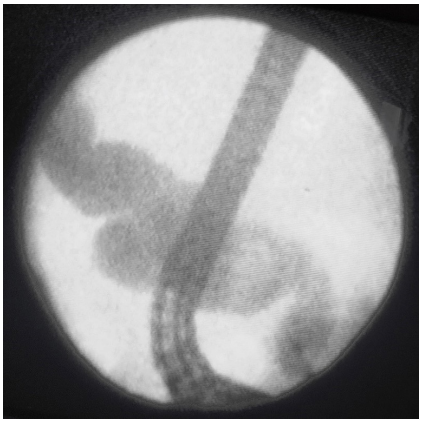


Fig. 1.22 Type II MS with a fistula and a stone at the level of he distal third of the common bile duct

The number and size of stones in Type II MS varies significantly – there can be a single large stones or multiple stones of different sizes.

The formation of a fistula between the gallbladder and common bile duct with "falling out" of stones leads to biliary obstruction – partial or complete. The proximal ducts are always dilated. However, the distal part of the common bile duct may or may not be dilated.

In our opinion, in Type II MS, it is advisable to distinguish subtype A – without dilatation of the common bile duct distal to the fistula, subtype B – with dilatation of the duct distal to the fistula (**Fig. 1.23**).

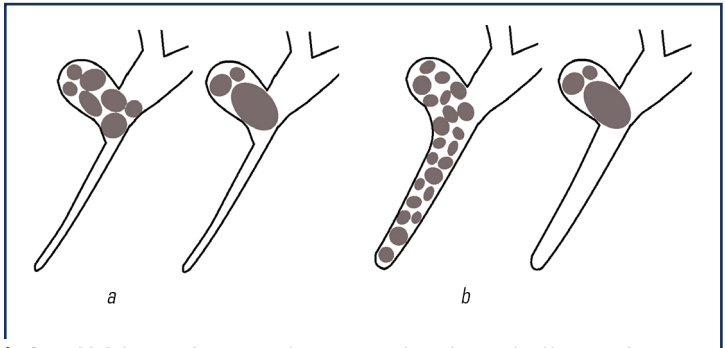


Fig. 1.23 Subtypes of Mirizzi syndrome Type II, depending on the dilatation of the distal common bile duct: *a* – subtype II A; *b* – subtype II B

This division is associated with the possibility of endoscopic lithoextraction – with an dilated distal duct – in Type II B, it is doable. In Type II A endoscopic lithoextraction is unlikely to be done.

In MS II, if lithoextraction has been failed, NBD or stenting can be performed, providing biliary decompression. If endoscopic stone removal is not possible, surgery should be considered, and this is contrindication for surgery, stenting should be done.

The analysis showed that both compression of the common bile duct in MS Type I and fistula in Type II can be observed throughout all lenghth of the extrahepatic biliary tract. The atypical confluence of the cystic duct, identified in patients with MS Type I, indicates that close contact of the bladder neck with common bile duct, with variant anatomy of the cystic duct, in conditions of recurrent inflammation of the gallbladder and involvement of the hepatoduodenal ligament, creates the prerequisites not only for compression of the common bile duct, but also to the subsequent formation of a cholecystobiliary fistula – MS Type II (**Fig. 1.24**). The observed different, especially low localization of compression in type I and fistula in type II indirectly indicates the role of atypia (variant anatomy) of the cystic duct confluence in the MS formation.

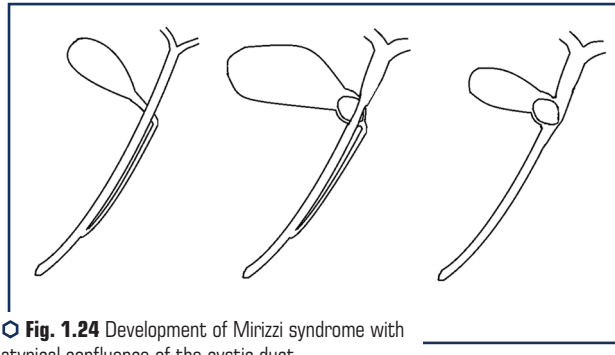


Fig. 1.24 Development of Mirizzi syndrome with atypical confluence of the cystic duct

An analysis of our experience of management of 17 patients with MS showes that out of 5 patients with Type I MS, endoscopic interventions, in addition to ERCP, included endoscopic sphincterotomy in 4 patients, NBD in 3, and stent placement in 1 case. There were no complications after ERCP. It should be noted that in 2 out of 5 cases of Type I MS, had acute cholecystitis, so the compression of the common bile duct was caused by an enlarged inflamed gallbladder.

Of the 12 patients with Type II MS, subtypes II A and II B were distributed equally – 6 patients each. In case of MS II A, in addition to ERCP, all patients underwent endoscopic sphincterotomy, for biliary decompression in 5 patients, NBD was used, and in 1 case, stenting was performed. In MS II B, lithotripsy and lithoextraction were performed in 4 out of 6 cases. NBD was placed in one patient, stent was placed in another.

Of the 17 patients with MS, complications after ERCP occurred in one (cholangitis). There were no lethal cases.

Seven patients with MS II were operated on.

1.7 TUMOR OBSTRUCTION OF THE BILIARY TRACT

The main causes of tumor obstruction of the biliary tract are pancreatic head cancer, papilla cancer, cholangiocarcinoma, gallbladder cancer. A more rare cause is a metastatic lesion of the lymph nodes of the hilum of the liver and hepatoduodenal ligament, the sources of which are malignant tumors of other localizations (stomach, colon, etc.) [33]. Painless jaundice is the main clinical feature in patients with tumor biliary obstruction. The main method of treatment of malignant tumors accompanied by biliary obstruction is surgical – radical intervention. Preoperative drainage of the bile ducts is aimed at eliminating jaundice, normalizing liver function and thus reducing the incidence of perioperative complications [34, 35]. If it is necessary to carry out neoadjuvant chemotherapy, a prerequisite is the normalization of liver function, which, in the presence of obstructive cholestasis, is possible only with the restoration of the passage of bile. By the time of the initial hospitalisation about 40–50 % of patients with tumor biliary obstruction need only palliative treatment, the main goal of which is to restore the outflow of bile [33].

ERCP allows to determine the location and extent of the obstruction. In order to decompress the bile ducts in malignant biliary obstruction, bypass biliodigestive anastomoses, percutaneous biliary drainage and endoscopic drainage could be used. Due to the less invasive intervention, ERCP and endoscopic drainage are preferred [33]. For this purpose, nasobiliary drainage and placement of plastic or metal stents are used [2, 8, 33]. Preference is given to metal stents, because plastic stents need to be changed after 1.5–4 months [33, 35].

The effectiveness of endoscopic drainage in tumor obstruction of the distal choledochus is 80–95 %. In Klatskin tumors, the effectiveness of endoscopic drainage is somewhat less, and the likelihood of developing cholangitis is higher. In MDP tumors, the efficiency of endoscopic drainage exceeds 90 % [33].

Our results show that out of 67 patients with malignant biliary obstruction who underwent ERCP, endoscopic decompression was achieved in 56 (80 %).

Complications occurred in 6 (9 %) of 67 patients: cholangitis – in 3 patients, acute pancreatitis – in 2 patients, and in another patient, non-severe bleeding from the EPST wound.

Of the 11 patients with unsuccessful endoscopic decompression, 6 used percutaneous drainage, 3 – bypasses, and another 2 used symptomatic therapy. Twenty three (34.3 %) patients underwent radical surgical treatment. 5 patients died – 4 from multiple organ failure (in 2 cases after drainage, 2 without drainage of the biliary tract) and one – in the postoperative period – after radical surgical treatment.

1.8 CHRONIC PANCREATITIS

Chronic pancreatitis (CP) is an irreversible inflammatory process leading to destruction and fibrotic changes in the pancreatic parenchyma with impaired exocrine and endocrine functions [36].

In CP, ERCP can play 2 main roles – diagnosis – with insufficient information content of other methods and therapeutic. The purpose of the latter is drainage of the common bile duct in case of its compression or intervention on the main pancreatic duct aimed at its decompression and/or removal of stones [2, 8].

ERCP is sensitive for detecting ductal changes in CP, but cannot assess parenchymal changes. In general, pancreatography reveals dilatation, strictures and irregular contour, filling defects (stones), communication of the duct with pancreatic cysts, etc. However, the diagnostic value of ERCP in identifying these findings is of low sensitivity and specificity, yielding to CT and MRI. In some cases, CP with wirsungography does not show obvious changes [36].

In CP, MPD obstruction was caused by strictures (47 %), stones (18 %), or a combination of both (32 %) [2].

MPS strictures may be single or multifocal. Most strictures occur in the head of the pancreas. Endoscopic treatment of strictures may include dilatation and stenting. At the same time, to provide access, a dissection of the mouth of the MPD is mandatory. The effectiveness of endoscopic treatment of isolated strictures is 65–80 %. The more numerous the stricture, the lower the clinical effectiveness of endotherapy. The presence of virsungolithiasis is always accompanied by MPD strictures. Complete or partial elimination of symptoms after pancreatic sphincterotomy, dilatation of strictures and mechanical extraction of the stone is observed only in 50 % to 67 % of patients.

At the same time, the effectiveness of endoscopic drainage that occurs in CP compression of the common bile duct is high and amounts to more than 90 % [2, 8, 36].

1.9 OTHER USES OF ERCP

ERCP is used in the diagnosis and treatment of postoperative bile duct injuries and allows determining the level of damage and the source of bile leakage. The latter is possible only with marginal injuries of the bile ducts or insufficiency of the cystic duct, that is, in those cases where the continuity of the bile tree is not broken. In the same cases, endoscopic treatment is successfully used, which is aimed at creating conditions for the fistula closing. This is most commonly achieved with sphincterotomy, endoscopic stenting, or NBD. The effectiveness of these measures in this cases is 80–95 % [37, 38].

Similarly, ERCP can be used for pancreatic fistulas after pancreatic surgery, such as distal pancreatic resection. Pancreatography allows visualization of contrast extravasation. Therapeutic interventions include sphincterotomy, stenting, or transnasal drainage of the MPD [2, 8].

In postoperative biliary strictures, ERCP allows to determine the location and extent of the stricture, and endoscopic treatment of patients includes: endoscopic balloon dilatation and/or placement of biliary stents, including several of them at the same time.

The efficiency of primary endoscopic treatment is high – 80–94 %. However, these patients develop complications in 20–33 %, mainly cholangitis, which is associated with prolonged use of stents. Approximately 25 % of patients after removal of stents develop a recurrence of the stricture [2, 8].

CONCLUSIONS

Summing up, it is possible to conclude that the technological capabilities of ERCP and related endoscopic interventions have now reached a plateau in their development. Nowadays despite the limited diagnostic potential, due to advances in CT and MRI, ERCP is the gold standard in the diagnosis and, especially, treatment of common bile duct stones, and is the method of choice for decompression in malignant biliary obstruction. ERCP may be useful in some cases of chronic pancreatitis, biliary and pancreatic fistulas.

Further development of ERCP, apparently should be associated with the prevention of complications, clarification of indications for certain methods of treatment, as well as the development at the combination of various methods – ERCP, endoultrasound, cholangio-, pancreatoscopy, etc.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this paper.

REFERENCES

1. McCune, W. S., Shorb, P. E., Moscovitz, H. (1968). Endoscopic Cannulation of the Ampulla of Vater. Annals of Surgery, 167 (5), 752–756. doi: https://doi.org/10.1097/00000658-196805000-00013
2. Cotton, P., Leung, J. (2006). Advanced Digestive Endoscopy: ERCP. Malden: Blackwell Publishing.
3. Kawai, K., Akasaka, Y., Murakami, K., Tada, M., Kohli, Y., Nakajima, M. (1974). Endoscopic sphincterotomy of the ampulla of Vater. Gastrointestinal Endoscopy, 20 (4), 148–151. doi: https://doi.org/10.1016/s0016-5107(74)73914-1

4. Classen, M., Demling, L. (1974). Endoskopische Sphinkterotomie der Papilla Vateri und Steinextraktion aus dem Ductus choledochus. DMW – Deutsche Medizinische Wochenschrift, 99 (11), 496–497. doi: https://doi.org/10.1055/s-0028-1107790
5. Soehendra, N., Reynders-Frederix, V. (1980). Palliative Bile Duct Drainage – A New Endoscopic Method of Introducing a Transpapillary Drain. Endoscopy, 12 (1), 8–11. doi: https://doi.org/10.1055/s-2007-1021702
6. Lammer, J., Lepuschütz, H., Sager, W. D., Kratochvil, P., Brandstätter, G., Zalaudek, G. (1980). ERCP und CT in der Diagnostik von chronischer Pankreatitis, Pseudozysten und Pankreaskarzinom – ein Vergleich. Rontgenblatter, 33 (12), 602–611.
7. Shimizu, S., Yokohata, K., Mizumoto, K., Yamaguchi, K., Chijiiwa, K., Tanaka, M. (2002). Laparoscopic choledochotomy for bile duct stones. Journal of Hepato-Biliary-Pancreatic Surgery, 9 (2), 201–205. doi: https://doi.org/10.1007/s005340200019
8. Baron, T. H., Kozarek, R., Carr-Locke, D. L. (2008). ERCP. W. B. Saunders, 493–505. doi: https://doi.org/10.1016/B978-1-4160-4271-6.50051-4
9. Yuen, N., O'Shaughnessy, P., Thomson, A. (2017). New classification system for indications for endoscopic retrograde cholangiopancreatography predicts diagnoses and adverse events. Scandinavian Journal of Gastroenterology, 52 (12), 1457–1465. doi: https://doi.org/10.1080/00365521.2017.1384053
10. Shah, S. L., Carr-Locke, D. (2020). ERCP for acute cholangitis: timing is everything. Gastrointestinal Endoscopy, 91 (4), 761–762. doi: https://doi.org/10.1016/j.gie.2019.12.010
11. Mamontov, I. N. (2019). Shkala opredeleniia pokazanii k ERKhPG i endoskopicheskim vmeshatelstvam u bolnykh s obstruktciei vnepechenochnykh zhelchnykh putei. Kharkivska khirurgichna shkola, 3-4 (96-97), 108–113.
12. Talukdar, R. (2016). Complications of ERCP. Best Practice & Research Clinical Gastroenterology, 30 (5), 793–805. doi: https://doi.org/10.1016/j.bpg.2016.10.007
13. Johnson, K. D., Perisetti, A., Tharian, B., Thandassery, R., Jamidar, P., Goyal, H., Inamdar, S. (2019). Endoscopic Retrograde Cholangiopancreatography-Related Complications and Their Management Strategies: A "Scoping" Literature Review. Digestive Diseases and Sciences, 65 (2), 361–375. doi: https://doi.org/10.1007/s10620-019-05970-3
14. Ak, Ç., Aykut, H., Pala, E., Sayar, S., Tarikçi Kiliç, E., Adali, G. et al. (2022). Post-ERCP Complication Analysis of an Experienced Center. Surgical Laparoscopy, Endoscopy & Percutaneous Techniques, 32 (6), 707–713. doi: https://doi.org/10.1097/sle.0000000000001113
15. Tryliskyy, Y., Bryce, G. (2018). Post-ERCP pancreatitis: Pathophysiology, early identification and risk stratification. Advances in Clinical and Experimental Medicine, 27 (1), 149–154. doi: https://doi.org/10.17219/acem/66773
16. Mine, T., Morizane, T., Kawaguchi, Y., Akashi, R., Hanada, K., Ito, T. et al. (2017). Clinical practice guideline for post-ERCP pancreatitis. Journal of Gastroenterology, 52 (9), 1013–1022. doi: https://doi.org/10.1007/s00535-017-1359-5

17. Cahyadi, O., Tehami, N., de-Madaria, E., Siau, K. (2022). Post-ERCP Pancreatitis: Prevention, Diagnosis and Management. Medicina, 58 (9), 1261. doi: https://doi.org/10.3390/medicina58091261
18. Shen, C., Shi, Y., Liang, T., Su, P. (2017). Rectal NSAIDs in the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis in unselected patients: Systematic review and meta-analysis. Digestive Endoscopy, 29 (3), 281–290. doi: https://doi.org/10.1111/den.12816
19. Bae, S. S., Lee, D. W., Han, J., Kim, H. G. (2019). Risk factor of bleeding after endoscopic sphincterotomy in average risk patients. Surgical Endoscopy, 33 (10), 3334–3340. doi: https://doi.org/10.1007/s00464-018-06623-8
20. Yilmaz, H., Koçyiğit, B. (2022). Predictors of postendoscopic retrograde cholangiopancreatography associated cholangitis: a retrospective cohort study. Turkish Journal of Medical Sciences, 52 (1), 105–112. doi: https://doi.org/10.3906/sag-2109-84
21. Chen, M., Wang, L., Wang, Y., Wei, W., Yao, Y.-L., Ling, T.-S., Shen, Y.-H., Zou, X.-P. (2018). Risk factor analysis of post-ERCP cholangitis: A single-center experience. Hepatobiliary & Pancreatic Diseases International, 17 (1), 55–58. doi: https://doi.org/10.1016/j.hbpd.2018.01.002
22. Boonsinsukh, T., Viriyaroj, V., Yodying, H. (2016). Risk Factors for Post Endoscopic Retrograde Cholangiopancreatography Cholangitis. Journal of the Medical Association of Thailand, 8, S166–S170.
23. Cao, J., Peng, C., Ding, X., Shen, Y., Wu, H., Zheng, R., Wang, L., Zou, X. (2018). Risk factors for post-ERCP cholecystitis: a single-center retrospective study. BMC Gastroenterology, 18 (1). doi: https://doi.org/10.1186/s12876-018-0854-3
24. Ting, P.-H., Luo, J.-C., Lee, K.-C., Chen, T.-S., Huang, Y.-H., Hou, M.-C., Lee, F.-Y. (2020). Post endoscopic retrograde cholangiopancreatography cholecystitis: The incidence and risk factors analysis. Journal of the Chinese Medical Association, 83 (8), 733–736. doi: https://doi.org/10.1097/jcma.0000000000000383
25. Manes, G., Paspatis, G., Aabakken, L., Anderloni, A., Arvanitakis, M., Ah-Soune, P. et al. (2019). Endoscopic management of common bile duct stones: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy, 51 (5), 472–491. doi: https://doi.org/10.1055/a-0862-0346
26. Trikudanathan, G., Navaneethan, U., Parsi, M. A. (2013). Endoscopic management of difficult common bile duct stones. World Journal of Gastroenterology, 19 (2), 165–173. doi: https://doi.org/10.3748/wjg.v19.i2.165
27. Cianci, P., Restini, E. (2021). Management of cholelithiasis with choledocholithiasis: Endoscopic and surgical approaches. World Journal of Gastroenterology, 27 (28), 4536–4554. doi: https://doi.org/10.3748/wjg.v27.i28.4536
28. Mamontov, Y. N. (2016). Rezultati lechenyia bolnikh po povodu syndroma Mirizzi. Klinichna khirurhiia, 9 (890), 25–27.

30. Mirizzi, P. L. (1948). Sndrome del conducto heptico. J. Int. Chir., 8, 731–777.
31. McSherry, C. K., Ferstenberg, H., Virshup, M. (1982). The Mirizzi syndrome: Suggested classification and surgical treatment. Surg Gastroenterol, 1, 219–225.
32. Beltran, M. A., Csendes, A., Cruces, K. S. (2008). The Relationship of Mirizzi Syndrome and Cholecystoenteric Fistula: Validation of a Modified Classification. World Journal of Surgery, 32 (10), 2237–2243. doi: https://doi.org/10.1007/s00268-008-9660-3
33. Aadam, A. A., Liu, K. (2019). Endoscopic palliation of biliary obstruction. Journal of Surgical Oncology, 120 (1), 57–64. doi: https://doi.org/10.1002/jso.25483
34. van der Gaag, N. A., Rauws, E. A. J., van Eijck, C. H. J., Bruno, M. J., van der Harst, E., Kubben, F. J. G. M. et al. (2010). Preoperative Biliary Drainage for Cancer of the Head of the Pancreas. New England Journal of Medicine, 362 (2), 129–137. doi: https://doi.org/10.1056/nejmoa0903230
35. Tamura, T., Itonaga, M., Ashida, R., Yamashita, Y., Hatamaru, K., Kawaji, Y. et al. (2021). Covered self-expandable metal stents versus plastic stents for preoperative biliary drainage in patient receiving neo-adjuvant chemotherapy for borderline resectable pancreatic cancer: Prospective randomized study. Digestive Endoscopy, 33 (7), 1170–1178. doi: https://doi.org/10.1111/den.13926
36. Riff, B. P., Chandrasekhara, V. (2016). The Role of Endoscopic Retrograde Cholangiopancreatography in Management of Pancreatic Diseases. Gastroenterology Clinics of North America, 45 (1), 45–65. doi: https://doi.org/10.1016/j.gtc.2015.10.009
37. Rio-Tinto, R., Canena, J. (2020). Endoscopic Treatment of Post-Cholecystectomy Biliary Leaks. GE – Portuguese Journal of Gastroenterology, 28 (4), 265–273. doi: https://doi.org/10.1159/000511527
38. Gawlik, C., Carneval, M. (2021). A Review of the Management of Bile Leaks. Cureus, 13 (5), e14937. doi: https://doi.org/10.7759/cureus.14937

DOI: 10.15587/978-617-7319-65-7.CH2

Olha Yuryk, Lukyan Anatychuk,
Roman Kobylianskyi, Nadiia Yuryk

CHAPTER 2

MEASUREMENT OF HEAT FLUX DENSITY AS A NEW METHOD OF DIAGNOSING NEUROLOGICAL DISORDERS IN DEGENERATIVE-DYSTROPHIC DISEASES OF THE SPINE

ABSTRACT

Osteochondrosis of the lumbar spine and its neurological manifestations is one of the most common diseases, which leads to impaired working capacity and disability of people mainly at a young age. The issue of tactics for choosing a treatment method (conservative or surgical) remains debatable.

The chapter presents the results of the development of a thermoelectric device for diagnosing inflammatory processes and pain syndrome in degenerative-dystrophic diseases of the Lumboischialgia. Such a device makes it possible to save, process and visualize measurement results on the display of the device and on a personal computer in real time.

It was established that moderate indicators of temperature and heat flux density (HFD) in the paravertebral zone were recorded in the control group. In patients with lumboschialgia without signs of instability, there was a parallel fluctuation of temperature and HFD on the side of pain and low values on the intact side. In the case of lumboischialgia against the background of vertebral instability, the symptom of "scissors" on the side of pain and an increase in both thermal indicators on the intact side were positive.

With stenosis of the spinal canal, temperature and HFD decreased on both sides, but more intensively on the side of pain.

The results of clinical studies of thermometric indicators in the lumbosacral region of the spine in persons with chronic pain syndrome against the background of degenerative-dystrophic pathology of the spine in the presence of hernias and protrusions of intervertebral discs are also presented.

The effectiveness of the proposed thermoelectric device in medical practice has been confirmed.

KEYWORDS

Heat flux density, temperature, thermometric indicators, inflammatory processes of the human body, osteochondrosis of the spine, thermoelectric device.

Degenerative-dystrophic changes in the spine are one of the most common pathologies of the musculoskeletal system. Such changes can be of different nature: it can be osteochondrosis, spondyloarthrosis, spondylosis, etc.

According to statistical studies, more than 80 % of the world's population in one way or another face pathological changes in the spine. The situation is aggravated by the modern way of life: poor ecology, sedentary lifestyle, bad habits, improper nutrition, chronic stress [1].

Since practicing doctors in their activities most often face with osteochondrosis of the spine and its neurological manifestations, we found it necessary to pay more attention to this problem.

Osteochondrosis of the spine and its neurological manifestations are one of the urgent problems of modern medicine. This is due to the widespread prevalence of the pathology in the active working age, the frequent tendency of the disease to a persistent, protracted course of the process with frequent relapses; relentless progression of the number of such patients with age. A prominent place in this series is occupied by neurological manifestations of osteochondrosis of the lumbar spine, which make up 60–70 % of all diseases of the peripheral nervous system and are the cause of more than 70 % of cases of temporary disability. The prevalence of this pathology in Ukraine, according to statistical data of the current pre-war period, is currently 10,044.7 per 100,000 population. Among able-bodied persons, these indicators are the highest in Dnipropetrovsk (11,560.6) and Volyn (11,440.3) regions [1]. And although the fact that osteochondrosis of the spine is a multifactorial, multimorphic disease is undeniable, many aspects of the pathogenesis and clinical manifestations of this pathology have not been studied until now.

We found [2] that determining the pathophysiological mechanisms of back pain based on of clinical and paraclinical methods of examination of the patient is the main step towards prescribing the most effective and safe therapy and predicting the course of the disease. The most common cause of lower back pain is a herniated disc – a disease of the musculoskeletal system that occurs as a result of the rupture of the fibrous ring of the intervertebral disc (the upper shell of the disc) and the pushing out of the part of the annulus pulposus (the inner part of the disc). The main clinical neurological signs of intervertebral disc herniation can be manifested separately or in combination with the following syndromes: local pain (lumbargia), reflected pain (lumboischialgia), radicular syndrome (radiculopathy), spinal cord injury syndrome (myelopathy).

When examining patients, first of all, it is necessary to exclude serious pathology that requires immediate special medical interventions (spine fracture, tumour, infection, diseases of internal organs and other) [3]. After the survey, the patient is examined, which includes the following tests [2]:

1) examination of the patient (walking problems, antalgic postures, symmetry of body parts);

2) palpation (pain in the back, especially in the places where the pain is localized, pain in the Valleix and Gara points);

3) examination of the degree of paravertebral muscle tension (muscle-tonic syndrome);

4) examination of the mobility of the lower back (static-dynamic disorders);

5) examination of skin sensitivity (if there is a violation, determine by which type – central, segmental or non-aural);

6) assessment of muscle strength in the limbs (if there is a violation – determine in which group of muscles, to which myotome belongs);

7) assessment of tendon reflexes (live, increased, decreased, prolapsed);

8) assessment of nerve root tension symptoms (Neri, Lasegue, Dejerine, Wasserman, Sicard, Seletsky, Mackevich, Turin);

9) assessment of vasomotor, trophic and secretory symptoms.

In clinical practice, the investigation of the symptoms of tension of the roots of the lumbar spine, most of which are based on reflex myofixation of the affected motor segment of the spine due to irritation of the receptors of its deformed tissues, is carried out with the help of such symptoms as Neri, Lhermitte, Lasegue and others [4]. A thorough clinical examination allows the practitioner to choose the further tactics of treating the patient – conservative treatment or directing him to surgical treatment.

Since in our clinical practice we most often examine patients who are referred for surgical treatment, we consider it appropriate to highlight the features of neurological disorders in this category of patients.

2.1 SOME FEATURES OF NEUROLOGICAL DISORDERS IN PATIENTS WITH DEGENERATIVE-DYSTROPHIC SPINE PATHOLOGY WHO UNDERWENT SURGICAL TREATMENT OF THIS PATHOLOGY

With long-term pain syndrome, the presence of symptoms of "falling out" in clinical practice, surgical methods of treating herniations between the vertebral discs in the lumbar spine are quite often used. There are a number of modern methods of treatment of such pathology.

Microdiscectomy is a minimally invasive operation during which a herniated disc is removed through a small incision on the back.

The word "micro" is used in connection with performing an operation under an operating microscope with special microsurgical instruments. This technology has come a long way in its development, starting with the technique proposed by the American orthopedist and neurosurgeon William J. Mixter and Joseph S. Barr in 1934 [5]. In those days, removal of hernias was carried out by a wide laminectomy, possibly even transdurally. With the introduction of microsurgical technology, this operation has become truly minimally invasive. As a standard, resection of part of the arch (most often the lower edge of the upper arch) is used during the operation, sometimes resection of the medial part of the intervertebral joint is performed in the case of paramedian or mediolateral disc herniation. The use of microsurgical equipment with a magnification of 6–8–10 times allows you to clearly visualize the nerve root, hernia, and, if necessary, perform coagulation of the epidural veins [6].

One of the ways to prevent the development of postoperative fibrosis is the intraoperative use of special gels. The works of domestic and foreign authors [6] indicate the promising development of this direction, but note that the problem is far from a final solution [6, 7].

Methods of surgical treatment of hernias between the vertebral discs of the lumbar spine are progressively changing each other. And although the "gold standard" of surgical treatment of hernias between the vertebral discs is open microdiscectomy, recently numerous techniques have appeared, the authors of which seek to minimize the trauma of the surgical approach without reducing the radicality of the operation.

With the advent of surgical endoscopes, an opinion was constantly being expressed that the magnification obtained with the use of a microscope could be used for the microendoscopic technique. The advantage of the microendoscopic technique was even greater minimization of access. However, endoscopic technique requires specific tools, specific work skills and increases the duration of surgical intervention [8].

The technique of microendoscopic discectomy was described by Kevin T. Foley and Maurice M. Smith in 1997 [9]. The technique combines the principles of standard microdiscectomy with the use of endoscopic imaging. Indications for microendoscopic discectomy are the same as for microdiscectomy. Modern microendoscopic discectomy is a highly effective method of treating herniated intervertebral discs of the lumbar spine. This method should be used in case of paramedian, mediolateral hernias of the intervertebral discs.

The technique is positioned as less traumatic for soft tissues, which allows for faster occupational rehabilitation of patients. According to the reports of various authors, patients after microendoscopic discectomy are able to return to work 2–4 weeks after the operation [8].

Complications encountered with microendoscopic discectomy are similar to those with microdiscectomy. Suppuration of the surgical wound with the first technique occurs with a frequency of up to 1 %, with the second – up to 5 %; discitis – 1 and 1 %, respectively; dural sac damage – 10 and 5 %, respectively; hernia recurrences – 5 and 7 %, respectively [7, 8].

One of the disadvantages of microendoscopic discectomy is the need for a certain amount of time for surgeons to master the endoscopic technique. However, with the advent of modern endoscopic systems for the removal of lumbar hernias, this drawback has been partially eliminated. Traditionally, paramedian, mediolateral herniations of the intervertebral discs, stenosis of the lateral recess were considered indications for the technique. However, recently this technique is used for decompression of the lateral recess and installation of interbody cages in cases of spondylolisthesis of small degrees. This technique is also used with a high degree of effectiveness in recurrent herniation of intervertebral discs.

The nature of neurological manifestations in osteochondrosis of the Lumboischialgia during various types of surgical intervention to remove hernias between the vertebral discs at this level has not been studied. This was the aim of our research.

The object of our study were 87 young, middle-aged and elderly patients (47 men and 40 women). Of them, microdiscectomy was performed on 49 people (24 men and 25 women). 33 young people, 12 middle-aged people, and 4 elderly people were operated on. Monoportal endoscopic discectomy was performed on 11 patients (6 men and 5 women): 6 young, 4 middle-aged, and 1 elderly. Biportal endoscopic discectomy was performed in 27 people (17 men and 10 women). Young people

predominated in that group (12 people). There were 9 middle-aged patients and 6 elderly patients. The time of exacerbation of the process was from several weeks to one year. Hernias between the vertebral discs in the Lumboischialgia were most often of medial and paramedian localization. In one case, the patient underwent surgery at the same level.

Anamnestic, subjective and objective data were studied in the studied patients during hospitalization and in the dynamics of the treatment. When collecting the anamnesis and objective examination of the patient, the following other factors were taken into account formation: sex and age of the patient; duration of the disease and age since the onset of the disease; duration and nature of the last exacerbation; provoking factors that increased or decreased back and leg pain; clinical characteristics of the first exacerbation; constitutional type of the patient; type of vertebral deformation; nature of surgical treatment, its scope. All patients underwent a detailed clinical and neurological examination.

All examined patients showed an antalgic position of the body with an angle of inclination in the direction of pain distribution. The position of patients in bed was forced due to persistent pain syndrome. Lameness was found in 69 % of people. In 28 % of the examined, dysfunction of the pelvic organs was detected. Kernig's symptom was positive in 18 % of patients, which indicated the involvement of the spinal meninges in the process. Foot paresis was present in 12 % of subject patients.

In young patients who underwent microdiscectomy, hernias between the vertebral discs were most often localized at the $L_5 - S_1$ level (31 out of 33: 19 men and 12 women). Pain and sensitive disorders were observed in 34 % of people along the course of the S_1 root. The intensity of the pain syndrome according to the VASH scale was 59 ± 1.2 mm. The angle of inclination when determining the Lasegue symptom was 40–45°. Most often, paravertebral muscle tension was II degree according to Yakov Popelianskii [10]. The strength of these muscles in 66 % of the examined patients was within three points. The venous pattern on the legs was strengthened in 9 % of the examined.

In middle-aged patients of this thematic group, in 47 % of cases, hernias were localized at the level between the vertebral disc $L_4 - L_5$, in 29 % – higher localization ($L_2 - L_3$, $L_3 - L_4$). Sequestered hernias, instability of the I–II age vertebrae were observed more often. VAS was within 53 ± 2.4 mm. Lasegue symptom was 40–45° in 70 % of patients, 30–40° in 22 %, and more than 45° in 8 %. The tension of the paravertebral muscles was mostly II degree, and the strength of the paravertebral muscles in 79 % of people was 3 points, in the rest – within 4–5 points. Twisting of the body and limping were characteristic. Enhancement of the venous pattern on the legs was not characteristic.

For the elderly in this thematic group, the presence of instability in the Lumboischialgia, the presence of a sequestered hernia, the appearance of meningo-radicular symptoms, more often at the $L_5 - S_1$ level of the radicle, were characteristic; paresis of the foot on the side of pain. VAS varied within 51 ± 2.8 mm. Tension of paravertebral muscles is mostly II degree, and muscle strength is 2–3 points. In one patient, the angle of inclination when measuring the Lasegue symptom

was 25°, in others it was 40–45°. Enhancement of the venous pattern in the lower back and legs was not characteristic.

The results of the neurological examination of persons who underwent mono- or biportal endoscopic diskectomy were combined into one clinical group. 48 % of young people, 33 % of middle-aged and 19 % of elderly people were examined. Antalgic posture was characteristic of all patients, limping was almost absent. Spinal canal stenosis was present in 10 % of the examinees, foraminal stenosis in 23 % of the examinees. The strength of the paravertebral muscles in one patient was 3 points, in the other 37 people – 5 points. Tension of paravertebral muscles in one patient was II degree, in all others – III degree. In 92 % of the examined, an increase in the venous pattern on the legs, in the paravertebral area was characteristic, and in one patient, the "symptom of the breech" appeared. The dysfunction of the pelvic organs was not characteristic.

In young people, the intervertebral disc herniation was located at the level of $L_5 – S_1$. Pain in 75 % of patients of this age group radiated along the root of S_1, more often to the left or to both sides. Disorders of superficial types of sensitivity were not characteristic. One patient had stenosis of the spinal canal. VAS indicators were 74 ± 3.9 mm. In 80 % of patients, the angle of inclination of the Lasegue symptom was 30–35°, in others it was more than 45°.

In middle-aged people, 61 % of spinal disc herniation (SDH) hernias occurred at the $L_4 – L_5$ level. The pain most often radiated along the root of L_5 to the right. VASH indicators were within 66 ± 3.8 mm. Lasegue symptom was 25–30° in 29 % of the examined, 30–35° in 37 %, 40–45° in 26 %, more than 45° in others. In one patient, the process occurred against the background of spondylolisthesis of the L_4 vertebra.

In the elderly, endoscopic discectomy was mainly performed in women (62 %). SDH hernias at this age in 90 % of cases were localized at the $L_5 – S_1$ level and most often occurred according to the type of lumbago. VAS in this age group was equal to 68 ± 1.5 mm. The Lasegue symptom in the vast majority of operated patients was 25–30°.

Thus, the presence of weakly or moderately pronounced ischemic neuropathy of the corresponding spinal root is characteristic of persons who underwent microdiscectomy against the background of severe pain syndrome. The process primarily involved the short branches of this root, the spinal cord. The presence of reflex changes in the corresponding segment of the spine, damage to nociceptive receptors at this level, and the presence of chronic venous insufficiency in the lower back and legs are characteristic of persons who underwent endoscopic discectomy. Identified neurological signs can contribute to improving the treatment of this category of patients.

At the next stage of our research, we studied the indicators of fatigue in a decreed group of patients.

It is known that fatigue is a complex, multidimensional, mostly subjective phenomenon, which is described by different terms: "subjective feeling of lack of physical and (or) mental energy, which prevents normal daily activities and purposeful activity" [6], "sensation early exhaustion during physical and (or) mental activity, avoidance of loads" [4], "a feeling of exhaustion or fatigue that differs from a feeling of sadness or lethargy" [2].

From a biological point of view, fatigue is one of the oldest adaptive physiological processes. Physiological (normal) fatigue is a common phenomenon and is a signal for rest after a certain amount of activity in order to restore energy balance and prevent injuries [4].

From an anatomical point of view, fatigue is conventionally divided into fatigue of central origin (with changes in the central nervous system) and fatigue of peripheral origin (with changes in the metabolism of skeletal muscles, neuromuscular transmission, cardiovascular system) [4, 6].

According to the qualitative characteristics, fatigue is a multifaceted phenomenon consisting of various components: physical, cognitive/mental, motivational, somatic, and others [4, 6]. Physical fatigue occurs with muscle exhaustion and is manifested in the inability to maintain a constant level of effort or pace of performance when performing a certain activity. Mental fatigue is described as a feeling of exhaustion, lack of energy and reduced initiative in mental activity, which does not allow the patient to maintain a certain level of the latter for a normal period of time. Motivational (psychological) fatigue – a decrease in interest and lack of motivation when performing any activity. Somatic fatigue is a manifestation of the pathology of internal organs. As a rule, the patient simultaneously has different types of fatigue in different ratios [4, 6].

According to the duration, fatigue is conditionally divided into acute (lasts up to six weeks) and chronic (present more than 50 % of the time during the last six weeks or longer).

The phenomenon of fatigue consists of both subjective (own feeling of fatigue) and objective (quantitative characteristics of fatigue when performing certain activities) components [11]. External techniques cannot measure the feeling of fatigue, and it is a purely subjective feeling of exhaustion. Instead, fatigue, both in general and its individual components (physical, mental, and others) can be objectified with the involvement of physical, cognitive and other tests [8, 11].

Today, the most accessible method of assessing fatigue remains the patient survey. Until now, there is no specific diagnostic tool for the diagnosis of somatic pathology. All the questionnaires and scales that we used to assess degenerative-dystrophic spine pathology were originally intended to investigate fatigue of other origins.

In our studies, we determined fatigue indicators using standardized scales MFIS-20, FAS and FSS.

At this stage of the research, the object of our study were 71 patients with neurological manifestations of osteochondrosis of the spine in the lumbosacral section caused by herniations and protrusions of the intervertebral discs at this level. 50 patients underwent surgical interventions: 25 – open microdiscectomy and 25 – bipolar microendoscopic discectomy. 21 people made up the control group, which underwent conservative treatment for lumbago and lumboischialgia in the stage of exacerbation of the process. The duration of the pain syndrome in all patients was more than six months.

Fatigue diagnosis and determination of its characteristics were performed using the MFIS-20, FAS, and FSS fatigue scales.

The MFIS-20 scale consists of 20 questions, each of which has 5 possible answers.

MFI-20 includes 5 subscales (with four questions each):

– subscale for assessing global (general) fatigue (questions № 1, 5, 12, 16);

– subscales for assessing individual components of fatigue – physical (questions № 2, 8, 14, 20), mental (questions № 7, 11, 13, 19), motivational (questions № 4, 9, 15, 18) and reduced activity (questions № 3, 6, 10, 17) [11]. **General fatigue** describes a general feeling of tiredness and reduced activity, combines physical and psychological aspects. **Physical fatigue** encompasses the physical aspects of feeling tired. **Mental fatigue** refers to cognitive functioning, including impaired concentration. **Motivational fatigue** reflects a decrease in the level of motivation to perform a certain activity. Reduced activity implies a negative effect of fatigue on the patient's activity level. The value of each of the MFI-20 subscales ranges from 4 to 20 points; higher values indicate a higher level of the corresponding component of fatigue. A global fatigue subscale value of 12 or more points out of a possible 20 is considered a marker of chronic fatigue [6, 11].

The FAS scale consists of 10 questions: 5 questions about the mental component of fatigue and 5 questions about the physical component of fatigue. There are 5 possible answers to each question. The value of the questionnaire ranges from 10 to 50 points. A scale indicator of 22 points and above indicates the presence of fatigue in the patient [11].

The FSS scale consists of 9 questions, each of which is rated from 1 to 7 points. The scale indicator is calculated as the arithmetic mean of the sum of points. The critical value is 4 points and above, indicating the presence of fatigue in the patient. The scale assesses the impact of fatigue on the patient's quality of life (questions № 1–4, 6) and on his motor and cognitive functions (questions № 5, 7–9) [11].

All patients were asked to rate the presence and nature of fatigue, if it was observed during the last four weeks before hospitalization.

The research was carried out in compliance with the main provisions of the "Rules of Ethical Principles of Scientific Medical Research with Human Participation" approved by the Declaration of Helsinki (1964–2013), ICH GCP (1996), EU Directive № 609 (from November 24, 1986), orders of the Ministry of Health of Ukraine № 690 dated 23.09.2009, № 944 dated 14.12.2009, № 616 dated 03.08.2012. Each patient signed an informed consent to participate in the study, all measures were taken to ensure patient anonymity.

We found that open microdiscectomy was performed in 69 % of young men and 56 % of middle-aged women. In old age, men and women were operated on almost equally often: 19 % of men and 22 % of women. Men in middle age and women in young age were less often operated (12 %). The side of the lesion in men and women differed slightly among themselves: in men, in 44 % of cases, the operation was performed on the left, in 38 % – on the right, and in 18 % – there was a bilateral injury; in women, the left and right sides were equally damaged (22 % of cases each), and bilateral damage was most common – 56 %.

The following indicators were found in patients who were operated on by the method of microscopic endoscopic bipolar discectomy. This treatment method was preferred by young people (73 % of men and 44 % of women). In middle and old age, women underwent surgery equally often: 28 % in each age group. Among men in these age groups, the distribution was as follows: 18 % of middle-aged people and 9 % of elderly people.

Regarding the side of the injury in this type of operation, the following was found. In 18 % of men, damage was observed on the left, in 45 % – on the right, in 37 % – a bilateral process. In women, 64 % of cases had a left-sided process, 21 % – right-sided, 15 % – bilateral.

There were almost equal numbers of people in the control group: 11 men and 10 women. The age groups were almost equally distributed: approximately 33 % in each age group. The side of the injury in 9 % of men was on the left, in 45 % – on the right, in 36 % of cases there were bilateral symptoms. In women, left-sided symptoms were observed in 60 % of cases, right-sided in 30 %, and a bilateral process in 10 % of cases. Such differences in the course of the process can be explained by the specifics of the physical load on the Lumboischialgia, which is not equally loaded by men and women. The results of studying the nature of fatigue are given in **Table 2.1**.

Table 2.1 Characteristics of fatigue in people with various types of discectomy for localization of hernias in the Lumboischialgia

Type of operation	MFIS-20	FAS	FSS
Open microdiscectomy	3.57 ± 0.15**	2.18 ± 0.49**	2.00 ± 0.81*
Bipolar microendodiscectomy	1.80 ± 0.54*	1.22 ± 0.65**	0.63 ± 0.02
Control group	0.36 ± 0.08	0.33 ± 0.03	1.6 ± 0.14*

*Note: * – $p < 0.5$; ** – $p < 0.05$*

The conducted studies showed that all the examined patients had no signs of chronic fatigue, since according to the data of the MFIS scale out of 20 possible points, all the examined indicators were below 12 points (from 12 to 20 points – markers of chronic fatigue).

We found differences in the assessment of fatigue indicators between two groups of patients who underwent surgical interventions.

When examined using the MFIS-20 scale, the following complaints were found in the first clinical group (open microdiscectomy). In 53 % of cases, patients complained about their physical abilities: their movements were clumsy and uncoordinated; they felt weakness in the leg muscles, there were problems with prolonged physical activity; they did not move much during physical activity. The average score in this subscale reached 34 ± 1.5. When analyzing statements related to cognitive issues, such as memory, concentration of attention and decision-making, patients of this group in 47 % of cases complained of their forgetfulness, concentration of attention, it was difficult for them to make decisions; had trouble performing tasks that require thinking. The average score was 27 ± 0.9. Regarding the psychosocial aspects of their health, they were less motivated to participate in social activities; they were limited in their ability to do things outside the home. The subscale range in the psychosocial subscale was 5 ± 0.4 points.

The FAS and FSS scales also determined the presence of physical and mental fatigue in them, which in 68 % and 61 % of cases were of a mild degree, but in 32 % and 39 % of cases, respectively, approached a moderate degree.

With regard to the individuals of the second clinical group (individuals who underwent bipolar microscopic endoscopic discectomy), in a significant number of patients (47 %) the presence of global fatigue of a mild degree was also detected, but with lower indicators, which can be seen from **Table 2.1**.

Some differences were also found in the survey on the MFIS-20 subscales. In the physical subscale, the range in 41 % of respondents was from 11 to 29 points. Patients complained mainly about problems even with minor physical exertion; they were often clumsy and uncoordinated, sedentary. In the subscale of cognitive functions, 31 % of respondents had problems with concentration of attention, sometimes they had forgetfulness. Their average score on this scale reached 18 ± 2.1. In the psychosocial subscale, the average score was 2 ± 0.4 points.

The values of the FAS and FSS scales ranged within the limits of the mild degree, but they were lower than those of the first clinical group.

In the subjects of the control group, the values of the subscales of physical fatigue, mental fatigue, motivational fatigue, and reduced activity did not have any significant differences between individual observations of patients of this clinical group and approached indicators close to normal values.

Therefore, the determination of fatigue indicators using the standardized scales MFIS-20, FAS and FSS helps to improve the selection of patients for one or another type of surgical microsurgery on the Lumboischialgia for herniated intervertebral discs at this level and to improve the development of individual rehabilitation programs for patients in postoperative period.

For many years, issues of assessing the degree of neurological disorders have been developed as a criterion for selecting patients for conservative or operative intervention in this pathology. Therefore, in our research, we paid special attention to the assessment of the quality of life in the decreed group of patients using the SF-36 questionnaire.

At this stage, the object of our research was 63 patients aged 20 to 74 years. All patients were divided into three clinical groups, which were comparable in terms of age, gender, and duration of the disease. 21 individuals were examined in each clinical group: *group I* – patients who underwent biportal endoscopic discectomy; *group II* – patients who underwent open microdiscectomy; *group III* is a comparison group that underwent conservative treatment with the use of acupuncture reflexology.

The control group also consisted of 21 practically healthy individuals, comparable in age and sex, with X-ray signs of osteochondrosis of the spine, but without neurological manifestations of this pathology. There were 24 men (38 %), 39 women (62 %). Herniated intervertebral discs at the level of L_{IV}–L_V vertebrae were present in 23 % of men and 60 % of women; at the level of L_V–S_I – vertebrae – in 31 % of men and in 20 % of women; 38 % of men and 20 % of women had two to three hernias in the lumbar spine; a combination of herniated intervertebral discs at the lumbar level with protrusions of intervertebral discs was present in 8 % of men. Hernias were in the range of 4.5–7 mm and were mainly posterolateral. All patients underwent a detailed clinical and neurological examination.

In order to assess the quality of life of patients and practically healthy persons at work, we used the general questionnaire SF-36 (Heals Status Survey). The SF-36 [12] is intended for use in clinical practice and scientific research to assess the general health of the population and health care tactics and is designed for patients aged 14 years and older. It contains 36 questions covering 8 main characteristics of health.

Measurement within the SF-36 has three levels:

1) points (questions);

2) 8 scales, each of which combines from 2 to 10 points;

3) 2 generalized indicators that combine scales together.

8 scales form 2 different highly ordered groups (total assessments of psychological and physical health). The scales are grouped into two generalized indicators as follows:

1. *Physical Component Summary* (PCS), which includes physical functioning (PF), role physical functioning (RP), and pain (BP) scales that measure physical health.

2. *Mental Component Summary* (MCS), includes scales of mental health (MH), role-emotional functioning (RF), and social functioning (SF) that correlate most closely with the psychological component of health and measure it.

When assessing the quality of life using the SF-36 scale before starting treatment (operative or conservative), the following was found (**Table 2.2**).

● **Table 2.2** Indicators of life quality in patients with herniated intervertebral discs in the Lumboischialgia, to whom various treatment methods were applied (data from the SF-16 questionnaire)

Groups of patients	Indicators of the SF-36 scales (M ± m)								Generalized indicators (M ± m)	
	PF	RP	BR	GH	VT	SF	RE	MH	PCS	MCS
Group I (n = 21)	45.4 ± 9.1	52.1 ± 6.4	61.9 ± 16.4	45.6 ± 21.2	50.3 ± 7.1	53.4 ± 24.1	58.1 ± 25.2	61.1 ± 19.3	43.1 ± 13.7	47.8 ± 12.5
Group II (n = 21)	41.7 ± 11.0*	33.5 ± 7.3**	49.2 ± 18.6**	39.7 ± 29.3	39.5 ± 6.9**	47.3 ± 18.6*	54.2 ± 23.1	59.3 ± 17.4	32.2 ± 16.8*	38.7 ± 11.5
Comparison group (n = 21)	56.3 ± 11.3	51.3 ± 13.4	69.7 ± 28.6	52.2 ± 19.8	50.3 ± 19.1	62.4 ± 23.0	68.4 ± 23.7	70.0 ± 17.6	49.7 ± 9.9	45.9 ± 9.3
Control group (n = 21)	85.7 ± 16.9	76.8 ± 23.8	83.2 ± 21.4	72.4 ± 19.0	70.11 ± 18.7	82.7 ± 25.3	86.0 ± 23.3	83.5 ± 24.1	68.2 ± 21.1	73.5 ± 17.6

*Note: the level of significance of differences in quality of life in patients with SDH hernias compared to controls: *p < 0.05; ** p < 0.01*

As a result of calculating quality of life indicators in patients with herniated intervertebral discs in the Lumboischialgia, who underwent operative or conservative treatment, compared to the control group, quality of life indicators were significantly lower both on individual scales and due to generalized indicators. The most significant was the difference on the scales of RP (role physical functioning), VT (scale of vital activity), BP (pain scale). Generalized indicators of quality of life also differed in I and II clinical patients: PCS (physical component of health) and MCS (psychological component of health).

As can be seen from the obtained data, in the II group of patients, where a significantly higher index of pain intensity is noted ($p < 0.05$), there is a significant prevalence of asthenic, depressive and cognitive disorders ($p < 0.05$; $p < 0.01$; $p < 0.05$, respectively), significantly lower indicators of quality of life were registered on several scales and generalized indicators.

In the process of conducting a comparative analysis of the quality of life in all three clinical groups, depending on the gender, the form of the course, the duration of the disease, the degree of severity of the process, we obtained a heterogeneous picture of the patients' perception of their disease. It turned out that the quality of life of men is lower than that of women. The difference on the RP scale is especially large: 27.4 and 46.3, respectively.

The quality of life of patients with a remitting form of the course of the disease is higher than with a progressive form. Thus, in patients with a remitting form of the disease, the indicators of the Pf scale are not grossly reduced compared to the control group, while in the case of a progressive form of the course, the severity of physical symptoms increases.

Therefore, the use of the SF-36 questionnaire contributes to a better understanding of the pathogenesis of the development of neurological complications in the case of herniated intervertebral discs in the lumbar region, both at the peripheral level and in case of damage to brain structures. Assessment of the quality of life and determination of the intensity of pain in the preoperative period in patients with herniated intervertebral discs in the Lumboischialgia allows for a more differentiated selection of the method of surgical intervention in this pathology.

At the next stage of our research, we drew attention to the fact that there are a number of neurological manifestations of degenerative-dystrophic pathology of the spine, which do not fit into the already described neurological phenomena of this pathology. Therefore, we grouped them into a separate group.

2.2 CLINICAL MANIFESTATIONS OF A NUMBER OF UNKNOWN AND LITTLE-KNOWN NEUROLOGICAL SIGNS OF DEGENERATIVE-DYSTROPHIC PATHOLOGY OF THE SPINE

Osteochondrosis of the spine and its neurological manifestations are among the most urgent problems of our time. This pathology affects the most able-bodied part of the population in young and middle age. The specific weight of clinical neurological manifestations of osteochondrosis among diseases of the peripheral nervous system is 67–95 %. According to data from an epidemiological study

by the International Association for the Study of Pain (IASP), 56 % of the population experience back pain up to 10 days a year and about 9 % – from 10 to 100 days. During life, back pain is diagnosed in 80 % of the population. Dorsalgia is one of the most frequent reasons for seeking medical help.

The issues of etiology, pathogenesis and treatment of this disease remain controversial. Existing classifications of neurological manifestations of this disease do not fully reproduce the variety of their clinical signs.

The nature of rehabilitation measures for vertebrae-neurological manifestations of degenerative-dystrophic lesions of the spine is determined primarily by clinical manifestations, the stage of the disease, and the presence of concomitant pathology both on the part of the spine and the body as a whole. An undifferentiated approach is unacceptable, as it can lead to the breakdown of compensatory processes.

The aim of our research was to identify an atypical clinical course of this process, which was not reflected in any of the existing classifications of neurological manifestations of spinal osteochondrosis.

The work is based on the results of long-term clinical observations of more than 2,000 thousand patients with neurological manifestations of osteochondrosis of the spine during the exacerbation of the process, who were examined and treated in the clinics of our institute. In addition to the usual neurological examination of patients, additional research methods were used: magnetic resonance imaging of the spine, brain and spinal cord structures; inspection and functional X-rays of the spine; electroneuromyography, various ultrasound research methods; electroencephalography; if necessary – study of cognitive functions and psycho-emotional disorders.

The result of our research was the identification of the following atypical manifestations of neurological complications of spinal osteochondrosis [2]:

1. Pseudotrigeminal syndrome (or syndrome of abnormal development of the IV ventricle of the brain). It was observed in 5 patients (4 men and 1 woman). It was characterized by paroxysmal facial pain that mimicked the picture of unilateral trigeminal neuralgia. The pain had a dull, diffuse character; provoked by a cold factor, neuroinfectious process, hypertensive crisis, etc. During the examination of the patients, the exit points of the trigeminal nerve were intact. Local hypo- or hyperesthesia in Zelder's zone on the side of the facial pain, irritation of the cervical sympathetic nodes on the side of the pain, and phenomena of sensitive ataxia on the same side were revealed. On the opposite side – light pyramidal signs, increased tendon and periosteal reflexes according to the hemi type, sclerotome hyperesthesia of the cervical spine. The patients were withdrawn, introverted. The clinical picture of pseudotrigeminal was combined with anterior spondylolisthesis of the II–IV cervical vertebrae and the presence of an hourglass-type abnormality in the development of the IV ventricle of the brain and moderate CSF hypertension syndrome.

2. Epileptiform-irritative syndrome. Diagnosed in 4 middle-aged people (2 men and 2 women) against the background of exacerbation of osteochondrosis, mainly in the thoracic spine. In three patients, the picture of pseudo-angina was simulated, and in one patient – pseudo-bronchial dyspnoea. Phenomena of pseudo-angina or pseudo-hypocardia were paroxysmal, more often in the evening or at night. The attack was preceded by a dull, diffuse, aching pain along the course of

the 3rd–4th or 5th–6th intercostal nerves (more often on the left) for 1–2 hours. Taking analgesic, sedative, vasodilator or bronchospastic drugs in usual therapeutic doses did not relieve pain. At the height of the pain, the patients had loss of consciousness, mild clonic-tonic convulsions of the limbs.

During the examination of the patients, sclerotome tenderness was detected at the level of the upper or middle thoracic spine; to one degree or another, the presence of hyperesthesia or hyperpathia along the course of the 3rd–4th intercostal nerves. Sometimes the tendon reflexes on the pain side increased slightly. Inconstant and vague symptoms of Babinski, Rossolimo, Chaddock, Pusepp were determined on the limbs on the homolateral side. The sharp general pallor of the skin could instantly change to redness or cyanosis. General tenderness of the cervical sympathetic ganglia was noted. The patients were quite pedantic, could talk about their feelings in detail, and often kept a diary of their illness. During X-ray and MRI studies, degenerative changes in the anterior parts of the vertebral bodies, and lateral or posterior disc herniations at the thoracic level were most often found. The electroencephalogram showed convulsive activity of the brain, most often in the parietal, central or occipital region. The condition of the patients improved after adding to the treatment complex chondroprotective and anticonvulsant drugs.

3. "Additional vertebra" syndrome. It was observed in three young and middle-aged patients who presented with long-term radicular pain in the lower back, sacrum and coccyx. The patients had hysteroid traits. Their actions had a somewhat theatrical character. Tasting and showing off to a certain extent, they talked about constant unbearable pain in the area of the lower back, sacrum or coccyx. The story was supplemented with active movements in all sections of the spine, showing the doctor their painful areas.

An X-ray examination revealed a developmental anomaly in one patient – the VI lumbar vertebra and a vestige of the VII lumbar vertebra. Three coccygeal vertebrae were found in another patient, and an additional XIII thoracic vertebra was found in the third patient. In all three patients, an EEG was diagnosed with a sharp decrease in the bioelectric activity of the brain in the frontal and parietal regions.

The behaviour of the patients can be explained to some extent by the fact that in the process of embryogenesis, a representation for 32 segments of the spinal cord was established in their cerebral cortex, while in fact impulses came here from 33 segments of the spinal cord. Therefore, a violation of higher nervous activity was observed.

4. Herpetic ganglionitis syndrome. It was found in 19 middle-aged and older patients. Pain and herpetic rashes were most often of the monoradicular type and were localized at the upper thoracic or lower thoracic levels or along the course of the 1st lumbar vertebra. Herpetic rashes were isolated, small. The development of the disease was preceded by excessive physical overload of the spine. During the neurological examination, reflex-muscle-tonic syndrome and local sclerotome tenderness of the spinous and lumbar processes of the vertebra were revealed; in MRI examination – a lateral disc herniation at the same level or one segment higher, which blocked the intervertebral foramen. The addition of dehydration therapy and light manual correction significantly accelerated the recovery of patients.

5. Paget-Schroetter pseudosyndrome. It was observed by us in two elderly patients with osteochondrosis of the cervical spine who were operated on for the cervical ribs of the C_{VI}–C_{VII} vertebrae. In the postoperative period, there developed pain and swelling in the area of the shoulder girdle of the upper limb on the side of the surgical intervention. The skin was pale, shiny. The pain spread mainly along the C_8 root. Weakness, paresthesias, and a feeling of heaviness in the damaged segment were also noted. At the height of the intensity of the pain component, signs of involvement of the C_6, C_7, T_1 roots were added to the process. There was no dilatation of subcutaneous veins and cyanosis of the skin. In one patient, this syndrome was also combined with Horner's triad, decreased visual acuity and mild hemiatrophy of the face on the side of the injury. No signs of thrombosis of the subclavian veins were detected during the ultrasound examination of the deep veins on the side of the injury. Spontaneous blood flow in all segments was preserved, retrograde blood flow was not determined. Coagulogram corresponded to age characteristics.

The origin of this syndrome can be explained by the fact that in the preoperative period,an additional cervical rib squeezed the root of C_7, and this led to the development of degenerative and dystrophic changes in it. In the postoperative period, after decompression of the root, it developed degenerative-dystrophic processes with a hyperpathic component. Against the background of neurodystrophically altered adjacent tissues and vertebrae, closely spaced segments of the spinal cord and cervical sympathetic formations were involved in the process. The use of nootropic drugs and sympathicotonic substances contributed to the improvement of the general condition of the patients.

6. Phantom limb defect syndrome. It was diagnosed in 12 patients with amputated lower limb who constantly used prostheses. This syndrome was formed no earlier than a year after the amputation of the lower limb. It was characterized by a certain increase in tendon and periosteal reflexes on the side of the limb defect, a slight decrease in superficial types of sensitivity on the same side. The electroencephalogram on the heterolateral side of the limb defect revealed zonal activity in all brain structures. On the homolateral side, the amount of brain biocurrent corresponded to the physiological norm. On X-rays at the segmental level of the amputated limb, the phenomena of osteochondrosis were observed on the convex side of the spine, and the phenomena of spondylosis were observed on the concave side. A significant improvement in the well-being of patients occurred when this group of patients used in the treatment nootropic and vascular drugs, chondroprotectors.

7. We have allocated **neuroosteoarthropathy syndrome** to a separate clinical group, since in our daily work we meet with this nosology quite often, and it is not mentioned at all in ICD-10 and in the well-known classification of 1982–1985, which was used in the territory of the former Soviet Union about this type of neurotrophic disorders of the musculoskeletal system.

Our studies in this regard mainly concerned neurotrophic changes in the hip joints. We grouped all these disorders into three clinical groups.

In patients of the first clinical group (69 people), we studied neuroorthopedic changes in Hip-Spine syndrome. Patients complained of pain in the hip joint, which quite often radiated to the knee

joint and the lumbosacral region of the spine; for burning pain on the outer surface of the thigh. The pain increased with physical exertion and decreased at rest.

During the clinical examination, point tenderness was detected in the place of attachment of the piriformis muscle, the middle and small gluteal muscles (area of projection of the greater acetabulum) on the side of the damaged hip joint; restriction of internal rotation of the hip; palpable tenderness of the outer surface of the thigh in the area of projection of the external femoral nerve. The angle between the bispinal line and the hip axis was 90–95°. Normally, this angle is 87°. With long-term irritation of the piriformis muscle, patients developed an abductor, external rotation contracture of the hip.

In the neurological status, there was a slight decrease in surface sensitivity on the outer surface of the thigh on the side of the painful hip joint (90 % of cases). In all patients of this clinical group, knee and Achilles reflexes were normal or slightly reduced on the injured side. Pain in the paravertebral points at the L_2–S_1 level on both sides (more clearly on the affected side) was also diagnosed – 87 % of cases. Lasegue's sign was negative in all patients. Muscle strength on the lower limbs was normal in 100 % of cases and amounted to 5 points.

During X-ray examination of the hip joint, patients of this group were diagnosed with increased subchondral sclerosis of the acetabulum, slight hyperostosis of the medial surface of the femoral neck. Patients gradually developed a bone-like remodeling of the femoral head and its subsidence. Pathology in the hip joint developed against the background of a decrease in the height of the intervertebral discs L_3–S_1, hernias, protrusions of the intervertebral discs, stenosis of the spinal canal at the same level.

The second clinical group included 30 young and middle-aged patients (18 women and 12 men) with coxarthrosis in the I–II stages of the disease. During X-ray examination of the hip joint in patients of this group, signs of subchondral sclerosis of the acetabulum, marked hyperostosis of the medial surface of the femoral neck, and cystic remodeling of the femoral head were also diagnosed. The pathological process developed against the background of long-term pain syndrome in the lumbosacral region of the spine, caused by herniated intervertebral discs, stenosis of the spinal canal at this level. During the clinical and neurological examination of patients, we identified 3 types of the course of the disease:

1) benign (14 people);

2) permanent-progressive (11 people);

3) malignant (5 people).

With a *benign type of course*, the disease occurred 1–6 months after the clinical manifestations of vertebrogenic lumboischialgia or radiculoneuropathy at the same level. It occurred more often in women aged 30–60. There was almost no pain during passive rotation of the joint. The starting pain was not typical. The pain most often occurred during the day, worsened during walking, prolonged standing on the feet or external rotation, when going down the stairs. Nocturnal pain was not typical. An increase in knee and Achilles reflexes was observed in the first weeks of the disease, which gradually changed to their decrease on the side of the injury. Hypotonia and hypotrophy of gluteal muscles above the damaged joint were diagnosed; there was an asymmetry

of the gluteal folds on the affected side, a thickening of the lower edge of the middle gluteal muscle. There were changes in the skin of the segmental level on the side of the damaged joint.

The clinical signs of the *permanently progressive course* of neurogenic coxarthrosis were as follows. Osteoarthritis was most often observed in persons who were operated on for herniation of L_{III}–L_V intervertebral discs and had signs of spinal arachnoiditis and epiduritis. The time of onset of neurogenic coxarthrosis is 1–5 years after the surgical intervention. There were signs of moderate thickening of the skin over the damaged joint, pronounced hypotonia and muscle hypotrophy at the segmental level. The disease continued for a long time, over many years, with periodic exacerbations of the process. Short-term starting pain was combined with pain in the joint and spine while walking. Morning stiffness in the damaged joint and spine, restriction of movement in the damaged joint during the exacerbation period was characteristic; crepitation in the joint.

The malignant course of neurogenic coxarthrosis was characterized by the fact that the time from the first clinical manifestations of damage to structures at the lumbosacral level to the rapid development of grade III–IV neurogenic coxarthrosis took only 1–4 years. Clinically, it did not differ from ordinary coxarthrosis. During the neurological examination, there were signs of myeloradiculoneuropathy of the L_4–S_1 roots. Patients with a malignant course of the process needed endoprosthetics of the hip joint, because conservative treatment of the process was not effective for them.

Magnetic resonance spectroscopy of brain structures revealed unilateral stenosis or occlusion of the internal carotid artery or middle cerebral artery in our patients without signs of cerebral infarction. However, insufficiency of blood perfusion in the areas of the border zones of the brain, a decrease in the indicators of the main cerebral metabolites, especially in the area of the hippocampus, was found in them. Patients with the debut of coxarthrosis of metabolic dystrophic origin did not have such specific magnetic resonance spectroscopic signs. All this prompted us to conduct a study of cognitive functions in our patients.

All examined patients, compared to healthy individuals, especially patients of the third group, had significantly lower indicators characterizing the following mental functions: short-term verbal memory, attention, speed of sensorimotor reactions, mental capacity, volume of active attention, short-term and long-term visual and auditory memory, the ability to think logically, as well as distraction and generalization, understanding the meaning of words and the logical connection between concepts. Long-term use of nootropic and vascular drugs against the background of basic therapy made it possible to significantly improve cognitive functions in such patients and improve metabolic processes in the cartilage tissue of damaged joints.

The third clinical group included 12 patients with signs of aseptic necrosis of the femoral head. During MRI and clinical examination, signs of compression radiculoischemia, reactive epiduritis, slowly progressing chronic myeloischemia in the basin of the Adamkiewicz artery (AKA) artery against the background of herniated intervertebral discs of the L_1–L_V vertebrae were revealed. Quite often, the removal of a herniated intervertebral disc did not contribute to the improvement of clinical symptoms, and in four cases it led to hip joint replacement.

8. Elongated limb syndrome. Over the course of several years, we observed a woman with chronic pain in the lumbosacral region of the spine, which radiated to the left lower limb. At the age of 54, she was diagnosed with a 6.5 mm paramedian hernia at the level of L_{IV}–L_V vertebrae. Gradually, for no apparent reason, the patient's left lower limb lengthened evenly in all segments. At the age of 58, the difference between the left and right limbs reached 5 cm. The patient had to compensate for the static scoliosis due to the elevating insole on the right leg. During the in-depth examination, no signs of pathology of the brain structures, neuroendocrine disorders and malformations of the blood vessels of the legs, which would cause such pathology, were found. On examination, the left limb was slightly swollen, with a marble shade. Left knee and left Achilles reflexes were decreased. Lasegue's symptom on the left was moderate. Sclerotome and paravertebral pain in the Lumboischialgia were determined.

9. The "pepper knife" syndrome. We observed a 56-year-old woman who had pain in the lower chest and lumbosacral region of the spine, weakness and numbness of the left leg. The patient moved with difficulty, leaning on a cane. The body was rapidly tilted to the left. When asked to stand on her left leg without additional support, her body rapidly bent down to the left and folded like a penknife. At the same time, she could stand straight and for a long time on her right leg, without using a stick. During the examination, there was smoothing of the lumbar lordosis, moderate paravertebral tenderness at the level of Th_{11}–S_I vertebrae on the left; moderate increase of periosteal and tendon reflexes on the left; Babinski's and Lasegue's symptoms on the left were moderate. An MRI study revealed a 5 mm herniation at the Th_{12}–L_1 level of the intervertebral disc, ante-spondylolisthesis of the body of the L_5 vertebra; initial signs of dyscirculatory encephalopathy were found in the structures of the brain. Electroneuromyography showed signs of moderate pyramidal insufficiency at the level of lumbar thickening of the spinal cord.

10. Syndrome of damage to the arcuate joints. Predominance of reflex neurological signs over organic (especially radicular) neurological manifestations in patients with osteochondrosis of the spine allowed us to establish that in 83 patients they were caused by pathology of the arcuate joints. The clinical picture of damage to these joints has some specific features.

As is known, the posterior arcuate joints are true synovial connections between the upper and lower articular processes of adjacent vertebrae. With sudden movements, especially with excessive extension, each capsule can stretch or tear, after which the formation of a subluxation becomes possible. Contributing factors leading to injury are the patient's excess body weight, acute lumbosacral angle, degenerative changes, damage to the intervertebral disc, chronic occupational stress and excessive vertical displacement of joint surfaces. Repeated damage to the arcuate joints leads to degenerative changes and a significant tendency to recurrent exacerbations. The return of pain to the lower extremities is not characteristic, but they can radiate along the spine in the buttock. With significant subluxations or progressive changes, pinching of the root may occur.

In the anamnesis, patients, as a rule, note the presence of acute pain in the back, which is caused by excessive extension. Often, patients complain of a number of previous similar attacks. The pain increases when sneezing, coughing, slightly bending the spine or when sleeping on the stomach.

During the examination, the patient often stands in a position slightly bent in the hip joints. His movements are limited in all directions. Pain in the lumbosacral region of the spine is especially significant, which is often accompanied by a reflex muscle-tonic syndrome. If there is no tonic tension of the muscles, then quite often it is possible to palpate the arcuate joints of the spine on both sides between the adjacent spinous processes and near them (approximately one finger to the side). Local tenderness over the joints, increasing pain during excessive extension and the absence of organic neurological disorders convincingly indicate an acute syndrome of damage to the arcuate joints. The straight leg raise test can be positive for two reasons. With maximum lifting, the joint capsule is stretched, which causes local soreness. This test also becomes positive when the nerve is pinched. It is necessary to measure the length of the legs, since asymmetry can increase the load on the arcuate joints.

X-ray examination of the spine in the acute period in the lateral projection may be without deviations from the norm. When the process is chronic, degenerative changes in the arcuate joints are visible in the lateral projection. Radiography in an oblique projection better reveals subluxation of the articular process with displacement of the upper fragment to the back and slight narrowing of the posterior part of the intervertebral disc. At the same time, narrowing of the intervertebral foramen can also be observed.

Along with the above little-known clinical signs of damage to the arcuate joints, we managed to identify their new clinical manifestations. In particular, in 83 patients with reflex manifestations of osteochondrosis of different parts of the spine, we drew attention to the fact that when we asked the patient to draw on the surface of his skin the zones of sensitivity disorder (so-called "stripes"), they somewhat did not coincide with the well-known schemes of the radicular innervation on the surface of the skin.

Such patients complained that sensitive disturbances were manifested in the form of signs of hyperesthesia, sometimes with some hyperpathic sensation; the presence of a pinching painful sensation of a constant breath of light breeze or a feeling of slight swelling of the skin in one or another area.

During the objective examination, we found some thickening of the skin in the place of the painful sensation, an increase in skin turgor, and a change in its elasticity. During an acupuncture session, a specific cracking of the skin was often felt in this place, somewhat reminiscent of the sound of cutting frozen meat with a knife. In some patients, it was difficult to insert the needle into the skin due to its increased elasticity, up to the presence of "gutta-percha skin" syndrome.

Based on the above signs, we hypothesized that in the initial stages of osteochondrosis of the spine, when there is displacement of the intervertebral joints, partial narrowing of the intervertebral opening, root disorders may be preceded by the stage of dermatomal damage to the root branch, which is characterized by the above signs. Later, our assumptions were confirmed by a number of paraclinical studies. This allowed us to create our scheme of dermatome innervation of the surface of the human skin, which is somewhat different from the generally known literature data.

Thus, according to its clinical signs, osteochondrosis is quite multifaceted and sometimes does not fit into the framework of its known typical clinical manifestations. This requires constant clinical study and generalization of unknown and little-known cases of this process.

2.3 COMPREHENSIVE ASSESSMENT OF THE RESULTS OF A NUMBER OF PARACLINICAL STUDIES OF PAIN SYNDROME IN DEGENERATIVE-DYSTROPHIC SPINE PATHOLOGY

The next stage of our research was the study of some causal processes in the occurrence and development of osteochondrosis of the spine and its neurological pain syndromes. We used a comprehensive approach to solving the problem.

At the first stage, a whole series of specific morphological, including neuromorphological and histochemical studies was carried out. Simultaneous changes in the spinal cord and discs and vertebrae in 41 suddenly deceased young, middle-aged and elderly persons without concomitant signs of severe systemic organic diseases of the internal organs and nervous system at the level of the mid-thoracic spine as the least loaded were compared. The reliability of the obtained results was confirmed by X-ray studies of the section material.

Studies have shown that dystrophic changes occur first in the spinal cord, especially in its posterior and lateral horns. These changes precede pathomorphological changes in the vertebrae and discs. At a young age, the phenomena of dyscirculatory or metabolic dystrophic myelopathy gradually develop at the segmental level.

Moreover, if we compare the activity of the somatic and autonomic nervous systems during this period, then the autonomic nervous system is the first to react, which was proven by the example of histochemical studies of biogenic amines (their accumulation, especially norepinephrine, in the lateral and posterior horns of the spinal cord begins to decrease). The process from the rear and lateral horns is gradually transferred to the front horns of the grey matter of the spinal cord. Over time, degeneration of the nerve fibres of the white matter of the spinal cord develops. The membranes of the spinal cord are gradually involved in the process. Around the age of 30, degenerative-dystrophic changes also begin to appear in the vertebrae and discs, which are so thoroughly described in the literature.

According to our data, in middle age, degenerative-dystrophic changes in the spinal cord and in the vertebrae and discs proceed almost in parallel, but in the spinal cord they acquire a more widespread character and go beyond the limits of one segment.

Degenerative-dystrophic processes in all structures of the spinal cord continue to progress in the elderly, metabolic processes are suppressed (in particular, the production of biogenic amines slows down). Gradually, the spinal cord begins to lose its corrective and regulatory influence on metabolic processes in the vertebrae and intervertebral discs. This is manifested by the fact that degenerative-dystrophic changes in the vertebrae and discs begin to lag behind those in the spinal cord and may even become somewhat reversed.

Thus, in the series of studies we conducted, we found confirmation of the statement of Yurii Golovchenko [13] that the nervous system begins to age first in the ontogenesis of an individual, followed by all other organs and systems, including vertebrae and intervertebral discs.

To confirm our opinion that the nervous system plays a leading role in the formation of clinical and pathogenetic signs of osteochondrosis of the spine, a number of paraclinical studies were conducted.

The leading role of the cortical analyzer in the formation of neurological manifestations of spinal osteochondrosis was judged by electroencephalography data. So, in particular, when examining the bioelectric activity of the brain in 146 patients with neurological manifestations of spinal osteochondrosis, it was established that the greatest changes occur in the frontal, temporal, and central regions of the brain, where, according to Heorhii Yankovsky [14], there is a cortical representation of the bone analyzer, in particular the bones of the spine. These changes are most clearly recorded in patients with radicular and radicular vertebrogenic disorders. Changes in the deep structures of the brain, which take part in the formation of suprasegmental vegetative-trophic mechanisms, were also revealed. These changes were most pronounced in patients with reflex neurodystrophic symptoms. The phenomenon of hypoxia of the cerebral cortex was detected at the height of the pain component and in patients with hypokinesia.

Clinical examinations of 2,093 patients with neurological complications of spinal osteochondrosis showed that 66.5 % of them had an imbalance of autonomic reactions. Therefore, an in-depth study of the state of the autonomic nervous system was conducted using modern functional cardiovascular tests, as the most simple, reproductive, non-invasive, reliable and accurate methods of diagnosing autonomic disorders. As the conducted studies have shown, all patients with neurological manifestations of osteochondrosis of the spine have gross violations of the autonomic nervous system at the subclinical stage of the type of systemic degenerative process. They affect not only the autonomic structures of the disc or vertebra itself, but also segmental spinal centers, peripheral departments of the autonomic nervous system, and suprasegmental formations. Moreover, a sharp increase in the activity of the autonomic nervous system was observed in patients with autonomic vascular disorders, and its greatest suppression was observed in radicular vascular pathology.

These provisions were confirmed by a number of other paraclinical studies. In particular, with the help of the method of non-contact thermal imaging thermodiagnostics, the nature of vegetative-vascular disorders that occur with neurological manifestations of spinal osteochondrosis was established. Thus, in patients with reflex neurological signs, these manifestations did not depend on the variety of clinical symptoms, but on the nature of the vegetative direction of these vascular reactions at the segmental level and were most significant when the process was localized in the lumbosacral region in women with a parasympathetic tonic orientation, and in men with sympathotonic in the stage of subcompensation.

The reaction of the microcirculatory channel to a painful stimulus was judged by the data of television capillaroscopy during the examination of 77 patients. It was established that regardless of where the primary pain point was (on the arm or on the leg), the capillaries of the hand on the homolateral side always reacted first. The prevailing importance in the formation of reflex neuro-

logical syndromes in osteochondrosis of the vagus nerve spine was revealed. At the same time, with vertebrogenic reflex vegetative-vascular manifestations, trunk baroreflex mechanisms also suffer, and with vertebrogenic reflex muscle-tonic and neurodystrophic – changes occur in baroreflex mechanisms at the segmental level. Simultaneous activation of suprasegmental sympathetic and segmental parasympathetic reactions was detected in root neurological disorders. Capillaroscopic changes obtained in patients with radiculovascular syndrome showed that in this pathology, inhibition of both parasympathetic and sympathetic reactions develops, but the latter are more severe and intense.

The examination of the content of catecholamines in biologically active fluids (blood plasma and urine) in 104 patients with neurological manifestations of osteochondrosis of the spine showed a significant decrease in the content of noradrenaline in the urine and an increase in its indicators in the blood plasma in vertebral radicular, reflex muscle-tonic, autonomic vascular and, to a lesser extent, with neurodystrophic syndromes. This serves as proof that with these neurological signs of osteochondrosis of the spine, degeneration of peripheral autonomic nerve endings develops, the compensatory baroreflex mechanism decreases, and there is no normal reabsorption of this mediator from the blood plasma and its inclusion in further processes of exchange in the body and its excretion with urine. An increase in the ratio of noradrenaline to adrenaline in the urine of patients with vertebrogenic radiculovascular syndrome was also established, which could indicate the activation of mediator exchange processes in this pathology.

The genetic predisposition of the body to certain neurological syndromes of spinal osteochondrosis was established based on the results of studying HLA-immunogenetic markers in 116 patients with the aforementioned pathology. It was established that the largest number of histocompatibility antigens (125) was characteristic of patients with radicular syndrome. The smallest number of HLA antigens (51) was typed in reflex neurodystrophic syndrome and this suggests homozygosity of phenotypes in this syndrome. As you know, homozygosity for any genetic trait significantly reduces the body's ability to adapt and recover. And it is the manifestation of clinical symptoms of a neurodystrophic nature that has a progressive direction, is poorly amenable to treatment, prone to relapses and chronicling of the pathological process. "Indicator antigens" in this pathology have also been identified. Thus, in reflex muscle-tonic and neurodystrophic syndromes, antigen B27 was detected most often. With vertebrogenic root-vascular syndrome – A10, B40; with widespread osteochondrosis of the spine – B13 and B16. Detection of the HLA-Aw32 antigen in radicular syndrome indicated a certain frequency of development of systemic primary autonomic neuropathy in this pathology. Representatives of the HLA-C locus were completely absent in patients with reflex vegetative-vascular syndrome. With the progression of clinical signs of osteochondrosis of the spine, a high frequency of antigens A1, A2, A9, B5, B8, B12 was detected.

Thus, summarizing the results of the conducted research, it is possible to suggest that the primary basis for the occurrence of osteochondrosis of the spine and its neurological manifestations is the dysfunction of segmental nerve reactions at the level of the spinal cord, and not the intervertebral disc, as expressed by most authors. This dysfunction is due to the peculiarities of

the biomechanical properties of the spine, which arise primarily in its "key" zones as a result of unbalanced, excessive load on the spine. It can also be supported by frequent microtraumas of the spine, endocrine-humoral or vascular disorders, the effect of hereditary, infectious and intoxication agents, etc. An afferent impulse arises in the posterior and lateral horns of the spinal cord, and then in its anterior horns and lateral spines. This process is aggravated by the fact that the lateral horns and lateral spines in each specific segment are at the junction of the blood supply of the anterior and posterior spinal arteries. This leads to the emergence of a pathological action potential at the level of the spinal cord segment, primarily in its vegetative nerve formations.

Suprasegmental nerve structures are also included in the process, the so-called transsynaptic degeneration of the central genesis develops, which we proved, in particular, on the example of patients with the syndrome of the defect of the lost limb. This leads to an even greater imbalance at the level of the segmental spinal centers. Dyscirculatory or metabolic dystrophic myelopathy occurs. Systemic degeneration of peripheral vegetative fibers and, in particular, the sinuvertebral nerve (or Luschka nerve) is gradually formed. And only after that, vegetative-trophic disorders begin at the level of the intervertebral disc. The formation of systemic peripheral polyneuropathy leads to the fact that the process gradually covers the adjacent musculoskeletal segments, intervertebral discs; on this background, various neurotrophic disorders begin to form in the muscles, connective tissue, and internal organs. Therefore, in our opinion, changes in the spine such as osteochondrosis are only a "facade", behind the walls of which the main changes in the nervous system are played out, which are hidden from the researcher's view.

Therefore, the final solution to the issue of the pathogenesis of osteochondrosis of the spine and its neurological manifestations is not yet complete and needs to be resolved in time precisely from the point of view of its neurological concept.

The application of high-quality modern tools of functional methods of research of this pathology plays a significant role in solving many controversial issues. It was established that measuring the heat flow density of the human body is a new promising method of diagnosing neurological disorders in degenerative-dystrophic diseases of the spine. The study of changes in thermometric indicators of the skin in the lumbosacral region of the spine is a new highly informative diagnostic method. To confirm this hypothesis, a unique thermoelectric device was developed and manufactured for measuring the heat flow density from the surface of the human body, the design, technical characteristics and results of experimental medical research are given in the following sections of this work.

2.4 CONSTRUCTION AND TECHNICAL CHARACTERISTICS OF THE DEVICE FOR MEASURING THE HEAT FLOW DENSITY FROM THE SURFACE OF THE HUMAN BODY

The development of modern diagnostic methods, such as magnetic resonance and computer tomography, allows to determine the level and localization of a hernia or protrusion of the intervertebral disc. Today, there are already many works [2–6] in which it was shown that there is no direct

relationship between the presence or degree of severity of degenerative-dystrophic changes in the spine and the presence or intensity of back pain syndrome. That is, there is an urgent problem of studying other peripheral mechanisms that cause back pain. The mechanisms of the occurrence of back pain in the first hours/days of its occurrence in degenerative-dystrophic pathology of the spine, especially in its lumbosacral region, which is most often encountered in the clinical practice of neurologists and orthopedists, have not been fully studied. Medical practice also requires the introduction of new highly informative, portable devices for functional diagnostics, which would make it possible to reveal the nature of neurological damage in degenerative-dystrophic spine pathology in the first hours/days and to assess the degree of pain in this pathology [4–7].

Semiconductor thermoelectric heat flow sensors [15, 16], which combine miniaturization, high sensitivity, stability of parameters in a wide range of operating temperatures, and are compatible with modern recording equipment [17–28] are promising for the study of local human heat emissions. The use of such sensors makes it possible to achieve high locality and accuracy of thermometric measurements. This, in turn, makes it possible to obtain information about the characteristics of the objects under study and to analyze them in detail in order to detect inflammatory processes in the human body in the early stages.

Therefore, the aim of this work is to study thermometric indicators in patients with a number of neurological manifestations of degenerative-dystrophic pathology, in particular osteochondrosis, in the Lumboischialgia.

At the Institute of Thermoelectricity of the National Academy of Sciences and the Ministry of Education and Science of Ukraine, a thermoelectric device was developed for the diagnosis of inflammatory processes and pain syndrome in degenerative-dystrophic diseases of the lumbar-sacral spine [21] (**Fig. 2.1**). Technical characteristics of the device are given in **Table 2.3**.

The device includes a control unit 1 and thermoelectric temperature and heat flow sensors 2. Temperature and heat flow density are measured simultaneously by 2 thermoelectric sensors with measurement results recorded on a MicroSD memory card and computer display on a PC (with Windows 7–10 operating system). Data is recorded in "Comma-separated values" (CSV) format, which allows you to open measurement result recording files without any additional conversion in most programs for working with electronic spreadsheets, such as "Microsoft Excel", "Open office", as well as in the specialized program of the "TermoMonitor" device for plotting graphs of measurements.

The principle of operation of the device consists in converting the heat flow and temperature of the human body with the help of two thermoelectric sensors of heat flow density and temperature into electrical signals equivalent in magnitude, which are displayed on the digital display of the control unit in units of heat flow density (mW/cm^2) and temperature (°C).

Two connectors for connecting thermoelectric temperature and heat flow sensors and a power button are mounted on the upper wall of the device. On the right-side wall there is a connector for a micro-SD memory card and a mini-USB connector for connecting the device to a personal computer. The battery of the device is also powered through the mini-USB connector.

Fig. 2.1 Thermoelectric device for diagnosing inflammatory processes and pain syndrome in degenerative-dystrophic diseases of the Lumboischialgia:
1 – control unit; 2 – thermoelectric temperature and heat flow sensor

Table 2.3 Technical characteristics of the device

№	Technical characteristics of the device	Parameter values
1	The operating temperature range of the thermoelectric sensor	(0 ÷ 50) °C
2	Accuracy of temperature measurement	± 0.1 °C
3	The range of heat flow density measurement	(1 ÷ 100) mW/cm^2
4	The maximum error of heat flow density measurement	5 %
5	Number of thermoelectric sensors	2
6	Overall dimensions of the thermoelectric sensor	(14×14×3) mm
7	Overall dimensions of the control unit	(90×55×25) mm
8	The weight of the thermoelectric sensor	20 g
9	The weight of the device	150 g
10	Possible time of continuous operation of the device	48 h

A liquid crystal display is mounted on the front wall of the case, which shows the values of the density of heat flows of the corresponding areas of the human body and the temperature values in the form of graphs. Thus, the obtained measurement results can be analyzed directly from the graphs displayed on the display. The simultaneous presence of two thermoelectric sensors in the device makes it possible to compare the results of measurements of the diseased and healthy areas of the human body surface.

In addition, there are 6 buttons for controlling the operation of the device on the front wall of the device – "LEFT", "RIGHT", "UP", "DOWN", "OK", "MENU". The purpose of the "MENU" items of the device is as follows:

– "START RECORDING" / "STOP RECORDING" – the device starts recording measurement results in a new file, stops the corresponding recording and saves the information to the memory card;

– "MODE SELECTION" – calls up a sub-menu for choosing one of 9 modes of displaying information in the form of graphs in real time;

– "RECORDING PERIOD" – designed to select the time period during which the measurement results will be saved to a file on the memory card and displayed on the device display;

– "TIME/DATE" – switching to time and date setting mode;

– "ACCUMULATOR" – displays the voltage on the device's power supply battery;

– "INFORMATION" – displays information about the device.

The structural diagram of the device (**Fig. 2.2**) consists of the following functional units: a thermoelectric heat flow sensor with a built-in temperature sensor, an analogue-to-digital converter (ADC) for converting the analogue signals of the sensor into digital ones, a multiplexer for switching digital signals from the ADC and alternately transmitting them to microcontroller, which is used to process digital signals, save them to a memory card, and display information graphically on display and a personal computer.

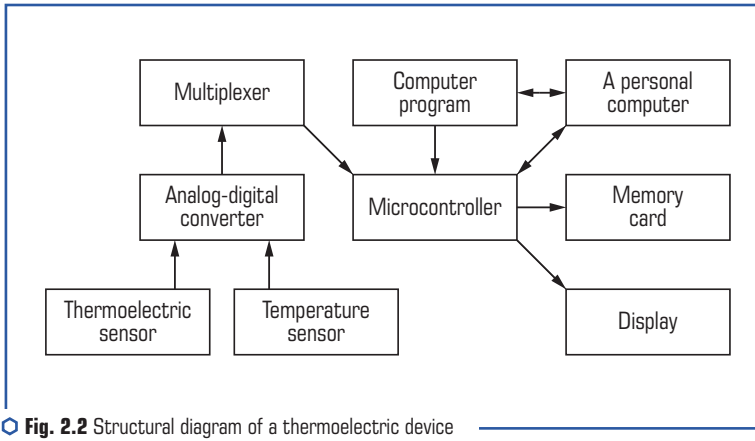


Fig. 2.2 Structural diagram of a thermoelectric device

The main functional piece of the control unit is a microcontroller that operates at a frequency of up to 20 MHz and provides a high speed of processing signals of the thermoelectric sensor of temperature and heat flow. With the help of a personal computer, programming of the microcontroller is carried out, which, in turn, controls the operation of other functional units of the device.

The device contains its own power source in order to ensure the possibility of its use in autonomous mode together with the patient. This, in turn, allows you to expand the functionality of the device. The device is powered by a lithium-ion battery with a capacity of 1200 mAh, which provides 48 hours of continuous device operation.

The computer program of the device (**Fig. 2.3**) is written in the Delphi programming language. The program allows you to exchange data with the control unit via the USB interface. Data exchange is carried out using the HID protocol (Human Device Interface), which makes it possible to connect the device to a personal computer without the need to install additional drivers.

When the "REFRESH DATA" checkbox is selected in the computer program, a cycle is started that sends data transfer requests from the control unit. In response to such requests, the control unit sends a packet of data on the temperature and heat flow of thermoelectric sensors with a specified time interval. The received data package is processed, after which the information is displayed on a personal computer in the form of tables and graphs.

When you click the "SAVE" button, all data from the table are converted into "string" values (plain text), separated by a dot and a comma and written into a file with the extension "CSV" that can be opened by any program for working with electronic spreadsheets (Microsoft Excel, for example). When the file is opened by such a program, the "CSV" format is decoded into a floating-point data package, which allows you to display the information in the form of a table and corresponding graphs on a personal computer.

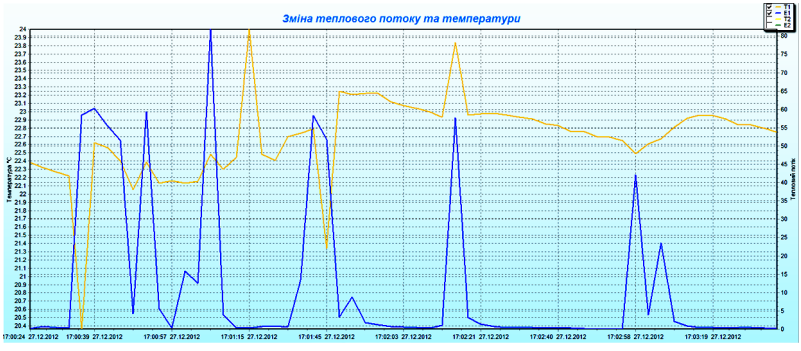


Fig. 2.3 The interface of the computer program "TermoMonitor" for processing the results of measurements, their accumulation and reproduction in a specified form on a personal computer (the change in temperature T_1 and heat flux E_1 of the 1st thermoelectric sensor is displayed)

2.5 THE RESULTS OF HEAT FLOW DENSITY MEASUREMENT IN A NUMBER OF NEUROLOGICAL DISORDERS IN DEGENERATIVE-DYSTROPHIC PATHOLOGY OF THE LUMBOISCHIALGIA

To study the effectiveness and feasibility of measuring heat flow density in patients with neurological pathology in degenerative-dystrophic diseases of the Lumboischialgia, these indicators were studied in a number of pathological conditions of this pathology [21, 24, 28].

In particular, we examined 71 patients aged from 39 to 69 years: 20 with signs of lumbosciatica on the background of herniated intervertebral discs, 20 with lumbosciatic pain on the background of herniated intervertebral discs in combination with instability of the vertebrae in this area, 11 patients with stenosis of the spinal canal and 20 people of the control group. Women predominated – 64 % of those examined. All patients underwent a detailed orthopedic and neurological examination. Heat flux density and body surface temperature of patients with neurological manifestations of spinal osteochondrosis were measured using a device designed at the Institute of Thermoelectricity of the National Academy of Sciences and the Ministry of Health of Ukraine.

In the room where the examination took place, the temperature was constantly maintained within the range of 20–25 °C, and the relative humidity was 50–60 %. There were no sources of infrared radiation. On the eve of the examination, all physiotherapeutic and warming procedures were cancelled for the patients; they also cancelled anti-inflammatory, antipyretic, vasodilator or vasoconstrictor medications. Patients had to stop smoking cigarettes 3–4 hours before the examination. 2–3 hours before the start of the examination, various ointment applications were removed from the patients, and the skin surface was degreased with a mixture of 40 % ethyl alcohol and ether (in a ratio of 4:1). Immediately before the examination, the patients underwent temperature adaptation for 15–20 minutes. At this time, they were at rest, without static or dynamic muscle tension. Measurement of thermometric parameters from the surface of the patient's skin was carried out in real-time within 3 minutes. We paid attention to the time of thermal adaptation (in seconds) – t (how much time passed from the moment the survey began to the output of the main indicators for thermal "saturation"), the temperature and heat flow density at the height of this "plateau", the appearance of the curves themselves. Sensors are applied symmetrically on both sides paravertebrally at the level of the spinous processes of the L4 – L5 vertebrae.

As the conducted studies showed, in the subjects of the control group (**Fig. 2.4**), the fluctuation of the main thermometric indicators in the paravertebral areas was symmetrical and practically did not differ according to the "left/right" test. Heat and thermal adaptation of the skin in contact with the surface of the thermoelectric sensors took place simultaneously and had the appearance of a smooth curve with the presence of clearly visible saturation. At the same time, all individuals of the control group maintained a full range of motion in the Lumboischialgia, there were no pain sensations of spinous processes and paravertebral areas in the lumbosacral area, there were no signs of sensitivity disorders, reflexes in the affected areas. In the control group, the time to thermal "saturation" was 45.3 ± 0.3 seconds. The temperature of the skin in the paravertebral areas was within 34.6 ± 0.5 °C, and the heat flow density was 17.1 ± 0.1 mW/cm^2.

During the clinical examination of patients with signs of lumboischialgia (**Fig. 2.5**), the cause of which was the presence of hernias or protrusions in the Lumboischialgia, we found the following. Patients complained of heartburn and pain in the lower back, lower limbs, trophic disorders. Their backs were fixed in a bent position. Unilateral tension symptoms were positive, and 20 % of patients had crossed Lasegue symptoms. There was a decrease in the range of motion in the lumbar region of the spine, tension in the muscles of the lumbar region, pain during palpation and percussion of paravertebral points, and a sharp limitation of tilting in the direction of the lesion. In the position of lying on the back and with the lower limbs bent, the pain in the hip joints decreased. The pain had a pulling character, was accompanied by chills, numbness and tingles in the lower limbs. The skin was pale, cold to the touch, dry (especially in the lower leg and foot) with signs of hyperkeratosis. White dermographism was noted. They had a parallel fluctuation of temperature and HFD on the pain side, (which can be seen in **Fig. 2.5**, in the extreme upper right corner, when the yellow and blue colours reached "thermal saturation") and low indicators on the intact side (**Fig. 2.4, 2.5**). The skin temperature indicators on the pain side were within 34.8 ± 0.5 °C, and the HFD was 101.6 ± 0.3 mW/cm^2, and on the intact side they were within 30.6 ± 0.7 °C and HFD = 71.8 ± 0.4 mW/cm^2. The time of reaching thermal "saturation" was 40.1 ± 0.2 seconds.

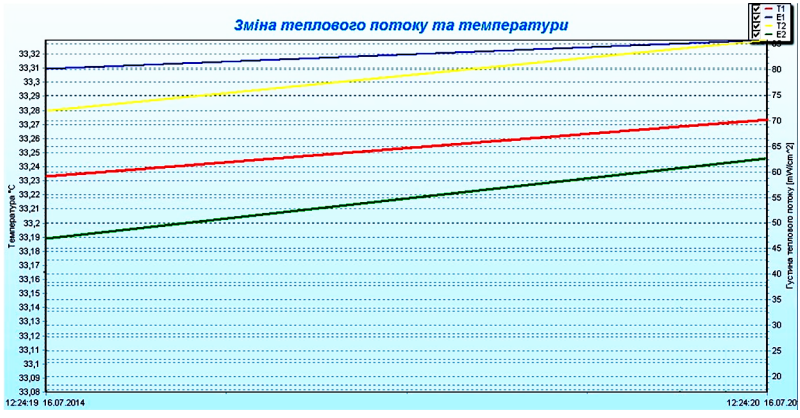


Fig. 2.4 Graphic representation of temperature and heat flow density indicators in the control group (patient Ch., 41 years old, medical history № 526475): T_1, T_2 – temperature values of the 1st and 2nd thermoelectric sensors; E_1, E_2 – density values heat flow of the 1st and 2nd thermoelectric sensor, respectively

In persons with signs of lumboschialgia, which arose against the background of hernias and protrusions between the vertebral discs in combination with instability in the lumbosacral spine (**Fig. 2.6**), the pain was bilateral, increased when bending or extending the spine and pro-

longed sitting, and decreased at rest. Movements in the lumbar spine were not limited, but painful, especially when bending. With the symptom of tension, there was bilateral pain in the lower back. Pallor of the skin, a feeling of burning, distension, asymmetry of white and red dermographism in the lower extremities were noted. Cyanosis, "marbling" of the skin was noted, mainly in the feet. Concomitant diseases were detected: varicose veins of the lower extremities and hemorrhoidal veins, which indicated a systemic weakness of the venous apparatus.

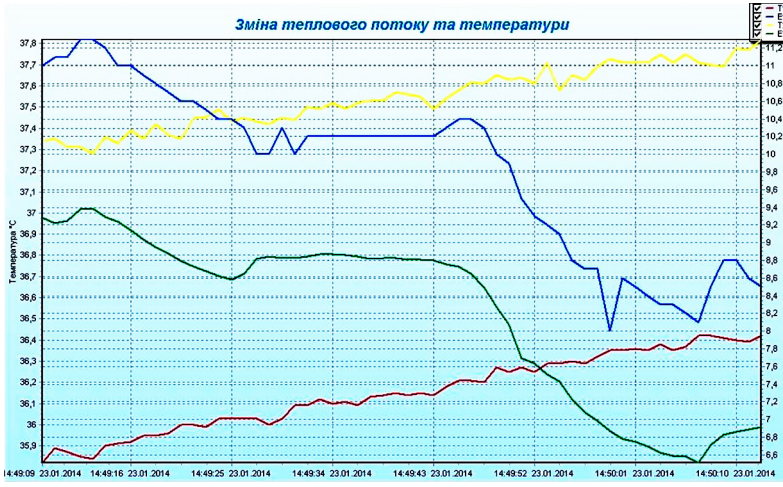


Fig. 2.5 Graphic representation of temperature and HFD indicators in patients with signs of lumboischialgia with hernias and protrusions between the vertebral discs without signs of instability in the Lumboischialgia (patient S., 36 years old, case history № 563818)

When thermometric studies were conducted in this group of patients, a tendency to the "scissors" symptom on the side of pain was observed (**Fig. 2.6** shows the intersection of the yellow and blue lines): a sharp rise in the heat flux density to 85.4 ± 0.6 mW/cm^2 with an almost unchanged skin temperature indicator on the side of pain (34.7 ± 0.2 °C); the time of reaching thermal "saturation" was reduced to 39.8 ± 0.8 sec. On the opposite side, in the paravertebral zone, there were slight fluctuations in thermometric indicators that did not go beyond the physiological norm (**Fig. 2.6**).

Patients whose pain syndrome arose against the background of stenosis of the spinal canal in the lumbosacral region of the spine noted that the pain syndrome lasted for more than two to three months and was not relieved by conventional painkillers and muscle relaxants. Only epidural adhesiolysis brought relief. During the focused examination, a decrease in HFD indicators was found in them on both sides, but more intensively on the dominant side of the pain (**Fig. 2.7**).

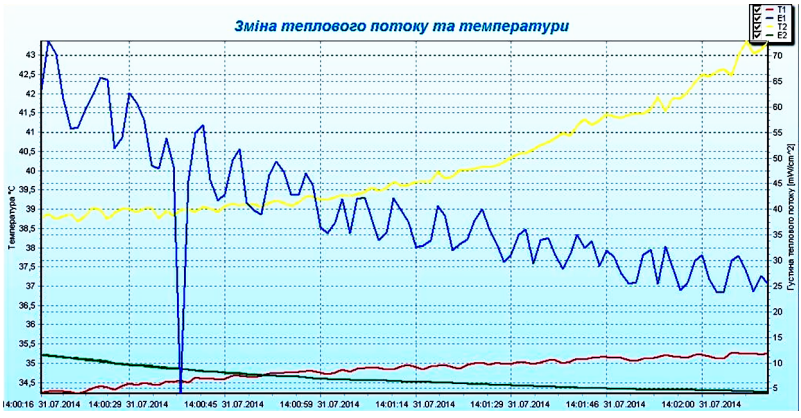


Fig. 2.6 Graphical representation of temperature and HFD indicators in patients with signs of lumboischialgia with hernias and protrusions between the vertebral discs in combination with instability in the Lumboischialgia (patient L., 50 years old, case history № 563009)

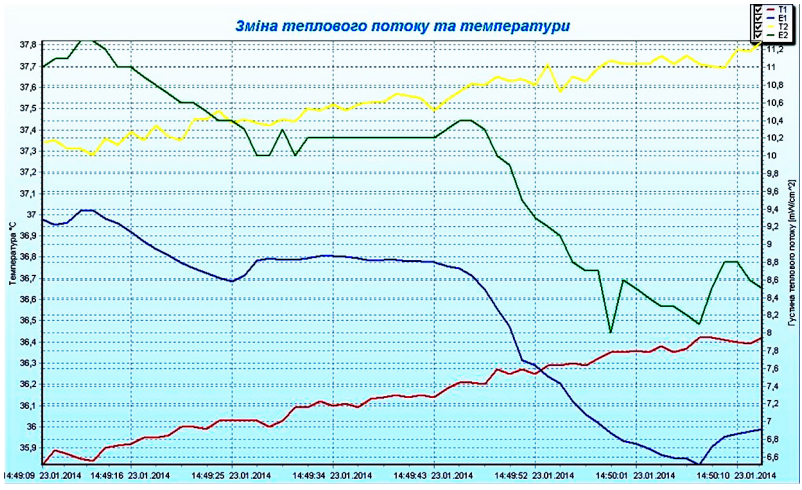


Fig. 2.7 Graphic representation of temperature indicators and HFD in patients with pain syndrome against the background of stenosis of the spinal canal at the lumbosacral level (patient A., 41 years old, medical history № 578193)

The object of this study was also 55 patients with chronic pain in the lumbosacral region of the spine. The pain was constant, radiated to one of the lower limbs, significantly limited their daily

activities, and worsened at night. Along with the use of nonsteroidal anti-inflammatory drugs, patients had to use anticonvulsants and antidepressants. The duration of the disease was 1–5 years. Age of patients: 49 ± 3.5 years. All patients were divided into two clinical groups.

The 1st clinical group included 39 people with unilateral lumboschialgia in the presence of hernias and protrusions of the intervertebral discs with signs of linear instability of the Lumboischialgia, who were subject to conservative treatment (main group).

The 2nd clinical group included 16 patients with unilateral lumboschialgia in the presence of hernias and protrusions of intervertebral discs without signs of linear instability of the Lumboischialgia, who were also subject to conservative treatment (comparison group).

The control group consisted of 10 people with no pain syndrome, in the presence of hernias and protrusions of the intervertebral discs, without signs of linear instability of the Lumboischialgia.

In all patients, the level of pain intensity was assessed using the verbal analogue scale (VAS). A scale of 100 mm length with millimeter divisions was used, which additionally every 20 mm contains words characterizing the intensity of pain: 0 – means no pain (initial point of the line), 20 mm – corresponds to the descriptor "weak", 40 mm – "moderate", 60 mm – "strong", 80 mm – "extremely strong", 100 mm – "unbearable" (endpoint of the line). Pain intensity was estimated in millimeters [3].

Thermoelectric sensors, in this case, were applied in the region of the spine symmetrically on both sides paravertebrally at the level of the spinous processes of the L_4–L_5 vertebrae. In addition to measuring thermometric indicators, heart rate variability was also determined, since both of these indicators are regulated by the autonomic nervous system, and the main centers of regulation of heat exchange and vascular tone are located nearby in the brain stem.

Spectral analysis of the heart rhythm made it possible to distinguish high-frequency respiratory waves (HF – high frequency), which reflect the tone of the parasympathetic nervous system, low-frequency waves (LF – low frequency), which reflect the state of the segmental baroreflex regulatory sympathetic mechanisms, and very low-frequency slow waves (VLF), which reflect the degree of activation of cerebral ergotropic systems. In addition, time characteristics were also analyzed: for the parasympathetic nervous system (RMSSD and Pnn 50 %), the sympathetic nervous system (SDNN), fluctuations of cerebral metabolic processes (SDANN), and the ratio of vegetative balance was determined by the formula of this ratio LF/HF. The obtained results were processed using the STATISTIKA 6.0 computer program package.

As research has shown, patients of the I clinical group complained of heartburn and pain in the lower back, lower limbs, and trophic disorders. Their backs were fixed in a bent position. Unilateral tension symptoms were positive, and 23 % of patients had crossed Lasegue symptoms. There was also a decrease in the range of motion in the lumbar region of the spine, tension in the muscles of the lumbar region, pain during palpation and percussion of paravertebral points, and a sharp limitation of inclinations in the direction of the lesion. In the position of lying on the back and with the lower limbs bent, the pain in the hip joints decreased. The pain had a pulling character, was accompanied by numbness and tingling in the lower limbs. The skin was pale, cold to the touch,

dry with signs of hyperkeratosis. White dermographism was noted. The intensity of the pain syndrome according to the VAS scale was 76.2 ± 4.1 mm.

In persons of the II clinical group, the pain was also unilateral, sometimes at night it tended to be bilateral, increased when bending or extending the spine and sitting for a long time, decreased at rest. Movements in the lumbar spine were not limited, but painful, especially when bending. With the symptom of tension, there was pain in the lower back. Pallor of the skin, a feeling of burning, distension, asymmetry of white and red dermographism in the lower extremities were noted. Cyanosis, "marbling" of the skin was noted, mainly in the feet. Concomitant diseases were detected: varicose veins of the lower extremities and hemorrhoidal veins, which indicated a systemic weakness of the venous apparatus. The intensity of the pain syndrome according to the VAS scale was 49.4 ± 3.9 mm.

The control group (10 people) had uniform temperature and heat flux density indicators on both sides within the limits: $T_0 = 33.2 \pm 0.5$ °C, $E_0 = 171.3 \pm 0.6$ mW/cm^2.

People of the main I group (39 people) had a symptom of "scissors" on the side of pain (temperature and heat flow density intersect on the side of pain), with a significant decrease in the values of heat flow density and a moderate increase in temperature on the injured side. The temperature indicators in the paravertebral area on the side of the pain were $T_1 = 34.2 \pm 1.7$ °C, and the heat flux density $E_1 = 26.8 \pm 4.9$ mW/cm^2 (**Table 2.4**). In our opinion, the occurrence of the symptom of "scissors" in the examined persons can be explained based on the well-known experimental studies of Viktor Veselovskyi [29], who found that when a peripheral nerve fiber is damaged, cold receptors are the first to suffer, which are 2–2.5 times more, than thermal ones.

In the II comparison group (16 people), a moderate decrease in heat flow density and a slight increase in temperature on the side of pain were found. The main thermometric parameters are as follows: $T_2 = 39.8 \pm 6.3$ °C, $E_2 = 120.6 \pm 99.2$ mW/cm^2 (**Table 2.5**).

As the analysis of the obtained results showed, in persons of the main I clinical group, the severity of the long-term chronic pain process is caused by a high degree of activity of metabolic processes both at the cellular level and at the level of cerebral ergotropic systems; there is a relative activation of both the sympathetic and parasympathetic autonomic nervous systems. Along with this, a weighted combination of drugs contributed to the maintenance of a weighted autonomic balance between the sympathetic and parasympathetic departments of the nervous system.

As the correlation analysis showed, in patients of the I clinical group, a high degree of correlation was recorded with indicators of skin temperature fluctuations in the superficial paravertebral areas in the lumbar region. A high degree of correlation was also observed when measuring the heat flux density. But these correlational changes indicated that the patients had more significant changes in the deep nervous processes with a tendency to form a predominance of the activity of the parasympathetic part of the nervous system, and this was indicated by the ratio of the LF/HF ratio, when a high correlation between this indicator was found and heat flow density indicator; reliability was $p < 0.05$.

In the comparison group (II clinical group), all negative weak correlations between heat flow density and heart rate variability were found, except for the HFn indicator, which also indicated the

role of parasympathetic reactions in the formation of heat flow density indicators in patients with signs of lumboschialgia according to absence of linear instability in the lumbar spine.

Table 2.4 Parameters of spectral and time characteristics of HRV in the I group

N = 39	**M ± m**	**T_1 = 34.2 ± 1.7 °C**	**E_1 = 26.8 ± 4.9 mW/cm²**
		Correlation coefficient, r	
Indicators (spectral characteristics):			
VLF, ms²	13,768.07 ± 7,361.08	0.65	0.28
LF, ms²	23,417.68 ± 14,962.65	0.76	0.37
HF, ms²	32,919.18 ± 21,321.92	0.84	0.44
LF/HF, c. u.	2.01 ± 0.55	–0.15	0
LFn, %	54.86 ± 4.37	–0.2	–0.3
HFn, %	45.14 ± 4.37	0.2	0.3
Indicators (time characteristics):			
SDNN, ms	156.11 ± 61.38	0.76	0.41
Pnn50, %	18.35 ± 7.01	0.65	0.57
RMSSD, ms	186.58 ± 86.67	0.81	0.46

Table 2.5 Parameters of spectral and time characteristics of HRV in the II group

N = 16	**M ± m**	**T_2 = 39.8 ± 6.3 °C**	**E_2 = 120.6 ± 99.2 mW/cm²**
		Correlation coefficient, r	
Indicators (spectral characteristics):			
VLF, ms²	21,608.2 ± 11,315.41	–0.09	–0.10
LF, ms²	60,093.9 ± 31,361.08	–0.06	–0.11
HF, ms²	114,969.2 ± 60,523.87	–0.07	–0.10
LF/HF, c. u.	1.0 ± 0.37	–0.13	–0.14
LFn, %	37.4 ± 3.57	–0.17	–0.28
HFn, %	60.5 ± 3.72	0.21	0.30
Indicators (time characteristics):			
SDNN, ms	287.5 ± 108.02	–0.02	–0.06
Pnn50, %	54.0 ± 22.07	0.08	–0.08
RMSSD, ms	383.7 ± 153.47	–0.02	–0.04

Therefore, the conducted preliminary clinical studies make it possible to diagnose inflammatory processes, in particular in the case of neurological manifestations of osteochondrosis of the spine, and to monitor the effectiveness of conservative treatment in degenerative-dystrophic diseases of the Lumboischialgia. Thus, the statistical set of clinical material will allow to improve the method of automatic processing of the obtained results, which in the future will allow to implement the proposed thermoelectric device in the primary medical care at the level of the family doctor's office and to automatically establish a diagnosis of persons with neurological vertebral disorders without the use of expensive radiation diagnostic devices.

CONCLUSIONS

1. It has been established that measuring the heat flow density of the human body is a new effective method of diagnosing neurological disorders in degenerative-dystrophic diseases of the spine. The study of changes in thermometric indicators of the skin in the lumbosacral region of the spine is a highly informative method of diagnosis and allows you to truthfully and effectively study these changes depending on the age and gender of the patient and to identify the main trends in the change in their condition over a certain period of time.

2. A thermoelectric device for measuring temperature and density of heat flows was developed and manufactured at the Institute of Thermoelectricity of the National Academy of Sciences of Ukraine and the Ministry of Education and Science of Ukraine. It was established that the simultaneous measurement of the temperature of the skin and the density of the heat flow with such a device allows to establish the nature of neurological complications in osteochondrosis of the human spine already in the early stages.

3. Determination of thermometric indicators in the lumbosacral region of the spine in persons with chronic pain syndrome against the background of degenerative-dystrophic pathology of the spine in the presence of hernias and protrusions of intervertebral discs allows to improve the diagnosis of neurological manifestations of this pathology, predict the course of this disease and choose an effective method of treatment.

4. It has been established that patients who undergo modern methods of spinal surgery for spinal disc herniation (SDH) require a balanced comprehensive examination by a neurologist to choose effective treatment tactics. Assessing the quality of life and determining the intensity of pain in the preoperative period in patients with SDH hernias in the Lumboischialgia allows for a more differentiated selection of the surgical intervention method for this pathology. Conducted studies have shown that individuals with neurological manifestations of osteochondrosis of the Lumboischialgia due to SDH herniations have hidden signs of fatigue, which can be detected by conducting studies using standardized fatigue scales.

5. The effectiveness of the application of the proposed thermoelectric device in medical practice has been confirmed, which in the future at the level of the family doctor's office will allow automatic

diagnosis of persons with neurological vertebral disorders without the use of expensive radiodiagnostic devices. The proposed device is promising for monitoring the temperature and thermal state of a person in real time, which makes it possible to detect inflammatory processes, various diseases in the early stages and carry out express diagnostics during a mass examination of patients.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this paper.

REFERENCES

1. Yuryk, O. Ye.; Krynsky, A., Galovidin, A., Rudnicki, M. (Eds.) (2022). Features of some neurological disorders by degenerative-dystrophic pathology of the spine. Polonia University in Czenstochova. Modern science and education in Ukraine and EU countriesi gimperatives, transformation, development vectores. Riga: Baltia Publishing, 246–263. doi: https://doi.org/10.30525/978-9934-26-240-1-13
2. Yuryk, O. Ye. (2001). Nevrolohichni proiavy osteokhondrozu: patohenez, klinika, likuvannia. Kyiv: Zdorovia, 344.
3. Murashko, N. K., Morozova, O. H.; Murashko, N. K. (Ed.) (2013). Refleksoterapiia. Vol. 2. Kyiv: Tov SYK Hrup Ukrayna, 421.
4. Sviridova, N. K., Sereda, V. H., Dovhyi, V. L., Popov, O. V., Shcherbatyi, A. A. (2018). Diagnosis of vertebrogenic pain syndromes. Skhidno-Ievropeiskyi nevrolohichnyi zhurnal, 1, 4–12.
5. Mixter, W. J., Barr, J. S. (1934). Rupture of the Intervertebral Disc with Involvement of the Spinal Canal. New England Journal of Medicine, 211 (5), 210–215. doi: https://doi.org/10.1056/nejm193408022110506
6. Macheret, Ye. L., Dovhyi, I. L., Korkushko, O. O. (2006). Osteokhondroz poperekovoho viddilu khrebta, uskladnenyi hryzhamy dyskiv. Vol. 1, 2. Kyiv.
7. Jensen, M. P., Dworkin, R. H., Gammaitoni, A. R., Olaleye, D. O., Oleka, N., Galer, B. S. (2005). Assessment of pain quality in chronic neuropathic and nociceptive pain clinical trials with the Neuropathic Pain Scale. The Journal of Pain, 6 (2), 98–106. doi: https://doi.org/10.1016/j.jpain.2004.11.002
8. Kovacs, F. M., Arana, E., Royuela, A., Estremera, A., Amengual, G., Asenjo, B. et al. (2012). Vertebral Endplate Changes Are Not Associated with Chronic Low Back Pain among Southern European Subjects: A Case Control Study. American Journal of Neuroradiology, 33 (8), 1519–1524. doi: https://doi.org/10.3174/ajnr.a3087

9. Foley, K. T., Smith, M. M. (1997). Microendoscopic Discectomy. Techniques in Neurosurgery, 3, 301–307.
10. Popelianskii, Ia. Iu. (1989). Bolezni perifericheskoi nervnoi sistemy. Moscow: Meditcina, 464.
11. Kalka, N. I. (2015). Profilaktyka i podolannia syndromu khronichnoi vtomy u pratsivnykiv OVS. Lviv: LvDUVS, 84.
12. Chupryna, H. M., Macheret, Ye. L., Kovalenko, O. Ye. (2007). Astenichni syndromy v strukturi nevrolohichnoi patolohii. Zbirnyk naukovykh prats spivrobitnykiv NMAPO im. P. L. Shupyka, 16 (4), 751–762.
13. Golovchenko, Iu. I. (1985). O diagnostike i klassifikatcii zabolevanii perifericheskogo otdela nervnoi sistemy. Vrachebnoe delo, 7, 98–102.
14. Iankovskii, G. A. (1982). Osteoretceptciia. Riga: Zinatne, 316.
15. Anatychuk, L. I. (1979). Termoelementy i termoelektricheskie ustroistva. Kyiv: Naukova dumka, 768.
16. Demchuk, B. M., Kushneryk, L. Ya., Rublenyk, I. M. (2002). Termoelektrychni datchyky dlia ortopedii. Termoelektryka, 4, 80–85.
17. Anatychuk, L. I., Kobylianskyi, R. R., Konstantynovych, I. A. (2014). Hraduiuvannia termoelektrychnykh sensoriv teplovoho potoku. Suchasni informatsiini ta elektronni tekhnolohii. Odesa, 30–31.
18. Kobylianskyi, R. R., Boichuk, V. V. (2015). Vykorystannia termoelektrychnykh teplomiriv u medychnii diahnostytsi. Naukovyi visnyk Chernivetskoho universytetu. Fizyka. Elektronika, 4 (1), 90–96.
19. Hyshchuk, V. S. (2013). Modernizovanyi prylad dlia vymiriuvannia teplovykh potokiv liudyny. Termoelektryka, 2, 91–95.
20. Anatychuk, L. I., Ivashchuk, O. I., Kobylianskyi, R. R., Postevka, I. D., Bodiaka, V. Yu., Hushul, I. Ya. (2016). Termoelektrychnyi prylad dlia vymiriuvannia temperatury i hustyny teplovoho potoku "ALTEK-10008". Termoelektryka, 1, 76–84.
21. Anatychuk, L. I., Yuryk, O. Ye., Kobylianskyi, R. R., Roi, I. V., Fishchenko, Ya. V., Slobodianiuk, N. P. et al. (2017). Termoelektrychnyi prylad dlia diahnostyky zapalnykh protsesiv ta nevrolohichnykh proiaviv osteokhondrozu khrebta liudyny. Termoelektryka, 3, 54–67.
22. Anatychuk, L. I., Kobylianskyi, R. R., Konstantynovych, I. A., Lysko, V. V., Puhantseva, O. V., Rozver, Yu. Yu., Tiumentsev, V. A. (2016). Stend dlia hraduiuvannia termoelektrychnykh peretvoriuvachiv teplovoho potoku. Termoelektryka, 5, 71–79.
23. Anatychuk, L. I., Kobylianskyi, R. R., Konstantynovych, I. A., Kuz, R. V., Manyk, O. M., Nitsovych, O. V., Cherkez, R. H. (2016). Tekhnolohiia vyhotovlennia termoelektrychnykh mikrobatarei. Termoelektryka, 6, 49–54.
24. Yuryk, O. Ye., Anatychuk, L. I., Roi, I. V., Kobylianskyi, R. R., Fishchenko, Ya. V., Slobodianiuk, N. P. et al. (2017). Osoblyvosti teplovoho obminu u patsiientiv z nevrolohichnymy proiavamy osteokhondrozu v poperekovo-kryzhovomu viddili khrebta. Travma, 18 (6).

25. Anatychuk, L. I., Luste, O. Ya., Kobylianskyi, R. R. (2017). Informatsiino-enerhetychna teoriia termoelektrychnykh sensoriv temperatury i teplovoho potoku medychnoho pryznachennia. Termoelektryka, 4, 5–20.
26. Anatychuk, L. I., Kobylianskyi, R. R., Cherkez, R. G., Konstantynovych, I. A., Hoshovskyi, V. I., Tiumentsev, V. A. (2017). Thermoelectric device with electronic control unit for diagnostics of inflammatory processes in the human organism. Tekhnologiia i konstruirovanie v elektronnoi apparature, 6, 44–48. doi: https://doi.org/10.15222/tkea2017.6.44
27. Anatychuk, L. I., Ivashchuk, O. I., Kobylianskyi, R. R., Postevka, I. D., Bodiaka, V. Yu., Hushul, I. Ya., Chuprovska, Yu. Ya. (2018). Pro vplyv temperatury navkolyshnoho seredovyshcha na pokazy termoelektrychnykh sensoriv medychnoho pryznachennia. Sensorna elektronika i mikrosystemni tekhnolohii, 15 (1), 17–29.
28. Anatychuk, L. I., Yuryk, O. Ye., Strafun, S. S., Stashkevych, A. T., Kobylianskyi, R. R., Chev'iuk, A. D. et al. (2021). Thermometric indicators in patients with chronic lower back pain. Termoelektryka, 1, 52–66.
29. Veselovskii, V. P. (1995). Prakticheskaia vertebronevrologiia i manualnaia terapiia. Riga, 394.

DOI: 10.15587/978-617-7319-65-7.CH3

Liliia Yukhymenko, Sergii Khomenko, Lidiia Iliukha

CHAPTER 3

DIAGNOSIS AND MONITORING OF THE FUNCTIONING OF THE HUMAN NERVOUS SYSTEM

ABSTRACT

The significance of the study of the main nervous processes and typological combinations for deepening the general idea of the state of the body, as well as the possibility of using their indicators in the diagnosis and monitoring of the nervous system of young people, is analyzed. Various contingents of the population were examined: students, athletes, mobile operators, people with deprivation of auditory function, post-COVID syndrome and psychophysiological lability developed under martial law.

It was found that when performing real activity, individual typological properties are manifested, which determine the current psycho-emotional background, the speed and efficiency of sensorimotor reactivity, and the effectiveness of mental performance. The features of information processing by subjects with different gradations of functional mobility of nervous processes are reflected. It was found that the deprivation of the auditory function, post-COVID syndrome, psychophysiological lability, developed in a state of war, significantly reduce the level of the course of nervous processes and the possibility of processing information.

The evaluation scales of neurodynamic and sensorimotor functions proposed for use in the medical field can be used to optimize the diagnosis and increase the effectiveness of monitoring neurological morbidity, including in people with special needs.

Taking into account the peculiarities of neurodynamic and sensorimotor functions, they will also be useful in the physiology of labor, the professional selection of healthy people and the individualization of educational trajectories in higher education.

KEYWORDS

Monitoring, diagnostics, nervous system, basic nervous processes, individual typological properties, functional mobility, central nervous system, higher nervous activity, sensorimotor reactivity.

Health is not everything, but everything is nothing without health
Socrates

At all times, the problem of preserving human health has been and remains an urgent task of medicine. Due to its complexity of solution, it cannot be limited only to clarifying its biological or medical aspects. In modern conditions, human health should be considered in conjunction with its clinical, theoretical and methodological factors.

At present, there is an extensive arsenal of accumulated scientific biomedical information devoted to both elucidating the very concept of health and its physiological, psychological, social, and other components. Equally important is the experience of various ways of maintaining and improving health: clinical methods, rehabilitation practices, innovative habilitation technologies, the results of recreational activities, etc. At the same time, theoretical and methodological developments are still rather limited, few in number, and fragmented [1, 2].

Scientific and technical, social and medical and technological achievements of versatile studies of the human body should contribute to the digitalization of society, leveling various risks, maintaining and developing the health of the nation. A special priority is given to research to elucidate the fundamental foundations of individual health, concerning a comprehensive study of its mechanisms, factors of influence, diagnostics of intermediate states, creation of physiological information bases, predictive models, experimental intelligence and expert systems for evaluating and monitoring functional systems, intersystem interaction to ensure health-preservation.

From the point of view of a systematic approach, any functional state (FS) is regarded as a reflection by the human body of the consequences of exposure to environmental factors. Each FS is always an integral result of certain parameters, functions, characteristics of an organism and, at the same time, an indirect indicator of its adaptive strategies, reserve capabilities, etc. Therefore, FS should be considered as a complex of uncoupled interrelated reactions of the body to ensure its adequate functioning in accordance with the existing environmental conditions.

To understand all the risks of exposure to the body and ways to adapt to them, the task arises of diagnosing complexes of physiological reactions, numerous functional indicators, understanding of heterogeneous processes and their physiological mechanisms.

In recent decades, scientists around the world have been focusing society's attention on the disappointing dynamics and exponential growth in the incidence of neurotic disorders, neurological diseases among young people, the main reasons for which are called the acceleration of the pace of life, the introduction of new technologies in education and production, the reassessment of priorities and values, environmental, social and etc. aspects of human life [4].

Modern researchers are increasingly turning to the consideration of functional relationships between sensory and motor areas of the cerebral cortex, various morphological and functional systems of the body [5]. At the same time, in the literature there are few works performed on modern equipment that concern the study of the role of individual and typological properties of higher nervous activity (HNA), awareness of their significance in identifying predictors of various mental and autonomic disorders.

So, the issue of diagnosing and monitoring the functional state of the human nervous system, the need to return to physiological truths, understanding the mechanisms of regulation of functions, rec-

ognizing the role of the coordinating, regulating and integrating functions of the central nervous system and its importance in the occurrence of pathological disorders and the development of diseases.

Based on the concept of modulating brain systems, the reticular formation (ascending excitatory subcortical influences) belongs to the leading regulatory and integrating systems that determine the formation of a certain functional state. Having a grid-like structure hidden in the depths of the brain stem, and in contact with adjacent afferent sensory fibers, the reticular formation has an activating effect on the cortical structures of the brain at their slightest excitation, causing global shifts in the overall level of functioning, generalized.

An important contribution to the development of the functional state of the nervous system and the organism as a whole is made by the activity of the thalamic part of the diencephalon, which receives the flow of sensory afferentation, generates rhythmic activity, and synchronizes local effects on the cortex. The emergence of a functional state is also impossible without the participation of the limbic system, which has both activating and inactivating components, the coordinated work of which ensures the flow of cognitive functions and the activity of the emotional structures of the brain.

The leading place among the most influential regulatory structures, on which the formation of functional states depends and have a powerful downward influence, is occupied by the frontal areas of the cerebral cortex. They control the activity and reticular formation of the brainstem and thalamic part of the diencephalon, as well as the formation of a modulation vector corresponding to the current needs.

At the same time, in our opinion, equally important in this sense should be given to understanding the universality of the significance of the main nervous processes, their typological features in the development, deployment and maintenance of the functional state of the body. In this case, the functional state can be considered a synergy of both the modulating systems of the brain, the higher parts of the central nervous system of the cerebral cortex, and the support systems, which include the main nervous processes: strength, balance and mobility.

The next step, which leads to ensuring the state of health, is an attentive attitude to monitoring the vital signs of the body and, first of all, the functional state of the nervous system, and, if necessary, the use of psychophysiological diagnostics.

Among the sensitive indicators of the functional state of the central nervous system (CNS), which can be used to judge the dynamics of brain activation levels, the parameters of the electrical activity of the brain are of paramount importance. These include indicators of the rhythmic components of the EEG, their spatiotemporal characteristics, the value of the coherence of biocurrents, etc. It is known that the dynamics of the FS of a healthy person is manifested by the transformation of spatio-temporal relationships of the electrical activity of the brain, demonstrating connections between its individual sections or spectral indicators of a different nature. Most authors emphasize that in response to the complication of the task being performed, the intensity of interregional ties, for the most part, is growing.

Indicators of the cardiovascular and respiratory systems of the body obtained by electrocardiography, echocardiography, rheography, magnetic resonance imaging, which are at the intersection

of medicine and physiology (heart rate, force, minute volume of the heart, blood pressure, regional circulation, tidal volumes, 3D reconstructions of the coronary arteries). They are indispensable for diagnosing the course of processes that occur in the body during the development of emergency conditions, in particular acute coronary syndrome, cardiac arrhythmias and conduction disorders, myocardial infarction, treatment of strokes, hypertension, diseases of the bronchopulmonary apparatus, etc.

At the same time, it should be noted that there is an urgent need for modern inexpensive express methods, mobile innovative methods for studying the functional state of the nervous system, including those developed using the neurodynamic approach. Recently, there has been a growing interest in such innovative methods of studying the body, the results of which would have both high efficiency, objectivity, ease and speed of obtaining, etc. From our point of view, such needs can only be satisfied by a research methodology based on genetically determined properties of the nervous system of the human body.

Scientists note that the features of HNA should be considered as a biological basis for the formation of possible vectors of adaptive behavioral reactions, further manifestation in the functions of the autonomic nervous system, and primarily the activity of the heart. Diagnostics and monitoring of the functional state of the nervous system, its characteristics in different conditions of existence in people with different levels of development of the main nervous processes will expand the criteria base for the sphere of career guidance and selection, prediction and prevention of neuropsychiatric pathology.

The aim of this study is to analyze the significance of the study of the characteristics of the main nervous processes and typological combinations for a general idea of the state of the body, as well as the possibility of their application in the diagnosis and monitoring of the nervous system of young people. The work used neurodynamic and sensorimotor hardware-test methods, analytical and statistical analysis.

3.1 MODERN IDEAS ABOUT THE PROPERTIES OF THE MAIN NERVOUS PROCESSES AND THEIR ROLE IN THE FORMATION OF FUNCTIONAL STATES

It is known that the main processes of nervous activity are excitation and inhibition. The leading properties of the main nervous processes are recognized as their strength, balance and mobility.

More than one century has already passed since Ivan Pavlov at the XIV International Medical Congress in Madrid made his famous report on the basics of higher nervous activity, intriguing the world scientific community with a new look at the existence of biological disagreements between people, at the same time basing their study and the need for diagnostics. Today, an extremely large number of works have already been accumulated devoted to the study of the property of the mobility of human nervous processes, as one of the leading ones, but to this day its problem remains unresolved [3].

The possibility of a rapid transition from one nervous process to another, depending on the conditions of the external environment, as well as the rate of occurrence, flow and termination of nervous processes, is the basis of Pavlov's idea of the concept of mobility. Later, the concept of mobility was divided into the understanding of mobility itself according to Ivan Pavlov, the rate of onset and termination of excitation according to Nikolai Vvedensky, and the ability of nervous processes to process an associative pair of conditioned reflexes according to Alexei Ukhtomsky.

Although the history of the study of mobility did not end there, but was enriched by the discovery of a new property by Mykola Makarenko – the functional mobility of nervous processes. According to the author, it is an integral speed characteristic of the whole functional system in which the signal is perceived, analyzed, decision is made, and a command is issued to the effector, taking into account the peculiarities of the work of the higher parts of the central nervous system – cortical structures [6].

It should be noted that the new discovered property not only does not contradict Pavlovian ideas about mobility, but also agrees with them in taking into account both the rapid switching of actions to discriminate positive signals and the frequent change in the process of inhibition by excitation and vice versa.

No less important properties of the main nervous processes are their strength and balance. According to the views of Ivan Pavlov, balance is the relationship that exists between the absolute values of the processes of excitation and inhibition. In other works, this property is understood as a balance between the rate of formation of conditioned reflexes and differentiations, the number of positive and inhibitory reactions, the rate of extinction and reinforcement of conditioned reflexes, etc.

The property of the strength of the main nervous processes lies in the ability of ensembles of nerve cells to withstand prolonged or frequently repeated excitation that does not cause the development of foreign inhibition [6]. Strength characteristics include resistance to external stimuli, concentration and irradiation of the excitation process, absolute sensory sensitivity and various manifestations of the law of strength.

Both reflex (actually nervous) and mental activity of a person are inextricably linked with the environment and are the result of the interaction of an infinite number of receptor, central and effector circuits. The carriers of the psyche are the processes of organizing physiological processes, that is, systemic interactions.

The concept of the properties of the main nervous processes in the Pavlovian understanding is today the leading one in the presentation of the biological foundations of individual behavior, response strategies, etc. According to the teachings of Ivan Pavlov about HNA, it is the properties of the nervous system that are the neurophysiological basis of heterogeneous manifestations, reactions and their individual behavioral strategies.

At present, the genetic nature of the properties of the main nervous processes, and first of all, the mobility of nervous processes, is no longer in doubt. The external environment, constantly influencing the body, forms new qualities of HNA. Modern studies of the higher nervous activity

of a person have established a highly genetically determined property of nervous processes – their functional mobility (FMNP).

According to the research results, the reflection of the main properties of the human nervous system in the patterns of the electroencephalogram (EEG recorded at rest and under various functional loads) is genotypically determined. The Holzinger coefficient, which expresses the degree of genetic determination of FMNP, as well as the latent period of a simple sensorimotor reaction of visual and auditory modality, was in the range of 0.6–0.86.

Therefore, it should be noted that the diagnosis of individual indicators of FMNP is an important objective criterion for assessing the functional state of the nervous system [6].

It should also be noted that the range of various characteristics of the body's activity, its functions, properties, and, first of all, the indicators of the course of the main nervous processes are the result of the constant interaction of the human body with the environment, an indicator of its functional state. It does not matter what role in the creation of a certain functional state is played by the HNA properties, the initial level of activation of the nervous system, sensory systems, as well as numerous factors associated with the emotional background, motivations, and the type of activity performed.

Factors such as reactivity and lability are among the defining characteristics of the functional state.

Distinguish between the concept of normal, disturbed and pathological functional state of the body, where the neurophysiological component is given a leading role. The normal functional state of the nervous system is associated with the establishment of a relative dynamic balance between the main nervous processes, intersystem interaction in the body and external environmental influences, when the use and restoration of the body's functional resources is within its capabilities.

The signs of disturbed and pathological functional states include disturbances in reflex activity, disorganization of intersystem interaction, imbalance, discoordination of functions, depletion of nerve centers, an increase in inhibitory nervous processes, etc. The danger of a disturbed state is manifested by an exacerbation of neuro-emotional stress, the appearance of fatigue, the development of irritability, the spread of negative emotions that serve as the basis for psychosomatic disorders and their transformation into a pathological functional state. It is the pathological functional state of the body that is characterized by signs of shifts in nervous activity, the development of crisis physiological states, and cardio-respiratory insufficiency.

Among the modern technologies for studying the functional state in terms of the parameters of the main nervous processes, the psychophysiological hardware-computer method "Diagnost-1M", which is constantly developing and updated in our scientific school, has recently become the most popular in scientific laboratories of many educational, industrial, military institutions of Ukraine. A large body of research has already been accumulated, proving the essential importance of taking into account the functional indicators of the nervous system, established by neurodynamic characteristics, in order to optimize educational, labor operations, develop health-preserving principles of life for workers in various sectors of the national economy.

Psychophysiological studies of certain examined contingents (in normal and pathological conditions) open up opportunities for the practical application of the results of applied developments, for example, scientifically based proposals for the use of neurodynamic methods as diagnostic, screening for the possibility of monitoring (or treating or correcting) the functioning of the nervous system in the medical field, to which the present work is dedicated.

3.2 HARDWARE-COMPUTER METHOD FOR STUDYING THE FUNCTIONAL INDICATORS OF THE HUMAN NERVOUS SYSTEM "DIAGNOST-1M"

The "reverse side of the medal" of the current level of scientific and technological progress requires a person to exert high stress on many systems of its body, including the nervous one. Both the performance of many professional tasks and the everyday realities of communications in modern society constantly place ever greater demands on the nervous system, often causing overstrain of the main nervous processes, exacerbation of psycho-emotional personality disorders, the development of premature fatigue and asthenia of its functions.

The work of the nervous system under conditions of time limit is accompanied by excessive activation of cerebral processes, emotional zones of the brain, an imbalance in the processes of excitation and inhibition, and other shifts in the central and autonomic nervous system. There is a need to conduct monitoring examinations, develop and apply a differentiated approach in the diagnosis of neuropathology, which is designed to enrich the understanding of the neurological level of "safe" life activity, to contribute to updating the theoretical and methodological foundations of prevention and medical selection especially those that are based on non-invasive, but objective methods, which include psychophysiological developments.

To assess sensorimotor reactivity, let's determine the individual neurodynamic properties of HNA, create appropriate neurodynamic scales, with a detailed assessment of the functional quantitative and qualitative individual neurodynamic characteristics of certain contingents of subjects, in our opinion, the most suitable is the latest hardware-computer complex created by Mykola Makarenko and Volodymyr Lizogub and is constantly being improved by their scientific school [7].

Studies can be carried out in three main modes (in optimal, feedback, imposed rhythm) and the sub-mode "reaction to a moving object" using signals of various modalities and specifics: figurative (geometric shapes square, circle, triangle), auditory and visual (green, red, yellow colors of rectangles; pure tones in low, medium and high keys, described by a regular curve), associative (names of animals, plants, inanimate objects). In the optimal mode, the hardware-diagnostic computer complex allows to determine the indicators of a simple visual-motor or auditory-motor reaction, as well as to identify the characteristics of the reaction of choosing one signal from three proposed ones or to select and differentiate two signals from three.

When determining the indicators of a simple sensorimotor reaction (various modalities), at the beginning of the examination, familiarization with the rules for performing the task is carried out.

In particular, it is emphasized that when a certain type of signal (announced on the eve of the examination) appears on the monitor screen – geometric shapes, words, colors or sound tones, press and release the right button of the device as quickly as possible with the right (or left) hand. The task must be completed before the message about its completion appears on the screen. For a better acquaintance of the subject with the performance of the task, it is desirable to demonstrate the technique of its implementation by the researcher on a small number of presentation of signals.

The significance of identifying the characteristics of simple sensorimotor reactivity lies in the fact that they reflect the rate of the excitatory process in all links of the reflex ring (from the receptor to the higher centers of the central nervous system, analytical and synthetic processes in it and propagation in the opposite direction to the effector), including taking into account the time spent on perception, decoding, signal transformation into a nerve impulse, etc. This allows to regard a simple sensorimotor reaction as an indicator of the excitability of the central nervous system, giving the status of its latent period as an objective indicator of the functional state in which, it is under these conditions.

The performance of the sensorimotor task of choosing one signal out of the three proposed is also carried out with one hand: right (or left). Under these conditions, the subject is told that, for example, when a high-pitched sound tone (square, red, etc.) appears, it should press and release the right (or left) button as quickly as possible and not respond to other signals by pressing.

As in the previous task, the response must continue until the message about its completion appears on the screen. The content of this sensorimotor reaction is to find out how accurately (clearly) and quickly the subject is able to select only one signal from the three proposed. As a result, the number of erroneous reactions made by the subject during the performance of the task makes it possible to judge the accuracy of its performance, and the duration of the latent period indicates the speed of the operation of choosing one stimulus among others.

The implementation by the subject of the sensorimotor reaction of choice and the differentiation of two signals from the three proposed requires the use of both hands. So, the appearance of a signal (as in the previous tasks, its certain modality can be selected) requires the subject to quickly press and release the right button on the signals: a square, a red rectangle, a high-pitched sound, the names of animals. With the left hand, it is necessary to quickly respond to the figures of circles (names of plants, sound tones of low pitch or green rectangles) by pressing and releasing the button of the device as quickly as possible. Negative signals, which include: the shape of a triangle, the name of an inanimate object, a mid-tone sound tone, a yellow rectangle, should not be reacted to.

In the case of performing such a sensorimotor task, in addition to the operation of choosing a stimulus (carried out in the optimal mode), it is also complicated by the need to process information on the differentiation of positive and inhibitory signals, which occurs in the imposed rhythm mode and in the feedback mode, when the speed of signal presentation, and the number of stimuli used in the study. At the same time, since the task is as complex as possible, its implementation requires the participation not only of the peripheral departments and lower nervous levels of control,

but also requires the inclusion of the highest cortical coordinating and integrating centers of the nervous system.

Consequently, the value of the indicator of the rate of a complex reaction lies in its informativeness regarding the ability of the central nervous system to ensure the flow of a complex reaction and at the same time demonstrates the criteriality of this characteristic of the nervous system in relation to the development of individual typological properties of the human HNA.

Statistical processing of indicators is carried out automatically with the calculation of the average value of the latent period of the sensorimotor reaction, the error of the arithmetic mean, the standard deviation, the coefficient of variation, the number of errors; the average value of the motor reaction, which objectifies the obtained individual and group data. Thus, highlighting the values of sensorimotor reactions of different complexity, it should be stated that simple sensorimotor reactivity is an important measure for assessing the functional state of the nervous system, while complex sensorimotor activity is an indicator of the activity of many brain structures: neuronal networks, ensembles, columns of modules, and their inside-system and intersystem interactions.

The hardware-computer complex "Diagnost-1M" makes it possible to actually evaluate to a certain extent those processes that occur directly in the higher parts of the central nervous system, diagnosing the ability of the nervous system to provide sensorimotor reactivity of varying degrees of complexity. This becomes a possible means of studying both simple and complex sensorimotor reactions of selection and differentiation of stimuli.

To do this, on the basis of this examined device, a certain number of stimuli are presented with the determination of the average values of the latent periods of a simple sensorimotor reaction, then a certain number of stimuli are presented with the determination of the average values of the latencies of a complex sensorimotor reaction of selection and differentiation of two stimuli out of three, obtaining the speed of the central processing of information by the higher parts of the central nervous system. It is determined by the difference between the average latencies of a complex sensorimotor reaction and a simple sensorimotor reaction and is based on the fact that the average latency of a complex sensorimotor reaction is defined as the average value of the response time to stimuli presented in the "feedback" mode [8].

It is known that the time interval between sensory perception and the onset of motor wear reflects the total duration of the sensorimotor response. The procedure for applying at least three times consciously quickly pressing and releasing an unrestricted button of the measuring device and averaging the time spent on such movements makes it possible to identify the motor component of reactivity. This possibility can be useful in medicine as an express diagnostic of paresis, neurotic disorders, depressive states, etc.

After determining the latent period of a simple sensorimotor reaction and the motor component, it becomes possible to evaluate the sensory component of reactivity by calculating the difference between these obtained values. As a screening technique, such a procedure can be offered when determining the diagnosis of sensory disorders (visual dysfunction, deprivation of auditory function), the development of post-COVID syndrome, etc.

The study of the time (speed) of the central processing of information by the brain makes it possible to find out at what level (quantitatively and qualitatively) its analytical and synthetic activity can be carried out, which involves the participation of numerous and heterogeneous cerebral structures in the performance of any sensorimotor task of differentiating stimuli. With an increase in the complexity of the task (from a simple sensorimotor reaction to a reaction of choice and differentiation), the need to expand intersynaptic interactions also increases, proving the importance of the main nervous processes in their provision and the course of brain activity.

Studies of the brain functions of people with congenital deafness have revealed excellent characteristics of information processing by the brain compared to their healthy peers, which makes it possible to propose such a technique for monitoring the dynamics of nervous processes associated with dementia of various pathogenesis.

The "feedback" mode is used to directly determine the levels of properties of the main nervous processes: functional mobility and strength. It is possible to select the required number of signals (in the range from 120 to 360), as well as the duration of the study series (1–5 minutes). In this mode, the speed of signaling directly depends on the progress of the task by the subject: an error-free reaction causes a reduction in the next signal (no more than 20 ms), and an erroneous reaction is accompanied by its delay by the same amount of time. Signal exposures range from 20 to 900 ms.

To complete the task in the "feedback" mode, the subject is required to strictly follow the instructions that it read at the beginning of the study. Namely, the appearance of, for example, a square (or the name of an animal, a red rectangle, a high-pitched sound) requires the immediate pressing and releasing of the right button with the right hand. On the contrary, the appearance of a circle (or the name of a plant, a green rectangle or a low-pitched sound) is the reaction of pressing and releasing the left hand on the left button of the device. Shapes of triangles (or names of inanimate objects, yellow rectangles, mid-pitched sound tone) are inhibitory and do not require any response to them. If the task is executed without errors, the signaling rate will increase and decrease with an erroneous response.

The essential point is the execution of the task at the highest possible speed for the examined person, while making the least number of errors. To do this, the subject must respond to the signals as accurately as possible and maintain the acquired high pace for as long as possible. Of course, errors will inevitably occur during the reaction, but stopping tasks in the middle of its execution is not acceptable. As in the previous cases, the task must be completed before the completion message appears on the screen.

Important indicators of statistically processed and visualized on the computer display FMNP are: the number of signals proposed for selection / or selection and differentiation, the duration of the proposed task, the processing time of the proposed number of signals, the initial and minimum signal exposure time and the time to reach the minimum signal exposure.

The indicator of FMNP is the time of task execution as demonstrating the ability of the CNS to maintain the fastest possible rate of error-free sensorimotor response to successive positive and

inhibitory signals. It should be noted that the time to complete the task depends entirely on the characteristics of both the process of excitation and inhibition, therefore, is the resulting value of their functional mobility.

The main indicators that can be determined to characterize the strength of nervous processes (SNP) include the number of processed stimuli during the task, the minimum time and time to reach the minimum signal exposure, the ratio of signals that should be responded to the total number of proposed signals, the degree of growth exposure.

In the imposed rhythm mode, it is possible to study in detail the characteristics of FMNP and SNP with preliminary training, which can last from 30 to 60 s. The peculiarity of this mode is to change the speed of presentation of the signals displayed in the range from 30 to 150 per minute. For the optimal degree of gain applied in determining the FMNP and SNP in this mode, it is recommended to select 10 waveforms that will be attached to the waveform demo for processing per minute. For example, 40, 50, 60, and so on up to 150. When completing the task, the subject should press and release the right button as quickly as possible with the right hand when a square figure (or the names of animals, a red rectangle or a high-pitched sound) appears.

The appearance of a circle figure (or the name of a plant, a green rectangle, or a low-pitched sound) requires a quick press and release of the instrument's left button with the left hand. The shape of a triangle (as well as the names of inanimate objects, yellow rectangles, or a mid-tone sound) does not require pressing buttons. The execution of the task is terminated only when an inscription appears on the screen about its completion and in no case is interrupted if an error is made.

After carrying out the examination modes mentioned above, the levels of FMNP and SNP can be judged by the indicators that appear on the display: the rate of presentation of signals per minute, the total number of admitted false reactions, correctly processed signals, etc. The indicator of FMNP is the maximum possible rate of presentation of signals at the highest speed, when the subject allows up to 5.5 % of erroneous responses.

SNP is evaluated by the total number of erroneous reactions (as a percentage of the sum of all applied signals), which the subject allowed for the entire period of the task. Consequently, the fewer erroneous reactions the subject could make during the selection and differentiation of signals, the higher the level of strength of nervous processes it has (the working capacity of the brain).

The balance of nervous processes (BNP) is studied in the "reaction to a moving object" mode. The device allows to change the time of movement of the object from 500 to 2000 ms. The number of BNP determinations can vary from 10 to 40 with a pause between signal series of 500–2500 ms, necessary to restore the functions of the nervous system. Such an examination makes it possible to determine the ratio of the processes of excitation and inhibition in the cerebral cortex by the accuracy of the sensorimotor response to an object moving at a uniform speed in the place indicated on the monitor.

According to modern concepts, premature motor responses (anticipations) reflect the processes of inhibition, while delayed ones reflect the excitatory process. For medicine, no doubt, the identification of BNP by reaction to a moving object can be useful in the diagnosis of depressive

disorders, the development of acute stress, and the determination of the volume of sensory and motor anomalies.

To determine the BNP, the subject should press the right or left button in such a way that it is possible to stop the object moving on the monitor clearly opposite the cursor. Among the evaluation indicators, the number of error-free reactions, the sum of deviations and their average value, as well as the number of reactions ahead and late relative to the exact (error-free) reaction in the attempt that was the most successful, are important.

3.3 SETTING GOALS, ORGANIZATION AND APPLICATION OF THE HARDWARE-COMPUTER TECHNIQUE "DIAGNOST-1M" FOR THE STUDY OF THE NERVOUS SYSTEM OF THE EXAMINED VARIOUS CONTINGENTS

An analysis of modern methods of psychophysiological diagnostics, the practice of using hardware devices in the medical field has shown that an adequate assessment of the functioning of the human nervous system should be based on reliable criteria that can only be distinguished when examining different contingents of people (by age, professions, diseases). It is known that the main driving force, an important factor in socio-economic progress, the bearer of the intellectual potential of each country is the younger generation. The main hopes for the further development of Ukrainian society are pinned. The official age of young people in our state, according to Article 1 of the Law of Ukraine "On the promotion of social formation and development of youth in Ukraine" dated February 5, 1993, is 14–35 years.

It is also noteworthy that recently among the younger generation there has been an increase in neurological pathology. Today in Ukraine, as well as throughout the world, over the past 10 years, there has been a growing trend in the growth of vascular diseases of the brain, infectious and demyelinating lesions of the nervous system (in particular, multiple sclerosis), vegetative dystonia, diseases of the peripheral nervous system [9].

It is noted that 70 % of such patients are people of working age. The prevalence is acquired by chronic fatigue syndrome, which is clinically manifested by headache, weakness, dizziness, memory loss, and performance. Among the reasons are the unfavorable ecological situation, immune deficiency, allergization of the population, and viral neurodiseases. Cases of strokes in young and middle age are rapidly increasing, and they are increasingly being diagnosed in children. In this regard, the main emphasis should be placed on preventive treatment, and priority in the fight against neurological morbidity should belong to the development and application of methods for diagnosing and monitoring the state of the nervous system [10, 11].

Given the above, in recent years we have conducted studies of the functional parameters of the nervous system of the population of different categories: students, athletes, people of operator professions, people with pathologies of the auditory system, as well as post-COVID syndrome, psychophysiological lability, developed military condition. In order to clarify the characteristics of

the main nervous processes and their typological manifestations in terms of neurodynamic and sensorimotor parameters in young people aged 17–28 years.

The survey was conducted on 168 boys and girls who made up groups: students, athletes, mobile operators, people with deprivation of auditory function (congenital deafness), people with post-COVID syndrome, people with an unstable psychophysiological status, formed as a result of the declaration of martial law in the country. The examinations were carried out in accordance with the norms of bioethics and in compliance with the provisions of the Ministry of Health of Ukraine dated March 13, 2006, No. 66 and the Declaration of Helsinki (1975, later editions of 1996–2013).

The functional characteristics of the nervous system were studied using the hardware-computer method of Mykola Makarenko "Diagnost-1M". Sensorimotor reactivity was studied in terms of latent periods (ms) during reactions to stimuli of varying degrees of complexity: a simple sensorimotor reaction, a reaction of choosing one stimulus out of three, and a reaction of choosing and differentiating two stimuli out of three (stimuli used visual and auditory modality). Lower rates of latent periods indicated better sensorimotor reactivity.

The study of the neurodynamic individual typological properties of HNA was carried out in terms of functional mobility (FMNP), strength (SNP) and balance (BNP) of nervous processes. To determine the individual FMNP, the "feedback" mode was used to obtain results on the selection and differentiation of positive and inhibitory stimuli. The level of FMNP was judged by the time of the completed task: a shorter time corresponded to a higher level of the studied typological property.

The strength of nervous processes (SNP) was evaluated in terms of the total number of processed stimuli per 5 min of computer work. The highest level of SNP corresponded to a greater amount of processed information.

The time/speed of the central processing of information by the brain (CPI) was calculated [11]. To do this, we determined the latencies of a simple visual-motor (SVMR) or simple auditory-motor (SAMR) reaction and the reaction of selection and differentiation of two stimuli out of three ($RC_{2–3}$), taking into account the FMNP level.

The determination of the BNP was carried out in the "reaction to a moving object" submode with the evaluation of the results, which included taking into account the total number of advanced or delayed responses. A smaller sum of response deviations (ms) indicated a higher BNP.

Additional methods for examining indicators related to the activity of the nervous system were research methods:

– the level of personal anxiety (PA) and reactive anxiety (RA) according to the method of self-assessment by Charles D. Spielberg adapted by Yuriy Khanin;

– the level of self-assessment of well-being, activity and mood (WAM) according to the method of Valery Doskin [12];

– assessment of student learning in terms of semester performance (the number of positive and negative exams and tests passed, their quality, the existence of academic debt, its volume).

The results were processed by conventional methods of parametric and nonparametric statistics. Comparison between independent samples that did not fall under the normal distribution law was carried out by the Mann-Whitney method, between dependent samples – by the Wilcoxon method. When the data fell under the normal distribution law, Student's t-test was used for dependent and independent samples, respectively.

3.4 THE MAIN RESULTS OF THE STUDY OF FUNCTIONAL INDICATORS OF THE HUMAN NERVOUS SYSTEM

According to the tasks set in the work, the characteristics of the main nervous processes were studied. We found out the significance of the properties of the main nervous processes for assessing the functional states and general well-being of a person. The work used neurodynamic and sensorimotor methods of the hardware-computer system "Diagnost-1M", described in Paragraph 3.2.

The study of the parameters of sensorimotor reactivity included the determination of indicators of latent periods of simple sensorimotor reactions of visual and auditory modality (LPSVMR/LPSAMR), reactions of choosing one of three stimuli ($LPRC_{1-3}$) and reactions of selecting two stimuli out of three ($LPRC_{2-3}$).

The results of studies of the sensorimotor functions of a group of students (on the example of the processing of visual modality stimuli) are presented in **Table 3.1**.

Table 3.1 Average indicators of latent periods of visual-motor reactions of varying degrees of complexity among students

Age (years)	Latent periods (M ± m, ms)		
	LPSVMR	$LPRC_{1-3}$	$LPRC_{2-3}$
17–18	234.5 ± 5.1	353.8 ± 4.7	434.6 ± 6.7
19–20	233.5 ± 5.3	345.5 ± 6.8	416.3 ± 6.8
21–22	231.5 ± 5.4	342.3 ± 5.7	400.8 ± 5.8
23–24	243.4 ± 6.4	344.1 ± 6.0	403.2 ± 6.2
25–26	252.1 ± 6.6	346.2 ± 6.5	413.7 ± 6.5
27–28	256.2 ± 6.8	347.3 ± 7.2	417.2 ± 7.7

As can be seen from the Table, with the complication of the sensorimotor task, the time of perception, processing and response increased. The shortest latent periods of SVMR are typical for students aged 17–22; for RC_{1-3}, similar results were obtained from students aged 19–28,

with the lowest values at 21–22 years; and for $RC_{2–3}$, the shortest latencies were observed at 21–24 years. Subjects aged 21–22 had the lowest latencies, regardless of the degree of their complexity, both relatively younger (17–20 years old) and older participants (23–28 years old). Such remittance of indicators demonstrates the age periods of development and stabilization of simple and complex sensorimotor functions of a person.

Indicators of sensorimotor reactions of varying degrees of complexity of the examined group of athletes did not differ significantly from those of students (**Table 3.2**). It is known that the properties of perception, processing of information, appropriate response to various stimuli are important for a person as an evolutionary and ontogenetic heritage regarding the possibility of adaptation and development of a defense strategy. There is no doubt that the processing of information as an element of almost all types of human life depends on the capabilities of the central nervous system and the current functional state.

Currently, the prevailing majority of professions, to one degree or another, are associated with the implementation of operator functions (from a supermarket seller to a work office or a scientific institution).

Table 3.2 Average indicators of latent periods of visual-motor reactions of varying degrees of complexity in athletes

Age (years)	Latent periods (M ± m, ms)		
	LPSVMR	$LPRC_{1–3}$	$LPRC_{2–3}$
17–18	250.1 ± 6.1	347.1 ± 5.3	411.3 ± 6.9
19–20	240.2 ± 6.2	343.5 ± 5.0	389.7 ± 7.2
21–22	235.4 ± 5.1	337.3 ± 3.1	374.6 ± 6.9
23–24	238.4 ± 5.4	336.1 ± 5.3	372.1 ± 6.1
25–26	244.1 ± 5.8	338.2 ± 5.5	374.4 ± 5.1
27–28	253.2 ± 6.2	341.9 ± 4.3	484.8 ± 5.4

However, the best rates of SVMR were observed in the age range of 21–26 years; for $RC_{1–3}$ and $RC_{2–3}$ they were recorded in athletes aged 21–26. Consequently, athletes have a longer period of stabilization of complex sensorimotor reactions at the highest level compared to students.

There are more and more labor operations associated with the processing of auditory information (communications, dispatchers, military personnel, telephone operators, etc.). We conducted a survey of mobile operators, in whose intellectual activity processes associated with visual and auditory afferentation are activated, requiring quick and responsible decisions. The study of the sensorimotor functions of mobile operators made it possible to identify some features (**Table 3.3**).

Table 3.3 Average indicators of latent periods of visual-motor reactions of varying degrees of complexity in people with different statuses of auditory function by stimulus modality

Latent periods (M ± m, ms)	Stimulus modality	
	Visual	Auditory
LPSAMR	210.9 ± 8.2	181.2 ± 9.6*
$LPRC_{1-3}$	367.9 ± 7.8	331.2 ± 8.3*
$LPRC_{2-3}$	412.6 ± 6.8	430.5 ± 6.1*

*Notes: * – reliability of differences $p < 0.05$ between indicators of different modalities*

The time of latent periods of a simple sensorimotor reaction and a reaction with one choice turned out to be significantly shorter in the case of the application of an auditory modality stimulus. As regards the reaction of selection and differentiation of two stimuli out of three, the latencies recorded on presentation of stimuli of the visual modality were shorter. We are inclined to believe that the significantly shorter latency to auditory modality stimuli obtained by us is explained by the higher sensitivity threshold in this analyzer, as well as by the morphofunctional features of the auditory nerves. In turn, the best performance of a complex sensorimotor reaction of selecting and differentiating visual modality information can be associated with the specificity of the mechanisms of visual and auditory sensory processing.

At the same time, the modality of the stimulus in some cases is of decisive importance, especially for those categories of people who have limited or complete deprivation of certain sensory functions. The sad dynamics of the increase in the number of people with hearing problems requires the study of brain processes that occur in the "deaf" brain when processing information. After all, before making a decision adequate to the situation, information coming from the environment must go from the receptor-receivers to the control centers of the brain, and from them directly to the executive organs.

The brain of a deaf person is a unique model with adaptation mechanisms that have not yet been fully elucidated, allowing it to exist in a changing world. The disclosure of this secret can contribute to the development or at least partial restoration of lost mental, sensory, motor abilities, the development and application of new approaches in the field of microtechnologies of nerve impulses, self-regulation, brain twitching in order to treat and correct the functions of the central nervous system of millions of people suffering from sensory defects.

It should be assumed that the analysis of the principles of the brain with deprivation of analyzer functions on the basis of neurodynamic studies will help to identify the algorithms for the functioning of a number of brain structures, improve the diagnosis of pathology, prediction and monitoring.

To determine the features of the brain mechanisms of differentiation of visual stimuli in subjects with normal hearing and the deaf, sensorimotor characteristics were analyzed (**Table 3.4**).

Table 3.4 Average indicators of latent periods of visual-motor reactions of varying degrees of complexity in people with different statuses of auditory function by examined groups

Latent periods (M ± m, ms)	Examined groups	
	Healthy	Deaf
LPSVMR	230.4 ± 9.1	252.7 ± 9.6
$LPRC_{1–3}$	350.9 ± 10.8	366.1 ± 9.3
$LPRC_{2–3}$	426.6 ± 8.7	497.5 ± 11.2*

*Notes: * – reliability of differences $p < 0.05$ between the indicators of healthy and deaf subjects*

No significant differences were found between the sensorimotor parameters of the SVMR and $RC_{1–3}$ ($p > 0.05$). Comparison of the results of $RC_{2–3}$ indicated the predominance of latencies of a complex sensorimotor reaction in the deaf ($p < 0.05$). These results indicate that the performance of relatively simple sensorimotor reactions (SVMR, $RC_{1–3}$) does not require the participation of the higher parts of the CNS, but is an important characteristic of the rate of the excitatory process in neuronets, which is important from a medical point of view for assessing the work of the peripheral parts of the nervous system of such patients.

Indicators of a complex visual-motor reaction, reflecting the participation of cerebral neurostructures in the analysis of information, providing synthetic processes of the central nervous system, indicated that such processes in the deaf require much more time than in healthy people.

Consequently, deprivation of auditory afferentation, characterized by a deficit in the neural status, significantly impairs the effectiveness of information processing by the brain.

Each psychophysiological state of a person is a reflection of the interaction of the organism with the environment. It is influenced by the surrounding events of personal and social life, the ability to resist negative situations, the levels of situational and personal anxiety, and the tendency to develop depressive states. This aspect becomes especially acute in the conditions of martial law declared in the country. A survey of men who were engaged in professional duties (university workers), not being in the frontline zone, revealed significant changes in their psychophysiological sphere with a tendency to develop depression (**Fig. 3.1**).

Conducted pilot surveys of 19 men aged 20–25 years to assess the impact of adverse events on the general functional state of the nervous system in terms of sensorimotor functions revealed, on the one hand, the vulnerability of the CNS to the psycho-emotional factors of a military state (which was manifested by a predominant decrease in latencies), the other – testified to a rather high sensitivity of the indicators of sensorimotor reactivity to changes in the psychophysiological status of a person. Undoubtedly, martial law is one of the formative factors in the development of unbalancing of adaptive psychophysiological reactions.

Among other medical problems that need urgent solutions is the fight against the incidence of COVID-19 and, especially, the elimination of its consequences [13]. Today, medical workers are

concerned about both the rapid spread of the disease and the awareness of the severe consequences of the disease, manifested by the development of the so-called post-COVID syndrome. The most dangerous of its symptoms and complaints include disorders of the central nervous system.

On the other hand, scientists are optimistic about the opinion that the restoration and normalization of the functions of the central nervous system and GNI are quite possible. In addition, the results of studying the functioning of the brain in post-COVID syndrome can be extremely useful for optimizing preventive, therapeutic and rehabilitative measures.

A study of the sensorimotor functions of the examined 20 male subjects aged 19–26 years who recovered from COVID-19 (mild and moderate severity) at the 6th week after recovery and their comparison with the indicators of healthy peers revealed significantly worse sensorimotor indicators (≤ 0.05) (**Table 3.5**).

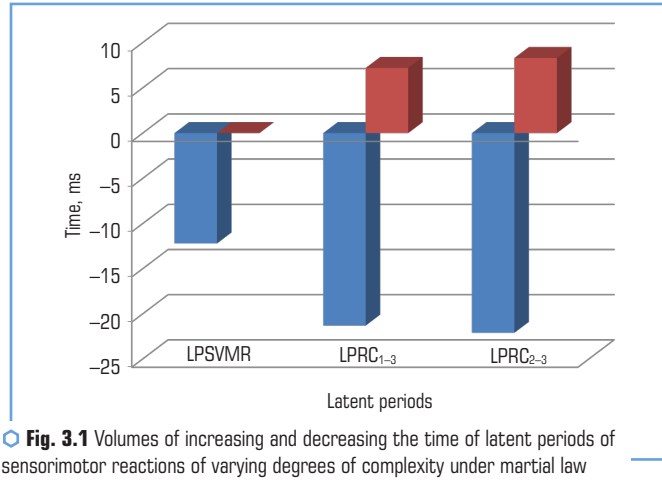


Fig. 3.1 Volumes of increasing and decreasing the time of latent periods of sensorimotor reactions of varying degrees of complexity under martial law

Table 3.5 Average indicators of latent periods of visual-motor reactions of varying degrees of complexity in healthy people with post-COVID syndrome

Latent periods (M ± m, ms)	Examined groups	
	Healthy	Post-COVID syndrome
LPSVMR	230.4 ± 9.1	299.1 ± 6.4*
$LPRC_{1–3}$	350.9 ± 10.8	375.2 ± 8.1
$LPRC_{2–3}$	426.6 ± 8.7	455.7 ± 7.3*

*Note: * – significance of differences $p \leq 0.05$ between indicators of healthy people and people with post-COVID syndrome*

Such results may be associated with the existence of residual changes in the walls of blood vessels, disturbances in reverberation processes in neural networks, the development of hypoxic phenomena in the brain tissue, the predominance of inhibitory processes in the cortex, etc.

3.5 FEATURES OF THE FUNCTIONING OF THE NERVOUS SYSTEM IN PEOPLE WITH DIFFERENT LEVELS OF BASIC NERVOUS PROCESSES

According to the tasks set in the work, typological combinations of the main nervous processes were studied. In the presented material, in order to reduce the volume and simplify the presentation of information, the results that illuminate the individual typological properties of HNA are presented only in terms of the functional mobility of nervous processes, as the most scientifically substantiated and studied.

Given that the study of the manifestation of individual typological features in mental activity is still relevant, a study of the neurodynamic properties of human HNA was carried out. Neurodynamic indicators were established (shown on the example of university students) obtained during the processing of information of different modality (**Table 3.6**).

Table 3.6 Neurodynamic parameters of the subjects during the processing of information of different modality

Statistical indicators	Neurodynamic properties		
	FMNP, irr/min	SNP, % of errors	BNP, ms
Visual modality			
max	140	28.5	26.4
min	70	10.3	11.8
X ± m	100.2 ± 3.4	19.1 ± 1.2	19.7 ± 1.3
Auditory modality			
max	110	38.7	–
min	50	15.4	–
X ± m	79.6 ± 1.5	26.8 ± 1.3	–

The distribution of subjects according to the FMNP level using the three-sigma method made it possible to identify the features of sensorimotor reactivity in individuals with its different gradations (**Table 3.7**).

Table 3.7 Sensorimotor parameters of subjects with different FMNP levels during processing of information of different modality (median, upper and lower quartiles)

Tested indicators	Level of functional mobility of nervous processes		
	high, $n = 38$	medium, $n = 97$	low, $n = 26$
LPSVMR / LPSAMR, ms	182.7 (241.4; 178.9) / 160.1 (180.2; 147.6)	211.4 (234.9; 234.6) / 181.0 (225.1; 154.0)	225.7 (252.1; 215.5) / 188.7 (224.1; 174.1)
$LPSVMR_{1-3}$ / $LPSAMR_{1-3}$, ms	322.1 (370.2; 336.2) / 300.9 (323.9; 286.8)	369.1 (382.2; 347.1) / 329.1 (366.4; 321.9)^	377.2 (387.4; 352.6)# / 374.2 (378.5; 346.1)#
$LPSVMR_{2-3}$ / $LPSAMR_{2-3}$, ms	362.5 (389.2; 353.6)+ / 383.2 (401.0; 367.3)+	414.1 (468.3; 406.9)^ / 434.3 (458.4; 417.5)^	462.7 (489.1; 447.5)## / 482.1 (500.3; 467.6)##
CPAI / CPVI	173.2 (198.4; 167.9) / 225.2 (258.3; 211.5)	202.8 (236.2; 192.3) / 254.6 (287.1; 223.3)	237.6 (267.1; 211.7)## / 292.9 (337.8; 274.6)##

Notes: + – significance of differences in differences $p < 0.05$ between the indices of subjects with high and medium; # – significance of differences $p < 0.05$; ## – $p < 0.01$ between the indices of subjects with high and low; ^ – with medium and low levels of FMNP

It can be seen from the table that subjects with high and medium FMNP differed in a shorter time of LPSVMR and $LPRC_{1-3}$ compared to its low gradation, although not significantly ($p > 0.05$). Similar results were established when comparing the results of individuals with high and medium levels of FMNP with lower latency in favor of the former ($p > 0.05$). At the same time, the values of $LPRC_{1-3}$ in subjects with low FMNP were probably higher than in those with high levels ($p < 0.05$).

The study of the results of complex sensorimotor activity revealed its significantly lower quantitative values in subjects with high and medium FMNP compared with those with low gradation ($p < 0.05$–0.01). The lowest $LPRC_{2-3}$ were recorded in individuals with high FMNP ($p < 0.05$).

Similar differences were established between the parameters of subjects with different FMNP recorded during the processing of auditory modality information. Except for the fact that the difference between the RC_{1-3} indicators in favor of large latencies in individuals with low FMNP was also established between individuals with its low and medium gradations ($p < 0.05$). This probably indicated an increase in the difficulties of information processing for these subjects.

It is known that the central processing of visual and auditory information (CPVI, CPAI) reflects the speed and quality of the current analytical and synthetic activity of the cerebral cortex and other brain structures, and each specific complex sensorimotor act in the cerebral cortex and subcortex is a consequence of the functioning of departmental spatially excitatory and inhibitory neurons, which is manifested in the individual characteristics of the HNA of the subjects [14].

Comparison of the characteristics of the CPI of visual and auditory modality in subjects with different gradations of FMNP revealed the existence of differences between them. Thus, the time of CPAI, as well as CPVI in individuals with low FMNP, differed significantly in higher values com-

pared to those in subjects with a high level of it ($p < 0.01$). An inverse relationship was established between the number of processed stimuli of both modalities and CPI ($p < 0.05$).

Probably, the faster the processing and differentiation of information took place in the higher parts of the CNS being examined, the greater the number of stimuli they could process. This once again confirms the leading role of the main nervous processes in the functional system to ensure the integrative activity of the brain.

From the point of view of the importance of taking into account scientific results in diagnostics and treatment, it was important to investigate how information is processed by the "deaf brain", because the morphological and functional consequences of hearing defects (congenital and acquired) cause degenerative changes in the receptor hair cells of the organ of Corti, subcortical and cortical auditory centers of the brain and not only [15]. The analysis of quantitative and qualitative indicators of information processing in healthy and deaf people and their comparison made it possible to confirm that subjects with auditory function deprivation achieve a less effective result in 5 minutes of work on the selection and differentiation of stimuli than subjects with normal hearing ($p < 0.05$) (**Table 3.8**).

Table 3.8 Information processing characteristics of people with different levels of auditory function in the "feedback" mode (M ± m)

Tested indicators	Examined groups	
	Healthy	Deaf
Number of processed stimuli	737.8 ± 39.1	612.2 ± 27.8**
Number of false reactions, %	46.8 ± 4.5	66.2 ± 5.3*
Minimum exposure time, ms	31.3 ± 5.4	48.3 ± 3.5*
Time to reach the minimum exposure, ms	117.9 ± 6.2	268.2 ± 4.5**
Speed of central information processing (CPVI), ms	197.9 ± 7.6	247.8 ± 6.3*

*Notes: * – reliability of differences $p < 0.0$; ** – $p < 0.01$ between indicators of healthy and deaf subjects*

This was confirmed by the probably longer time to reach the minimum exposure of the visual stimulus, its minimum exposure compared to the results of healthy individuals ($p < 0.05$–0.01). The CPI indicators of the deaf subjects showed higher values compared to the subjects with normal hearing ($p < 0.05$). This situation indicated a low rate of establishment of intersynaptic contacts in the CNS and reverberation of neuronal impulses.

Thus, it was found that auditory deprivation has a significant impact on the processing of visual information by the brain. The study of neurodynamic parameters obtained during the selection and differentiation of visual stimuli revealed a significantly lower brain performance and insufficient lability of the visual analyzer system in people with congenital deafness.

3.6 PSYCHOPHYSIOLOGY IN THE SERVICE OF HEALTH: PRACTICAL RECOMMENDATIONS, THE IMPORTANCE OF USING THE RESULTS OF THE STUDY OF THE NERVOUS SYSTEM IN MEDICINE

Thanks to the functioning of the nervous system, many current physiological processes are integrated into a functional system that works to adequately adapt the body to changing living conditions. The results of our study of the main nervous processes in terms of the parameters of sensorimotor and neurodynamic functions suggest that the diagnosis and monitoring of the state of the nervous system should be based on genetically determined indicators that reflect the dynamic stability of body functions. These include characteristics of the properties of the main nervous processes, sensorimotor reactions, analyzer systems, which objectively reflect the level of conditioned reflex activity and at the same time allow revealing the state of the analytical and synthetic activity of the brain, memory subsystems, attention, and emotions.

Since FMNP is one of the leading properties of the main nervous processes, it is related to the provision of a certain speed (why exactly there are interindividual differences in the choice and discrimination of stimuli) of the establishment of temporary connections, the formation of intersystem interactions in the CNS.

Persons with low FMNP, in contrast to those who are characterized by its high gradation, can be considered as those in whose brain neurons there are less favorable properties for the formation of axons, synaptic terminals, and more. Their synapses have moderate functional characteristics, are distinguished by lower levels of metabolic and trophic processes in the "neuron-glia" format, slower adaptive and regulatory properties of cerebral cells. This should be taken into account in the programs of preventive, curative, rehabilitation health-preserving design.

Among the practical recommendations, first of all, let's focus on the fact that during the diagnosis, monitoring and treatment of neurogenic diseases, optimization of psychophysiological states, it should be taken into account that human life is based on constant mutual influences of many systems of the whole organism in the conditions of the leading role of the higher parts of the CNS, in particular, the cerebral cortex. Regulatory adaptive mechanisms have individual and typological features that are manifested in the characteristics of the main nervous processes, mental performance, sensorimotor reactivity and are decisive for health and well-being.

The study of the functioning of the brain during mental stress, performed on the computer diagnostic complex "Diagnost-1M" allows to obtain objective information about the individual sensorimotor and neurodynamic characteristics of a person, which should be taken into account to build an individual patient's health trajectory, which will help assess the risk of neurodegenerative disorders, vegetodistonic and psycho-emotional shifts.

Based on the characteristics of the functioning of the brain, its relationship with the properties of psychomotor, emotional components of the personality, as well as its integrating effect on the body as a whole, it is desirable to focus on the current level of various parts of the nervous system in order to optimize the current functional state, predict and manage it, especially in people with

shortcomings of analyzer systems. This will make it possible to more confidently predict the first bells at the preclinical stages of the development of pathologies, to apply corrective preventive programs for the prevention of the development of deafness, failures of cognitive processes, and leveling the occurrence of parallel sensory anomalies.

It is proposed to use the psychophysiological scales developed by us on a sufficient number of subjects to identify the degree of latency of sensorimotor reactivity, neurodynamic functions of different categories of the population (**Tables 3.9 – 3.12**).

Table 3.9 Differential scales for evaluating the level of latent periods of sensorimotor reactions of varying degrees of complexity in individuals with normal and deprivation of auditory function

Information processing level	Latent period of visual motor reaction (ms)					
	Healthy			Deaf		
	LPSVMR	$LPRC_{1-3}$	$LPRC_{2-3}$	LPSVMR	$LPRC_{1-3}$	$LPRC_{2-3}$
High	≤ 183	≤ 282	≤ 337	≤ 213	≤ 321	≤ 412
Above medium	180–227	283–325	338–394	242–212	354–322	436–413
Medium	228–294	326–399	395–464	267–243	381–355	452–437
Below the medium	395–332	400–434	465–502	292–268	410–382	474–453
Low	≥ 333	≥ 435	≥ 503	≤ 293	≥ 411	≥ 475

Table 3.10 Scales for evaluating the level of speed, quality and quantity of visual information processing of varying complexity in persons with normal and deprivation of auditory function

Information processing level	Information processing speed		Quality and quantity of information processing	
	Feedback (s)		Feedback (number of signals)	
	Healthy	Deaf	Healthy	Deaf
High	≤ 54.2	≤ 61.3	≥ 851.2	≥ 743.4
Above medium	54.5–61.4	66.9–62.4	785.3–850.2	675.8–742.8
Medium	61.5–69.9	71.6–67.0	677.2–785.2	568.7–675.5
Below the medium	70.1–76.1	76.9–71.7	631.8–677.3	520.2–567.9
Low	≥ 76.2	≥ 77.0	≤ 630.9	≤ 519.5

Table 3.11 Differential scales for evaluating the level of individual neurodynamic and sensorimotor properties of a human mobile operator

№	Indicators	The level of tested property (visual/auditory modality)				
		High	Above medium	medium	Below the medium	low
	Scores	10	8	6	4	2
1	FMNP, c	≤ 54.1 / 66.3	53.9–61.5 / 66.2–70.9	60.8–69.1 / 70.8–75.2	69.2–76.3 / 75.5–80.0	≥ 76.4 / 80.1
2	SVMR/SAMR, ms	≤ 181.5 / 220.4	182.4–226.1 / 220.4–270.7	226.3–292.1 / 200.3–271.4	394.4–330.3 / 374.4–418.1	≥ 332.6 / 426.0
3	RC_{1-3}, ms	≤ 280.3 / 300.0	280.6–322.4 / 300.6–340.1	323.2–398.1 / 340.6–411.0	398.5–432.5 / 411.4–460.3	≥ 433.5 / 471.5
4	RC_{2-3}, ms	≤ 334.5 / 350.0	335–390 / 350.1–420.1	390.1–462.4 / 420.5–490.5	463.3–500.0 / 491.4–560.5	≥ 501.1 / 561.6
5	SNP, frames	≥ 851.5 / 735.8	784.4–848.5 / 700.2–684.5	677.3–783.3 / 680.5–630.4	631.3–676.7 / 633.9–605.2	≤ 630.1 / 604.9
6	BNP, ms	≥ 13.5 / 15.4	19–15 / 24.5–21.4	25.5–20.3 / 29.4–26.5	33.4–28.2 / 34.5–30.2	≤ 34.5 / 35.5

Table 3.12 Differential scales for evaluating the level of individual neurodynamic and sensorimotor functions of students during information processing

№	Indicators	The level of individual neurodynamic and sensorimotor functions				
		I	II	III	IV	V
	Scores	10	8	6	4	2
Visual modality						
1	FMNP, s	≤ 55.9	56.0–61.0	61.1–66.0	66.1–71.0	≥ 71.1
2	SVMR, ms	≤ 207.5	219.3–260.2	208.9–260.4	261.5–310.5	≥ 325.5
3	RC2–3, ms	≤ 360.6	360.5–410.1	410.2–480.5	499.4–570.5	≥ 571.5
4	SNP, frames	≥ 761.4	760.3–741.4	741.5–690.5	690.1–609.0	≤ 611.0
5	BNP, ms	≤ 15.6	16.0–21.0	21.5–30.4	30.5–36.5	≥ 37.4
Auditory modality						
1	FMNP, s	≤ 60.5	60.6–68.1	68.5–71.1	71.0–78.1	≥ 78.5
2	SAMR, ms	≤ 249.4	250.5–279.4	230.3–289.5	291.4–355.5	≥ 370.6
3	RC2–3, ms	≤ 418.2	420.4–449.5	430.1–520.5	524.1–593.2	≥ 595.4
4	SNP, sygnals	≥ 701.1	670.4–651.2	650.5–610.6	609.9–573.5	≤ 512.5
5	BNP, ms	≤ 15.5	15.9–22.3	22.4–30.0	29.6–35.8	≥ 36.6

The evaluation scales of neurodynamic and sensorimotor functions that we propose for use in the medical field can be used to optimize the diagnosis and increase the effectiveness of monitoring neurological morbidity in various segments of the population, including people with special needs.

Taking into account the peculiarities of neurodynamic and sensorimotor functions, they will also be useful in the physiology of labor, the professional selection of healthy people and the individualization of educational trajectories in higher education.

CONCLUSIONS

1. Indicators of the main nervous processes and typological combinations are important characteristics of the functional state of the organism.

2. Parameters of sensorimotor reactions of varying degrees of complexity and functional mobility of nervous processes can be used in the diagnosis and monitoring of the nervous system of young people.

3. Evaluation scales of neurodynamic and sensorimotor functions can serve as an objective basis for optimizing diagnostics and improving the effectiveness of monitoring neurological morbidity, including in people with special needs.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this paper.

REFERENCES

1. Andriuchenko, T., Vakulenko, O., Volkov, V., Dziuba, N., Koliada, V., Komarova, N. et al. (2019). Formuvannia zdorovoho sposobu zhyttia molodi. Navchalno-metodychni rekomendatsii. Kyiv: Blank-Pres, 120.
2. Markovych, I. F. (2016). Medychno-sotsiolohichne doslidzhennia faktoriv sposobu zhyttia, profesiinoi diialnosti ta osobystoho vidnoshennia do medychnoi dopomohy viiskovosluzhbovtsiv. Visnyk sotsialnoi hihiieny ta orhanizatsii okhorony zdorov'ia Ukrainy, 4, 57–65.
3. Makarenko, M. V., Kyrylenko, L. P. (2015). Rol indyvidualno-typolohichnykh vlastyvostei vyshchoi nervovoi diialnosti liudyny v uspishnosti navchannia ta nadiinosti profesiinoi diialnosti. Fiziolohichnyi zhurnal, 3, 118–126.

4. Prashko, Ya., Mozhny, P., Shlepetsky, M. (2017). Kohnityvno-bikhevioralna terapiia psykhichnykh rozladiv. Praha, 1072.
5. Chagas, D. V., Batista, L. A. (2017). Comparison of Health Outcomes Among Children with Different Levels of Motor Competence. Human Movement, 18 (2), 56–61. doi: https://doi.org/10.1515/humo-2017-0018
6. Makarenko, M. V. (2006). Osnovy profesiinoho vidboru viiskovykh spetsialistiv ta metodyky vyvchennia indyvidualnykh psykhofiziolohichnykh vidminnostei mizh liudmy. Kyiv: In-t fiziolohii im. O.O. Bohomoltsia, 395.
7. Makarenko, M. V., Lyzohub, V. S., Halka, M. S., Yukhymenko, L. I., Khomenko, S. M. (2011). Pat. No. 96496 UA. Sposib psykhofiziolohichnoi otsinky funktsionalnoho stanu slukhovoho analizatora. MPK: A 61V5/16. No. a 2010 02225; declareted: 01.03.2010; published: 10.11.2011, Bul. No. 21.
8. Makarenko, M. V., Lyzohub, V. S., Yukhymenko, L. I., Khomenko, S. M. (2014). Pat. No. 106028 UA. Sposib vyznachennia shvydkosti tsentralnoi obrobky informatsii vyshchymy viddilamy nervovoi systemy. MPK: A 61V5/16. No. a 2013 12529; declareted: 25.10.2013; published: 10.07.2014, Bul. No. 13.
9. Myshchenko, T. S. (2017). Epidemiology of cerebrovascular diseases and organization of medical care for patients with stroke in Ukraine. Ukrainskyi visnyk psykhonevrolohii, 25 (1 (90)), 22–24.
10. Sekeon, S. A., Warouw, F., Mantjoro, E. (2020). Sleep quality and cognitive dysfunction among acute stroke patients from coastal areas of north sulawesi, indonesia. Journal of Clinical and Diagnostic Research, 14 (1), 6–8. doi: https://doi.org/10.7860/jcdr/2020/41322.13414
11. Lockwood, C. (2017). Cognitive rehabilitation for memory deficits after stroke: A Cochrane review summary. International Journal of Nursing Studies, 76, 131–132. doi: https://doi.org/10.1016/j.ijnurstu.2017.02.011
12. Kokun, O. M., Pishko, I. O., Lozinska, N. S., Kopanytsia, O. V., Malkhazov, O. R. (2011). Zbirnyk metodyk dlia diahnostyky psykholohichnoi hotovnosti viiskovosluzhbovtsiv viiskovoi sluzhby za kontraktom do diialnosti u skladi myrotvorchykh pidrozdiliv. Kyiv: NDTs HP ZSU, 281.
13. Yukhymenko, L. I. (2022). Manifestations of the post-COVID Syndrome in the functional Characteristics of the human brain. The role of medical science in implementing innovative medical technologies in the eu countries and Ukraine, 264–277. doi: https://doi.org/10.30525/978-9934-26-240-1-14
14. Yukhimenko, L. (2016). Eletroencephalographic correlates of the speed (time) of the central processing of information by the higher parts of brain in humans with the different individual-typological features of the higher nervous activity. EUREKA: Life Sciences, 2, 51–56. doi: https://doi.org/10.21303/2504-5695.2016.00068
15. Yukhymenko, L. I., Makarchuk, M. Yu., Lizogub, V. S. (2019). Specificities of Cortical Processing of Visual Information in Subjects with Hearing Deprivation (Congenital Deafness). Neurophysiology, 51 (5), 344–352. doi: https://doi.org/10.1007/s11062-020-09828-7

DOI: 10.15587/978-617-7319-65-7.CH4

Dmytro Maltsev

CHAPTER 4

FOLATE-CENTRIC CONCEPT OF PATHOGENESIS AND GBINC PERSONALIZED MULTIDISCIPLINARY APPROACH TO THE CLINICAL MANAGEMENT OF CHILDREN WITH NEUROPSYCHIATRIC SYNDROMES

ABSTRACT

Solving the problem of childhood neuropsychiatric diseases is a priority task of modern medicine. Recent scientific achievements in the field of genetics, molecular biology and immunology, demonstrating biochemical and immune-dependent pathways for the formation of human neuropsychiatric disorders, shed light on the mechanisms of brain damage in children with ASD, which allows to look with restrained optimism at the prospect of overcoming this severe psychiatric pathology in the near future through the implementation of genetic, biochemical and immunodiagnostic approaches, as well as metabolic and immunotherapeutic interventions with neuroprotective effects. The folate-centric concept of polygenic inheritance of a tendency to develop neuropsychiatric syndromes in children with multisystem damage to the body has been established. Biochemical and immunodependent (infectious, autoimmune, immunoinflammatory and allergic) pathways for the formation of microbe-induced autoimmune inflammatory encephalopathy with neuropsychiatric clinical manifestations are discussed in the context of the folate-centric concept. Taking into account the new data, two personalized multidisciplinary approaches to the management of children with ASD and other neuropsychiatric syndromes are proposed James Jeffrey Bradstreet et al. first approach 2010 is based on an empirical analysis of a large group of laboratory biomarkers, the relevance of which has been demonstrated in clinical trials, and subsequent targeted correction of the identified disorders that these biomarkers describe (the so-called biomarker-guided interventions). Richard E. Frye in 2022 developed a multidisciplinary personalized approach called Bas-BISTOR (collect Baseline data, search by symptoms, measure Biomarkers, Select Treatment, Observe for Response), which systematizes and stratifies diagnostic and therapeutic interventions based on diagnostic and therapeutic biomarker-based interventions. In order to improve existing recommendations regarding specific subtypes of neuropsychiatric syndromes in children, this article puts forward an improved personalized multidisciplinary approach to the clinical management of patients with ASD and neuropsychiatric manifestations associated with genetic folate cycle deficiency.

There is reason to believe that the successful testing in clinical practice of evidence-based personalized multidisciplinary diagnostic and treatment strategies will make it possible in the near future to make a breakthrough in the clinical management of children with severe mental disorders, which will provide not only the possibility of recovery from a prognostically unfavorable and yet incurable neuropsychiatric disorder and will help to stop the large-scale threatening epidemic of neuropsychiatric syndromes in the modern child population.

KEYWORDS

Autism spectrum disorders, attention deficit hyperactivity disorder, obsessive-compulsive syndrome, immunodiagnostics, biochemical correction, immunotherapy.

Solving the problem of childhood neuropsychiatric diseases is a priority task of modern medicine. The greatest attention among the various pathologies of the mental sphere is riveted to the study of the etiology and pathogenesis of autism spectrum disorders (ASD) in children. ASD is a group of heterogeneous neuropsychiatric disorders that are phenotypically variable and clinically characterized by a lack of social interactions, impaired communication, and a narrowing of interests.

According to a systematic review by Heather K. Hughes, Emily M. Ko et al. (2018) in the United States for the period from 1972 to 2014, the frequency of reported cases of ASD increased from 1 case per 10 thousand people (0.01 %) to 1 case per 57 children (2 %), that is, 200 times, which is impossible can only be explained by the improvement in the quality of detection of this pathology by modern medicine [1]. According to the latest data from the Center for Disease Control and Prevention (USA, 2020), the frequency of ASD in the modern pediatric population has reached 1 case per 44 children, which indicates the continuation of a threatening trend towards a gradual increase in the prevalence of this neuropsychiatric pathology among people [2].

It is believed that ASD not only causes social maladjustment of the child due to communication disorders, but is also accompanied by a variety of comorbid pathologies, including obsessive-compulsive syndrome, attention deficit hyperactivity disorder, cognitive impairment and other forms of psychiatric syndromes, which aggravates the severity of the patient's clinical condition life both the most affected child and all members of its family.

The results of a recent systematic review and meta-analysis of Ferrán Catalá-López et al. – mortality from unnatural causes in children with ASD compared with healthy peers [3]. The results of the latest systematic review and meta-analysis of Laura O'Halloran et al., including data from 47 controlled studies, indicate suicidal ideation in children with ASD at least 25.2 %, suicide attempts – in 8.3 %, and completed suicidal acts – in 0.2 % of cases [4].

The results of a systematic review and meta-analysis by Zhen Zheng et al. covering data from epidemiological studies involving 1,950,113 participants, indicate a 3.55-fold increase in the inci-

dence of schizophrenia in children with ASD compared with the general population, and according to some of the studies analyzed in this meta-analysis, about 50 % of children with an initial diagnosis of ASD subsequently develop manifestations of schizophrenia [5].

However, the FDA has not yet registered a single drug that modified the course of the disease and/or ensured the recovery of the patient. As Richard E. Frye notes, specialized educational programs and behavioral therapy, which are traditionally used for children with ASD to at least partially adapt them to social conditions, have not passed clinical trials appropriate in number, volume and design in accordance with the requirements of evidence-based medicine, therefore their effectiveness has not yet been adequately confirmed [6]. The economic burden that creates ASD due to intensive and long-term educational, social and rehabilitation programs for sick children in the United States exceeds 7 trillion dollars a year, but the results obtained in many cases remain unsatisfactory [7].

Nevertheless, recent scientific achievements in the field of genetics, molecular biology and immunology, demonstrating biochemical and immunodependent pathways for the formation of human neuropsychiatric disorders, shed light on the mechanisms of brain damage in children with ASD, which allows to look with restrained optimism at the prospect of overcoming this difficult psychiatry pathology in the foreseeable future through the introduction of genetic, biochemical and immunodiagnostic approaches, as well as metabolic and immunotherapeutic interventions with neuroprotective effects.

4.1 GENETIC FACTORS

Accumulating scientific evidence suggests that genetic factors are key in the development of ASD and other neuropsychiatric disorders in children, but the penetrance of pathological genes varies depending on the influence of environmental factors, as shown, in particular, by the results of a systematic review and meta-analysis of twin studies covering clinical trial data of 6,413 pairs of mono- and dizygotic twins [8].

Only 4 % of children with ASD have classical genetic diseases, identified as separate nosological units, in which only one genetic disorder can fully explain the clinical phenotype of the disease (fragile X syndrome, tuberous sclerosis complex, Rett syndrome, etc.). [9]. In the vast majority of the studied cases of ASD, a polygenic nature of inheritance has been established with the simultaneous involvement of many genes encoding various proteins and controlling various physiological processes in the human body.

In a study of genetic associations Ioanna Mpoulimari and Elias Zintzaras, which studied 57 candidate genes and 128 associated polymorphisms according to 159 articles from the PubMed electronic scientometric database, showed a statistically significant association of ASD phenotype with genetic pathology (ADA), bone marrow stromal cell antigen-1 (CD157/BST1), dopamine receptor D1 (DRD1), engrailed homolog 2 (EN2), met proto-oncogene (MET), methy-

lenetetrahydrofolate reductase (MTHFR), solute carrier family 6 member 4 (SLC6A4), synaptosomal-associated protein, 25kDa (SNAP-25) and vitamin D receptor (VDR). In the allele contrast model of cases against healthy controls, a probable association of the ASD phenotype and nucleotide substitutions in the genes adrenoceptor alpha 1B (ADRA1B), acetyl serotonin O methyltransferase (ASMT), complement component 4B (C4B), dopamine receptor D3 (DRD3), met proto-oncogene (MET), neuroligin 4, X-linked (NLGN4), neurexin 1 (NRXN1), oxytocin receptor (OXTR), Serine/Threonine-Protein Kinase PFTAIRE-1 (PFTK1), Reelin (RELN) and Ras-like without CAAX 2 (RIT2) [10].

Given this, the genetic pathology associated with ASD can be combined into 3 main groups – metabolic, immunological and neurological disorders, including metabolic disorders, the functioning of the immune system, as well as neurogenesis, synaptic plasticity and the exchange of neurotransmitters in the CNS.

It is important to elucidate the role and place of each of the many ASD-associated genetic disorders contained in the child's genome in the development of neuropsychiatric disorders. The results of at least 5 systematic reviews and meta-analyses of RCTs published from 2013 to 2021, covering data from 8 to 25 trials, indicate an association of MTHFR C677T and the ASD phenotype in children [11–15]. The data of 2 meta-analyses of RCTs confirm the association of ASD manifestations with MTHFR A1298C [11, 15], and one meta-analysis of RCTs confirms the relationship of MTRR A66G [12].

Results of a controlled clinical study of Rosa Haghiri et al. (2016) with the participation of 103 children with ASD and 130 healthy peers of the control group showed a close association of MTR A2756G and ASD in children, demonstrating a 1.6-fold increase in the risk of developing ASD in MTR A2756G carriers [16]. In addition, the results of at least 4 systematic reviews and meta-analyses of RCTs indicate an association of the phenomenon of hyperhomocysteinemia, a specific disorder of one-carboxylic metabolism in MTHFR C677T and similar genetic disorders, with the ASD phenotype in children [12, 17–19].

These data allow the advanced folate-centric concept of the development of ASD and other associated neuropsychiatric syndromes in children with polygenic inheritance of the disease [20]. Wit is possible to agree with the position of Stephan Moll and Elizabeth A. Varga consider nucleotide substitutions in the folate cycle genes not as polymorphisms, but as pathogenic mutations, given the severe clinical consequences that may be associated with their presence in the patient's genome [21].

The folic acid cycle functions in close association with other biochemical cycles and pathways that, if genetically impaired, can lead to similar clinical outcomes. S. Jill James et al. in a controlled clinical study involving 360 children with ASD and 250 healthy controls studied mutations / polymorphisms in the folate cycle and functionally related metabolic pathways, establishing the association of ASD and damage to the genes reduced folate carrier (RFC 80G > A), transcobalamin II (TCN2 776G > C), catechol-O-methyltransferase (COMT 472G > A), methylenetetrahydrofolate reductase (MTHFR 677C > T and 1298A > C) та glutathione-S-transferase (GST M1) [22].

Genetic deficiency of folate cycle (GDFC) is believed to lead to the development of ASD in at least three ways – biochemically due to the induction of hyperhomocysteinemia and other associated manifestations of oxidative stress, genoregulatory due to the influence on the expression of many pathogenic and normal genes due to a violation of universal DNA methylation and epigenetic due to the methylation of proteins and lipids, which affects their functional activity. It has been established that the attachment of methyl groups to a pathological gene reduces its expression, and vice versa, demethylation of healthy genes contributes to the effective implementation of normal metabolic processes in the human body. There are cases of functional states of hypomethylation with a predominant lesion of MTHFR, when there is multiple activation of the expression of undesirable genes that should normally be repressed, and hypermethylation with a predominant lesion of MTRR and MTR, when a number of normal functionally important genes are erroneously disabled, without the participation of key biochemical processes in human body [20].

It is possible to talk about the biochemical-genoregulatory dualism of the impact of GDFC on the human body, and genoregulatory disorders may be stronger than direct GDFC-induced biochemical effects in many children with ASD.

So, Fumie Horiuchi et al. in the study of global gene expression in the blood of children with ASD, which included the analysis of 11,617 genes, 117 abnormally hyperactivated and 83 pathologically suppressed genes of innate and adaptive immunity were identified, which created an aberrant pattern of the functioning of the immune system of immunoresistance and immune dysregulation, which are important in the pathogenesis of ASD [23].

GDFC-induced biochemical disorders probably create an initial pathological stimulus, which is subsequently repeatedly transformed under the influence of other genes, the expression of which turns out to be pathologically altered due to a violation of their methylation, as well as due to multiple epigenetic disorders. These modulating effects from other genes can be divided according to the localization of the signal from the gene in the probable chain of pathological events during the development of the disease proximal, medial and distal.

Additional mutations in biochemical pathways adjacent to the folate cycle (methionine cycle, thiol transsulfuration pathway, purine metabolism, biopterin-neopterin pathway, mitochondrial dysfunction, etc.) [24–26] create proximal or biochemical modulating effects, induced metabolic disorders immediately after their onset [27].

The complex of biochemical disorders formed at this stage of pathogenesis forms the so-called biochemical pathway of CNS damage. The relevance of identifying a separate biochemical pathway of brain damage in children with ASD is confirmed by the proven clinical efficacy of a number of specific therapeutic interventions aimed at compensating for specific biochemical disorders [28, 29]. In addition to neurotoxicity, GDFC-induced biochemical disorders have an immunotoxic effect, leading to the development of immunodeficiency and associated immune dysregulation, but the final state of the immune system is affected by mutations in genes encoding certain immune factors (the so-called immunoresistance genes, for example, ADA genes,

CD157/BST1, C4B) and mutations in immunoregulatory genes that contribute to the development of a certain form of immune-dependent pathology in immunodeficiency conditions [22]. These genetically mediated effects can be considered medial or immunogenic modulation. They are important in the formation of immune-dependent pathways of CNS damage in children with ASD and other neuropsychiatric syndromes. There are four such pathways – infectious, autoimmune, allergic and inflammatory.

If only mutations in the immunoresistance genes are sufficient to activate infectious factors, then immunodependent complications – autoimmune, allergic and inflammatory mechanisms of CNS damage – require the collaboration of at least 2 heterogeneous mutations for their development – one in the immunoresistance gene, which, for example, contributes to the activation of a certain micro- and second – in the immunoregulation gene, which contributes to the implementation of the trigger effect of this microorganism for the development of a certain, for example, autoimmune, immuno-dependent complication with neurotropic effects. An example is deletions in the genes of constant regions of immunoglobulins that contribute to the formation of deficiencies of various classes of immunoglobulins, subclasses of IgG and specific antibodies [30–32], which, in turn, among other consequences contribute to the development of chronic infection caused by the beta-group A [33]. If these genetic disorders are combined with –308 G/A polymorphism in the gene of tumor necrosis factor alpha, which regulates the intensity of immune inflammation, then conditions are created for the disruption of immune tolerance to the autoantigens of the subcortical ganglic ganglions of the cerebral hemispheres induced by rheumatogenic streptococcusand the formation of the acronym PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections) [34].

Associated biochemical and immune-dependent pathological mechanisms lead to CNS damage, however, the final severity of brain damage is also determined by the influence of additional mutations in genes that regulate neurogenesis, synaptic plasticity, and neurotransmitter metabolism (distal, or neurogenic modulation, for example, the NLGN SNAP-25, DRD1 genes) [22].

Thus, it is possible to talk about an individual pathological system of genes that form the picture of ASD and other neuropsychiatric syndromes in each specific case, since the affected genes do not function in isolation, but, on the contrary, interact with each other in different ways at different stages of the pathogenesis of the disease, significantly transforming the initial pathological signal When analyzing such individual pathological gene systems that determine the polygenic nature of ASD inheritance, it should be taken into account that they lead to a qualitatively greater clinical result than the simple sum of their components. This substantiates the expediency of a comprehensive rather than separate analysis of genetic models in patients with ASD. For clinical practice, it is important to create specialized diagnostic genetic panels that allow routine determination of individual pathological genetic systems in children with neuropsychiatric syndromes according to the current evidence base.

For the convenience of clinical analysis, such genetic systems can be visually represented as a genetic tree, as shown in **Fig. 4.1**.

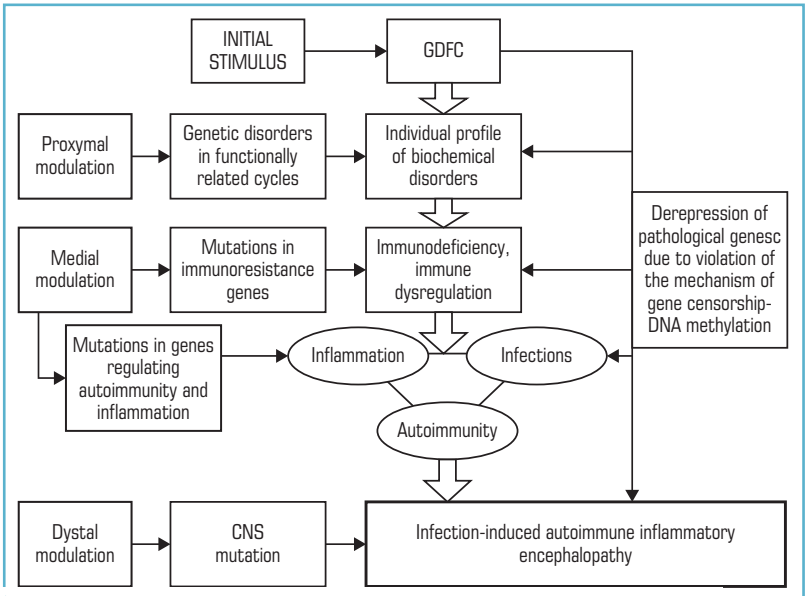


Fig. 4.1 The structure of individual pathological gene systems in the development of ASD and other neuropsychiatric syndromes in children in the context of the folate-centric concept of disease pathogenesis

4.2 BIOCHEMICAL DISORDERS

The functioning of the pathological system of genes leads to the formation of multiple metabolic anomalies related to both the central nervous system in particular and the child's body as a whole [35, 36]. The most vulnerable are the brain, immune system, and digestive organs, which constitute a kind of pathological organ triad in children with ASD [1, 37]. The clinical picture of the disease is largely due to the defeat of this particular organ triad, but, of course, is not limited to it.

In general, diverse biochemical disorders in the folic acid cycle and functionally related metabolic pathways (methionine cycle, thiol transsulfuration pathway, purine metabolism, biopterin-neopterin pathway, mitochondrial dysfunction, etc.) [24–26, 38] in the context of the folate-centric concept of pathogenesis, the disease can be characterized as a state of persistent oxidative stress [17, 18] (**Fig. 4.2**).

Results of a meta-analysis and systematic review of RCTs prepared by Alessandra Frustaci et al. in 2012 show signs of oxidative stress in children with ASD. A decrease in the serum concentration of the antioxidant compounds glutathione (27 %), glutathione peroxidase (18 %), methionine (13 %), and cysteine (14 %) and an abnormal increase in the concentration of oxidized glu-

tathione in the blood serum (by 45 % of the normal level) were established [18]. Results of a meta-analysis of RCTs by Lei Chen et al. in 2021, covering 87 clinical trials involving 4928 children with ASD and 4181 healthy peers of the control groups, demonstrate that in children with ASD, compared with healthy individuals, the serum concentration of prooxidant agents such as oxylen glutathione (GSSG), homocysteine, S-adenosylhomocysteine, nitric oxide and copper, and, conversely, the serum concentration of known antioxidants glutathione (GSH), total glutathione (tGSH), methionine, cysteine, vitamins B9, D, B12, E and calcium is probably reduced, as well as a reduced level of such laboratory parameters for assessing the antioxidant system of the human body as GSH/GSSG, tGSH/GSSG and S-adenosylmethionine/S-adenosylhomocysteine [17].

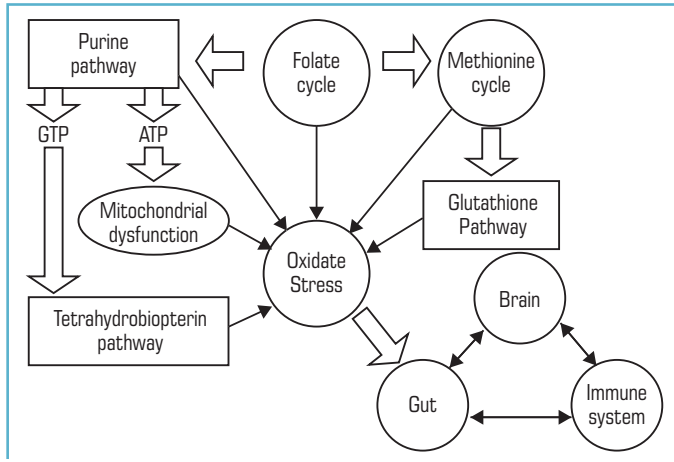


Fig. 4.2 Schematic diagram of the system of key functionally related biochemical cycles and pathways involved in the pathogenesis of neuropsychiatric diseases in children, according to the folate-centric concept

Data from RCT meta-analyses provide clinical practice with a number of informative laboratory biomarkers for assessing the individual pattern of biochemical disorders and associated oxidative stress. S. Jill James et al. in 2006, genetically induced metabolic endophenomena were identified in children with ASD, caused by damage to the folate cycle and functionally related metabolic pathways, leading to a state of oxidative stress in the child's body [22]. If to talk about a separate analysis of biochemical disorders in various metabolic pathways, then with a predominant lesion of the folate cycle, it is advisable to determine the serum concentration of 5-methyltetrahydrofolate, folic acid, folinic acid and tetrahydrofonite S, in the methioadenosylmethionine cycle. At the same time, the thiol system of transsulforation or the glutathione pathway is assessed by the concentration of glutathione, cysteine, cystathionine and choline in the blood serum, and 4-tetrahydrobiopterin metabolism – by the concentration of neopterin, monopterin, isoxanthopterin, biopterin, primapterin and pterin in the urine.

Genetically induced multiple metabolic disorders in children with neuropsychiatric syndromes form individual patterns of pathological biochemical disorders, or metabolic endophenotypes, for the evaluation of which in clinical practice it is necessary to develop specialized laboratory diagnostic panels for the analysis of specific disorders. Identification of an individual pattern of pathological biochemical disorders in each specific case is an important clinical task, since it allows choosing an individual program of biochemical correction to weaken the biochemical pathway of CNS damage, which can reduce neuropsychiatric manifestations. Thus, the results of a recent meta-analysis of controlled clinical trials prove the clinical efficacy of specific metabolic therapy with methylcobalamin at a dose of 64.5–75 mg/kg for the correction of specific biochemical disorders induced by GDFC and the associated reduction in the clinical manifestations of ASD in children [28]. The results of another systematic review and meta-analysis of RCTs indicate the clinical efficacy of long-term use of d,l-leucovorin at a dose of 0.5–1.0 to 6.0–9.0 mg/kg/day in cerebral folate deficiency caused by autoantibodies to folic acid receptors in the CNS in children with ASD [29]. Numerous results from controlled clinical trials have now been published that report the successful use of many other key metabolites for specific biochemical correction, including N-acetylcysteine, L-carnitine, and resveratrol. Key biochemical disorders and means of their correction in children with ASD are discussed in detail in a systematic review by Richard E. Frye and Daniel A. Rossignol [27]. Undoubtedly, the list of recommended means of biochemical correction in children with ASD will expand every year based on the results of new controlled clinical trials.

4.3 IMMUNOLOGICAL DISORDERS

By inducing biochemical, gene-regulatory and epigenetic disorders, GDFC and disorders in functionally related cycles damage the maturation and functioning of the child's immune system. As noted by Heather K. Hughes with singing. In a recent systematic review on the phenomenon of immune system dysfunction in children with ASD, in such cases, an aberrant cytokine profile, deviations in the absolute and relative number of immunocompetent cells and their subpopulations, signs of neuroinflammation, disorders of the system of adaptive and innate immunity, imbalance of classes and signs of autoimmunity [1]. As the results of some studies show, the depth of deficiency of immune factors correlates with the severity of clinical manifestations of neuropsychiatric disorders in children [30].

In children with neuropsychiatric syndromes, ambivalent disorders of the immune status are formed, including the simultaneous coexistence of deficiency/suppression of some immunity factors [39, 40] and excess/hyperactivation of others [41, 42], which for other reasons is associated with reciprocity between various components of the immune system, capable of self-regulation. The consequences of an imbalance in the immune status are the phenomenon of a decrease in immunoresistance due to the absence of certain immune factors that protect against infectious agents [43] and tumors [44], and the phenomenon of immune dysregulation with the development of immunoinflammatory, allergic and autoimmune reactions due to a violation of the endogenous

mechanisms of immune tolerance to a number of antigens [1]. In fact, it is about the immunemediated subtype of ASD in children, isolated by Christopher J. McDougle et al. in 2015 [45].

Multidirectional changes in the immune status were demonstrated in a recent controlled clinical study, which showed in children with ASD a decrease in the number of NK, NKT, CD8+ cytotoxic T-lymphocytes in the blood, serum concentrations of certain classes of immunoglobulins, IgG subclasses, and a decrease in the functional activity of myeloperoxide. circulating immune complexes, CD3+ and CD3+CD4+ T-lymphocytes, CD3-CD19+ B-cells, serum concentrations of IgE, IgM, IgA and IgG4 in a variable manner [46].

Due to the known variability of pathological changes in the immune status in different children with ASD, Milo Careaga et al. propose to isolate the so-called immune endophenotypes, which can lead to various immune-dependent complications and require various immunotherapeutic interventions for immunocorrection [47].

Currently, a specific form of primary immunodeficiency associated with GDFC has been isolated [48]. Clinically, immunodeficiency in children with ASD manifests itself as a pentad of syndromes, including infectious, allergic, immunoinflammatory, autoimmune, and oncological manifestations, which, according to the postulates of clinical immunology, are components of the phenotype of primary immunodeficiency (**Fig. 4.3**).

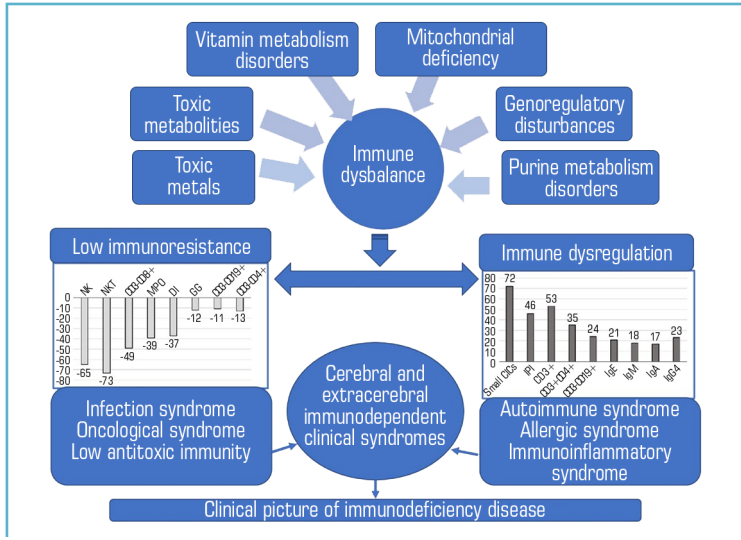


Fig. 4.3 Pathogenesis of a specific form of GDFC-induced immunodeficiency in children with neuropsychiatric syndromes and clinical consequences in the context of the folate-centric concept of disease pathogenesis

Note: DI – dysimmunoglobulinemia; GG – gypogammaglobulinemia; MPO – myeloperoxidase deficiency; CICs – circulating immune complexes; IPI – immunoregulatory index

Andrea A. Mauracher et al. in a systematic review covering the results of 186 scientific publications, identified a pattern of immune dysregulation characteristic of human primary immunodeficiencies, including autoimmunity (64 %), intestinal syndrome (38 %), lymphoproliferation (36 %) and allergy (34 % of cases) [49]. In patients with GDFC, the pattern of immune dysregulation characteristic of primary human immunodeficiencies is completely reproduced. The results of a recent large population-based singing study by Josef Isung et al. which studied the medical data of 14 million people in Sweden, indicate that children with primary immunodeficiencies have an increased risk of developing ASD by at least 3.2 times compared with peers who do not diagnosed with immune disease and show the close involvement of immune mechanisms in the pathogenesis of neuropsychiatric disorders in such cases [50].

Considering these data, the unprecedented correspondence between the clinical phenotypes of GDFC, which is widespread in the population and mainly affects the innate immune system, and the primary deficiency of mannose-binding lectin, as a genetically determined immunodeficiency common in the population, with a preferred one, looks obvious (**Table 4.1**).

Table 4.1 Comparison of clinical phenotypes of GDFC and primary deficiency of mannose-binding protein in humans

Sign	GDFC	Mannose-binding protein deficiency
Infectious syndrome	Reduced resistance to streptococcus and herpes viruses [51]	Tendency to streptococcal [52], herpes virus infection [53]
Autoimmune syndrome	Rheumatoid arthritis [54], systemic lupus erythematosus [55], rheumatic heart disease [56], spondyloarthritis [57]	Rheumatoid arthritis [58], systemic lupus erythematosus [59], rheumatic heart disease [60], spondyloarthritis [61]
Allergic syndrome	Bronchial asthma [62], atopy [63]	Bronchial asthma, atopy [64]
Psychiatric pathology	Bipolar disorder, depression, schizophrenia [65, 66]	Bipolar disorder, panic attacks, schizophrenia [67]
Neurodegenerative pathology	Alzheimer's [68]	Alzheimer's [69]
Cancer syndrome	Lung cancer and other tumors [70]	Lung cancer and other tumors [71]
Immunoinflammatory lesions	Nonspecific ulcerative colitis [72]	Nonspecific ulcerative colitis [73]
Aggravation of other genetic pathology	Increased risk of developing and aggravating Down's disease [74]	Aggravation of Down's disease [75]
Vascular lesions	Atherosclerosis and related complications [76]	Atherosclerosis and related complications [77]
Infertility	Multiple episodes of spontaneous abortions [78]	Multiple episodes of spontaneous abortions [79]
Hemocoagulation disorders	Predisposition to thrombosis [80]	Predisposition to thrombosis [81]

In clinical practice, it is necessary to type children with neuropsychiatric syndromes according to the nature of immunological disorders in order to identify the individual immune endophenotype of GDFC-induced immunodeficiency, since various disorders in the immune status can be associated with various infectious factors, immunodependent complications and require different approaches to immunotherapy. Thus, it has been shown that deficiencies of NK, NKT, CD8+ cytotoxic T-lymphocytes are associated with reactivated herpesvirus infections, deficiencies of immunoglobulin classes and subclasses are associated with streptococcal which affects the nature of the infectious syndrome and associated immune-dependent manifestations [51].

Indeed, immunodeficiency in children with GDFC needs immunocorrection, and the recently demonstrated benefit of combined immunotherapy with Propes and Inflamafertin in a controlled clinical trial is the first step towards the development of effective immunotherapeutic approaches to eliminate disorders in cellular immunity in children with ASD, whereas the manifestations of hypoimmunoglobulinemia, deficiencies of IgG subclasses and specific antibodies in such cases can be effectively compensated with low- and medium-dose IV immunoglobulin therapy, as shown by the results of a systematic review and meta-analysis of clinical studies by Richard E. Frye and Daniel A. Rossignol in 2021 [32].

4.4 INFECTIOUS FACTORS

Due to the immunocompromised state, children with ASD and other neuropsychiatric syndromes are characterized by reduced immunoresistance, which suggests an increased predisposition to a number of infectious agents, which are the first immune-dependent factor in damaging the nervous system in such cases. The concept of dualism of microbe-induced pathways of CNS damage in children with ASD has been confirmed. It is possible to single out a direct path of damage, when a microbe causes an acute or chronic neuroinfection, and indirect paths associated with brain damage by microbe-induced autoimmune and immunoinflammatory reactions.

Teresa C. Binstock in 2001 for the first time identified a subgroup of children with ASD with abnormally reduced immunoresistance to a number of intracellular (intramonocytic) infectious agents [43]. So far, it can be argued that the author has described the pattern of infection in children with GDFC. The data accumulated so far point to the selective sensitivity of children with ASD to opportunistic and opportunistic pathogens, which, as the results of a recent controlled clinical study show, is associated with heterogeneous damage to the components of the immune system during the formation of GDFC-induced immunodeficiency. It has been established that children with ASD are more likely to suffer from herpesvirus infections [43, 83, 84], TTV infection [51], mycoplasmosis and chlamydia [84], yersiniosis [43], borreliosis [85], candidiasis [86], streptococcal infection [31] and toxoplasmosis [87] than mentally healthy peers. These microbes constitute a specific microbial spectrum associated with GDFC-induced immunodeficiency in children with ASD [51].

Indeed, the immune status of a child with ASD largely determines the nature of the child's infection, since it is mainly about opportunistic and opportunistic ubiquitous pathogens. As the results of a controlled clinical study show, reactivated HHV-6-, HHV-7-, TTV-infections in children with ASD are observed mainly in deficiencies of NK-, NKT- and CD8+ cytotoxic T cells. Streptococcal infection is associated with hypo- and dysimmunoglobulinemia, as well as myeloperoxidase deficiency. Candidiasis is associated only with myeloperoxidase deficiency. Toxoplasmosis is noted with a deficiency of CD3+CD4+ T-helpers and combined immune disorders. Consequences of congenital CMV neuroinfection occur only in case of combined immune disorders [51].

Indeed, an infectious factor may form an independent mechanism of CNS damage in children with ASD in some cases, which is confirmed by clinical reports of the development of the ASD phenotype after postnatal viral encephalitis [88] (encephalitic mechanism), an abnormally high incidence of congenital cytomegalovirus neuroinfection [89] (teratogenic mechanism) and the development in some children of signs of mesian temporal sclerosis [90] (a neurodegenerative mechanism), which, according to the results of a recent systematic review and meta-analysis of controlled clinical trials, is associated with HHV-6 [91], penetrating into the mesolimbic system of the brain via the transolfactory pathway [92].

Microbes in children with ASD can be both triggers of abnormal cerebral hyperinflammation [93] (indirect inflammatory mechanism) and autoimmunity to neurons [94, 95] and myelin [96] of the CNS (indirect autoimmune mechanism). The phenomenon of selective action of microorganisms of various taxonomic groups in relation to autoantigens of the brain and extracerebral autoantigens is noted. As the results of a recent controlled clinical study show, serological signs of autoimmunity to autoantigens of the subcortical ganglia of the cerebral hemispheres are associated with Streptococcus pyogenes and Borrelia, to neurons of the mesolimbic system – EBV, HHV-6, HHV-7, Toxoplasma and TTV, HHV-6, HHV-7, Borrelia and TTV, in the nuclei of cells of the connective tissue and striated muscles – EBV, HHV-6, HHV-7, Borrelia and TTV [51]. In addition, microbes can determine the intensity, nature and localization of immunoinflammatory reactions. Thus, Heather K. Hughes and Paul Ashwood, P. showed that seropositivity to candidiasis in children with ASD is associated with the clinical severity of immunoinflammatory gastrointestinal lesions [86].

Thus, children with ASD have an individual spectrum of microbes involved in the pathogenesis, which dynamically changes during ontogenesis due to the interaction of the child's body with environmental factors, and the neuropsychiatric syndromes themselves are characterized by a specific set of pathogenetically significant microbes that form individual pathological microbial systems, interact with each other within the same macroorganism. So, synergy between EBV and Streptococcus pyogenes is well known, while Streptococcus pyogenes and Candida albicans show antagonistic interactions.

It is necessary to develop a special diagnostic panel for the identification of a specific microbial spectrum in children with ASD and other neuropsychiatric syndromes for clinical practice and to type such patients by predominant microorganisms with the determination of individual microbiological endophenotypes, as recommended by Xuejun Kong with singing [97], since this affects the

formation of mechanisms of CNS damage, the clinical picture, the consequences of the disease, and the need for certain therapeutic interventions. As the research results show, it is necessary to use different laboratory methods for microorganisms of different taxonomic groups. Thus, to identify HSV-1/2, VZV, specific IgM and IgA should be determined in the blood [51], EBV, HHV-6, HHV-7, TTV, PCR of blood leukocytes [51, 84], borreliosis and ersiniosis, immunoblots with simultaneous detection of IgM and IgG to many pathogen antigens [43, 85], mycoplasmosis and chlamydia – specific IgM in blood serum [51, 84], streptococcal infection – bacteriological examination on a selective medium and antitoxic blood immunity (ASLO, antistreptodornase, antistreptohyaluronidase) [31], candidiasis – mycological examination and specific IgM in the blood [86], toxoplasmosis – specific IgM in the blood and the method of paired sera [87]. In addition, microorganisms of different types are found in children with ASD with unequal frequency. Four groups of infectious agents were distinguished according to the frequency of their detection in children with ASD associated with GDFC (group I – TTV, HHV-6, HHV-7 – 87–68 %; group II – EBV, Streptococcus pyogenes, Candida albicans, Borrelia – 59–34 %; group III – Mycoplasma, Chlamydia, Yersinia – 27–23 %; group IV – Toxoplasmosis, Congenital cytomegalovirus infection, HSV-1/2 encephalitis – 19–5 % of cases) when planning a sequence of actions when assessing microbial load and determining the need for an antimicrobial drug [51].

Substantiation of the role of the infectious factor in the pathogenesis of the disease in GDFC creates the prerequisites for testing antimicrobial treatment strategies based on a personalized assessment of the patient's microbial profile. According to this Lisa A. Snider et al. performed a double-blind, placebo-controlled, randomized clinical trial of long-term prophylactic therapy with penicillin VK 250 mg twice daily and azithromycin 250 mg twice daily once a week for 1 year in PANDAS. A 96 % reduction in the frequency of exacerbations of streptococcal infection and a 61 % reduction in the number of relapses of PANDAS in patients treated with both penicillin and azithromycin compared with placebo was demonstrated [98]. It is clear that children with neuropsychiatric manifestations require antiviral, antifungal and antiprotozoal treatment, in addition to antibiotic therapy, if relevant infectious agents are identified, which should be studied in controlled clinical trials.

4.5 AUTOIMMUNE REACTIONS

The pathological immune reaction against brain autoantigens in children with ASD can be alloimmune (in the so-called feto-maternal immune conflict [99]) and autoimmune [41]. If alloimmunization is an antenatal phenomenon that is associated with immune dysregulation in the body of a pregnant mother, has a transient course and tends to self-limit a few months after birth due to the catabolism of alloimmune maternal antibodies in the child's body, then the autoimmune mechanism is chronic. dynamic course and develops postnatally during the first years of extrauterine ontogenesis, being associated with immune dysregulation in the child's body.

Microbial and non-microbial factors (for example, heavy metals such as haptens [100]) under conditions of GDFC-induced immune dysregulation in children with ASD and other neuropsychiatric syndromes induce both anticerebral [42] and extracerebral [101] autoimmune ones by damaging the CNS. Speaking of anticerebral autoimmunity, the production of autoantibodies to both neuron autoantigens [41] and myelin [96] has been described. It has been established that in children with ASD, not all nerve cells of the CNS, but neurons of individual anatomical zones, become the target of autoimmune aggression, that is, not a total, but a selective, or mosaic lesion of the gray matter of the brain. Janet K. Kern et al. after analyzing all available scientific reports on the identification of autoantibodies to CNS neurons in children with ASD in the period from 1985 to 2020, were established what is now known about autoimmunization to progenitor cells of neurons, neurons of the subcortical ganglia, hippocampus, thalamus and hypothalamus, serotonin receptors of neurons, folic acid receptors of the blood-brain barrier, brain endothelium and neuron-axon.

An autoimmune attack in children with ASD can also be directed to brain glial cells, in particular, to glial fibrillary acidic protein [100]. According to this, Paul Whiteley et al. in a specially prepared scientific review, they defend the idea of autoimmune encephalitis as the main form of CNS damage in children with ASD and put forward an autoimmune concept of the pathogenesis of the disease [102]. Speaking of extracerebral autoimmunity in children with ASD, autoimmunization to cell nuclei, striated muscles, collagen, and endocrine organs has been described [101].

Typical associations between certain microorganisms and certain autoantibodies are shown, which indicates selectivity in the implementation of microbe-mediated trigger effects in the induction of a breakdown in immune tolerance to brain and extracerebral antigens in children with ASD. Thus, EBV, HHV-6, and HHV-7 are associated with laboratory signs of autoimmune reactions to autoantigens of hippocampus, myelin, connective tissue cell nuclei, and striated muscles, while Streptococcus pyogenes is associated with neurons of subcortical ganglia. Borrelia is associated with autoimmunity to myelin, subcortical ganglion neurons, connective tissue cell nuclei, and striated muscles, while Toxoplasma is associated with hippocampal neurons [55]. Therefore, by determining the patient's individual microbial spectrum, it is possible to reasonably predict the most likely ways of microbial-induced autoimmunity, as well as by assessing the immune status, one can draw a conclusion about the most likely pathogenetically significant microbes that can affect a given child.

For clinical practice, it is necessary to develop specialized laboratory diagnostic panels to assess the specific profile of autoimmune reactions to cerebral and extracerebral autoantigens, or autoimmune endophenotypes in children with ASD and other neuropsychiatric syndromes to identify each individual patterns of autoimmunization in each case. This will allow justifying the appointment and adequately assessing the effectiveness of such immunomodulatory therapeutic agents as methylprednisolone, normal intravenous human immunoglobulin and rituximab, the benefits of which have so far been demonstrated in controlled clinical trials in children with ASD [32, 103].

4.6 IMMUNE INFLAMMATORY SYNDROME

Another manifestation of immune dysregulation in children with neuropsychiatric syndromes is the immunoinflammatory syndrome, which forms the third mechanism of immune-dependent brain damage in such cases. It is necessary to distinguish between primary and secondary immunoinflammatory syndromes, with the primary being a consequence of endogenous dysregulation of inflammation under conditions of immune dysregulation, and the secondary being a component of the infectious and autoimmune syndromes characteristic of immunocompromised children with GDFC.

Evidence for the development of a persistent systemic inflammatory response in children with ASD is based on the results of 2 systematic reviews and meta-analyses of RCTs. In particular, data from the first systematic examination and meta-analysis show an increase in the serum concentration of pro-inflammatory mediators interleukin-1beta (IL-1beta) ($p < 0.001$), IL-6 ($p = 0.03$), IL-8 ($p = 0.04$), interferon-gamma (IFN-gamma) ($p = 0.02$), eotaxin ($p = 0.01$) and monocytic chemotactic factor 1 ($p < 0.05$) and a decrease in the content of the anti-inflammatory cytokine transforming growth factor beta 1 ($p < 0.001$) in children with ASD ($n = 743$) compared with healthy patients ($n = 592$) [104]. Results of a meta-analysis of studies prepared by Amene Saghazadeh et al. (2019), covering 38 trials involving 2487 children, show a likely increase in serum concentrations of tumor necrosis factor alpha (TNF-alpha), IFN-gamma, IL-1beta and IL-6 in children with ASD compared with healthy individuals [105]. According to this, Harumi Jyonouchi et al. in a specially designed clinical study showed that an increase in serum concentrations of pro-inflammatory cytokines of monocytic origin, including TNF-alpha and IL-6, is associated with a sharp deterioration in the mental state of a child with ASD, which is explained as a well-known neurotoxic effect of serum pro-inflammatory molecules in the blood-brain barrier, and the associated induction of secondary low-productive intracerebral inflammation with subsequent dysfunction of CNS neuronal networks [106]. Robyn P. Thom et al. proposed to single out the immune-inflammatory mechanism as a separate link in the pathogenesis of cerebral damage in ASD, as well as to single out a separate subgroup of children with ASD, in which the multisystem immune-inflammatory pathway of CNS damage predominates [107].

As shown by the results of a recent controlled clinical study, tumor M2-pyruvate kinase, TNF-alpha and IL-6 in children with ASD show variability in sensitivity, lability and specificity, which suggests the need for complex data analysis. Tumor M2-pyruvate kinase is the most sensitive, however, the least specific indicator of inflammation, while IL-6 is the most specific, but the least sensitive indicator. TNF-alpha is the most balanced indicator among these three indicators in terms of specificity and sensitivity [108]. The parameters studied are associated with an increase in serum levels of neuronal damage of neuron-specific enolase [109] and protein S-100 [110], which confirms the idea of the role of systemic inflammation in the induction of CNS damage in children with GDFC-associated ASD and opens the way to approbation of new therapeutic strategies for anti-inflammatory therapy to reduce the severity of neuropsychiatric manifestations [111].

For clinical practice, it is necessary to develop specialized diagnostic panels for assessing systemic, intestinal and intracerebral inflammation according to the results of the above meta-analyses in order to identify the patient's individual cytokine status, or immunoinflammatory endophenotype, characterizing the state of the immune response in the body at a specific point in time in a specific compartment of the body as a separate mechanism of cerebral damage. The data obtained can serve as a basis for prescribing anti-inflammatory therapy, and the success of testing infliximab, a drug of monoclonal antibodies to the TNF-alpha molecule, in children with ASD is the first step towards the development of targeted anti-inflammatory strategies in children with neuropsychiatric syndromes that can modify the course of the disease.

4.7 ALLERGIC SYNDROME

Results of a large population-based clinical study involving 199,520 children conducted by Guifeng Xu et al. (2019) showed that food allergy, respiratory allergy, and skin allergy occurred in children with ASD in 11.25 %, 18.73 %, and 16.81 % of cases, respectively, while such disorders were less common in mentally healthy children (4.25 %, 12.08 % and 9.84 %, respectively). The odds ratios in children with ASD for different types of allergies were as follows:

– food allergies – OR = 2.29; 95 % CI95 % = 1.87–2.81;

– respiratory allergy, OR = 1.28; 95 % CI95 % = 1.10–1.50;

– skin allergy, OR = 1.50; 95 % CI95 % = 1.28–1.77 [112].

Allergic syndrome is a consequence of immune dysregulation that develops under conditions of GDFC-induced immunodeficiency in children with neuropsychiatric syndromes and is the fourth immune-dependent mechanism of CNS damage. It is possible to single out the central and peripheral mechanisms of the formation of an allergic syndrome in children with ASD.

The central mechanism of allergic depression, characterized by the scientific concept of Theoharis C. Theoharides et al., which involves the production of neurotensin in the hypothalamus of the brain in children with ASD under the influence of stress factors, activating mast cells in the perivascular spaces of the thalamus and hypothalamus, followed by the induction of allergic inflammation in the brain parenchyma with neurotoxic effects [113]. The authors identified a special allergic subtype of ASD in children, in which it is the intracerebral allergic reaction that is the leading mechanism of CNS damage [114].

The peripheral mechanism for the development of allergic inflammation as a pathway for CNS damage in children with ASD is associated with an allergy to certain foods, including gluten and casein, with the onset of allergic inflammation in the intestinal wall and the subsequent spread of such an inflammatory reaction to the blood and brain due to damaged hematoencephalus. The validity of the peripheral concept is confirmed by the results of an experimental study by Li-Hua Cao et al., who demonstrated the development of an inflammatory CNS lesion and associated autistic-like behavioral disorders in test mice during the induc-

tion of cow's milk casein allergy in the intestine under conditions of immune dysregulation, similar to that observed in children with ASD [115].

Results of a meta-analysis and systematic review of clinical studies prepared by Yuping Yu et al. in 2022, which analyzed the results of 7 RCTs involving 338 children, showed that an elimination gluten-free and casein-free diet can significantly alleviate the main clinical symptoms of ASD and improve the social behavior of children with neuropsychiatric syndromes, which is practical evidence [116].

4.8 THE CONCEPT OF THE FUNCTIONAL MICROBIOTA-GUT-BRAIN AXIS

The dynamics of the pathological process with an undulating course, suggesting periods of improvement and deterioration of the mental status of the child, is explained by the scientific concept of the functional microbiota-gut-brain axis.

Microbial antigens [97], food allergens [115], and toxins from the environment, including heavy metals [100], when exposed to the damaged GDFC mucosal-associated immune system (MALT), are labeled in the intestinal wall, inducing a state of local intraintestinal inflammation. Therefore, children with ASD often have signs of chronic enterocolitis, which is confirmed by the data of pathomorphological and immunohistochemical studies of intestinal tissue obtained by biopsy [37]. It can be said that children with neurosychiatric syndromes are characterized by a state of impaired interface of the intestinal-immune system, in which normally harmless stimuli from microorganisms, food products and pollutants lead to an abnormal hyperinflammatory reaction in the intestinal wall.

The state of chronic inflammation is accompanied by a pathological increase in the permeability of the intestinal wall, which allows a local inflammatory response to be easily generated, leading to a state of systemic inflammation with the characteristic phenomenon of persistent hypercytokinemia. The concept of impaired barrier function of the intestinal epithelium in children with ASD is currently substantiated by Maria Fiorentino et al. in a related systematic review [117]. Subsequently, systemic inflammation migrates to the CNS due to GDFC-induced disruption of the neuroimmune interface and the associated pathologically increased permeability of the blood-brain barrier, where intracerebral inflammation develops, associated with a deterioration in the mental status of the child (**Fig. 4.4**).

In said review Maria Fiorentino et al. also put forward and substantiate the scientific concept of impaired function of the blood-brain barrier in children with ASD [117]. Disruption in the functioning of the functional microbiota-intestine-brain system facilitates the implementation of both biochemical and immune-dependent mechanisms of CNS damage in children with ASD. A systematic review of the so far accumulated results of controlled clinical studies on the functioning of the microbiota-gut-brain mechanism in children with ASD was prepared by Atiqah Azhari et al. [118].

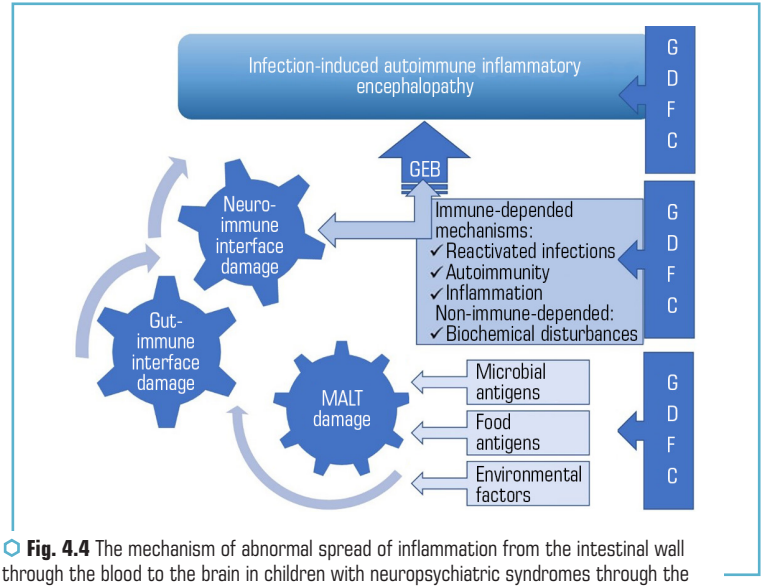


Fig. 4.4 The mechanism of abnormal spread of inflammation from the intestinal wall through the blood to the brain in children with neuropsychiatric syndromes through the functional microbiota-gut-brain axis within the framework of the folate-centric concept

4.9 THE CONCEPT OF GDFC-INDUCED ENCEPHALOPATHY

Making exclusively psychiatric diagnoses for children with GDFC addresses an outdated descriptive approach to understanding the problem, but does not allow demonstrating the true essence of the disease and going beyond symptomatic treatment by developing fundamentally different therapeutic interventions that would modify the course of the disease and lead to the patient's recovery. In fact, children with ASD develop brain damage, that is, encephalopathy occurs with a predominant lesion of the cerebral cortex, a violation of the phenomenon of neuron connectivity and the implementation of synaptic plasticity processes. Denis A. Bouboulis et al propose to call such encephalopathy the term microbe-induced autoimmune encephalopathy [119]. Since a separate immuno-inflammatory pathway of CNS damage has been demonstrated so far, not directly associated with an autoimmune reaction or infection, in our opinion, the term infection-induced inflammatory autoimmune encephalopathy should be more accurate. It is also possible to offer simpler and at the same time more capacious terms – immune-dependent encephalopathy or GDFC-induced encephalopathy. This encephalopathy is caused by the implementation of polygenic biochemical, immunodependent, gene regulatory and epigenetic disorders, which were mentioned above. Clinically, such encephalopathy is manifested by a complex of psychiatric and neurological syndromes that simultaneously or sequentially develop in a patient during ontogenesis in interaction with environmental factors. It is

about ASD, attention deficit hyperactivity disorder, obsessive-compulsive syndrome, hyperkinetic syndrome, sleep disorders, eating disorders, cognitive decline, epileptic syndrome and motor disorders [3, 33, 120]. If all these 9 syndromes are present, it is about the full clinical picture of GDFC-induced encephalopathy, if only some – about a partial phenotype of such encephalopathy (**Fig. 4.5**).

Currently, ASD is considered morbid, and other syndromes are comorbid, thereby emphasizing the primacy of ASD over other clinical syndromes, although the positioning of ASD as the primary source of the disease is exclusively traditional and has not been confirmed by the results of any controlled clinical trial. Within the framework of the concept of GDFC-induced encephalopathy, the division into morbid and comorbid clinical syndromes should be rejected as outdated and based solely on a descriptive understanding of the clinical picture of the disease. In fact, all clinical syndromes of encephalopathy have a common origin, reflect damage to various parts of the central nervous system and different mechanisms of cerebral damage, and in general are equivalent and mutually permeable phenomena, and in an individual child, the severity of the condition and the prognosis of the disease can be priority influenced by any of these syndromes, which is more pronounced. Some children with GDFC-induced encephalopathy do not develop ASD patterns at all during ontogeny, so this syndrome alone cannot be considered a key syndrome in the clinical phenotype of the disease. The death of a child as a result of an accident may not be directly due to ASD, but, for example, due to attention deficit hyperactivity disorder or an epileptic seizure [3].

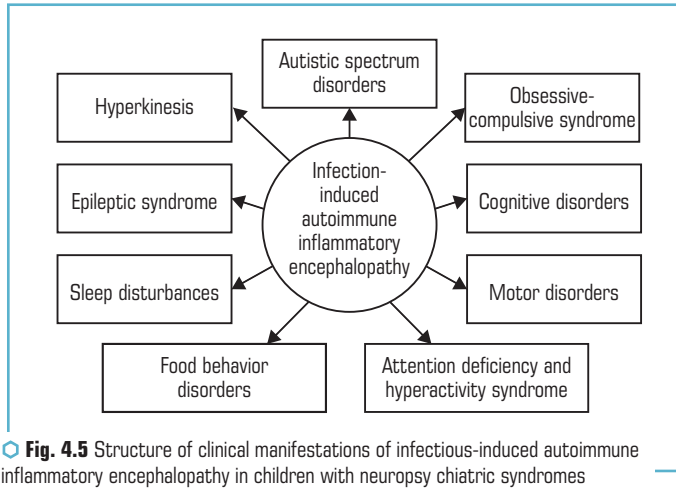


Fig. 4.5 Structure of clinical manifestations of infectious-induced autoimmune inflammatory encephalopathy in children with neuropsy chiatric syndromes

As shown by the results of pathomorphological [121] and neuroimaging [122] studies, encephalopathy in children with ASD is characterized by signs of cortical damage, impaired neuronal connectivity, and synaptic plasticity disorders. Currently, 5 major neuroradiological syndromes have

been described in children with GDFC-induced encephalopathy, namely, leukoencephalopathy [123], subcortical ganglion hypertrophy [33], mesian temporal sclerosis [90], signs of congenital CMV infection [89] and postnatally transferred neuroinfections [88] and minor anomalies development of the brain and spinal cord [124]. At the same time, links were demonstrated between neuroimaging phenomena and data on assessing the immune status, microbial spectrum, autoimmunity profile, and clinical syndromes with the formation of the so-called immune-infectious-rheumatological-neuroimaging-clinical complexes [125] (virus-induced temple 91), autoimmune subcortical encephalitis [33], autoimmune limbic encephalitis [126], autoimmune leukoencephalopathy [86], congenital CMV neuroinfection [89, 127], etc.). These complexes, like clusters, are combined into a single clinical and neuroimaging picture of GDFC-induced encephalopathy in a variable manner, reflecting the individual nature of the implementation of biochemical and immune-dependent mechanisms of CNS damage at a particular point in time in children with neuropsychiatric disorders. An example of such a cluster would be an IgG subclass deficiency associated with gene deletions in the constant regions of immunoglobulins – oropharyngeal infection caused by beta-hemolytic streptococcus of group A, – autoantibodies to type 1 dopamine receptors and tubulin – hypertrophy of caudate subcortical ganglia on MR images – obsessive-compulsive syndrome and tics in the clinical picture of the disease [33].

The advancement of the concept of GDFC-induced encephalopathy radically changes the understanding of appropriate approaches to treatment. The era of dominance of psychotropic treatments designed to temporarily reduce individual mental symptoms of the disease, which seemed to be the only obvious therapeutic intervention within the framework of the concept of ASD as a purely psychiatric pathology, should be replaced by neuroprotective approaches designed to protect the brain from GDFC. Successes in the use of methylcobalamin, folinic acid, and other biochemical correction agents not only confirm the relevance of the biochemical pathway of CNS damage in neuropsychiatric syndromes, but also provide practical medicine with effective means of neuroprotection by at least partially blocking the biochemical pathway of CNS damage [28, 29]. The validity of the proposed immune-dependent concept of the formation of encephalopathy in children with GDFC-associated ASD is confirmed by the clinical efficacy of immunotherapeutic interventions, including therapeutic approaches aimed at achieving neuroprotection by blocking infectious, autoimmune and immuno-inflammatory pathways of CNS damage. In particular, it is about the use of azithromycin or penicillin to prevent and mitigate PANDAS exacerbations [98], infliximab (anti-TNF-alpha therapy) to suppress FNS-alpha-induced systemic inflammation and associated cerebral damage [111], rituximab (anti-CD20 therapy) to suppress anticerebral autoimmunity and CNS neuronal damage caused by this autoaggression [103], and high-dose normal intravenous human immunoglobulin, which has an integral therapeutic effect inhibiting all known immune-dependent mechanisms of encephalopathy formation, through anti-inflammatory, anti-infectious and immunomodulatory effects [32, 128]. The results of clinical studies conducted in the field of ASD immunoglobulin therapy are summarized in the data of a systematic review and meta-analysis of clinical studies prepared by Daniel A. Rossignol, Richard E. Frye et al. in 2021. Twenty-seven relevant trials were analyzed, of which 4 were prospective controlled (one double-blind placebo

controlled), 6 were prospective uncontrolled, 2 were retrospective controlled, and 15 were retrospective uncontrolled. The overall clinical outcome of normal IV human immunoglobulin preparations in this meta-analysis is improvement in communication, hyperexcitability, hyperactivity, cognition, attention, social interaction, eye contact, echolalia, speech, response to commands, drowsiness, decreased activity and, in some cases, complete elimination of ASD symptoms [32]. The results of a recent retrospective analysis covering the experience of using a 6-month course of normal intravenous human immunoglobulin at a dose of 2 g/kg/month in 225 children with ASD add to the evidence base for the efficacy and safety of intravenous immunoglobulin therapy in children with neuropsychiatric disorders [128]. According to this, data from a double-blind, placebo-controlled, randomized clinical trial of Susan J. Perlmutter et al. showed equivalent clinical efficacy of high-dose IV immunoglobulin therapy and plasmapheresis in children with PANDAS [129].

Successful testing of combined immunotherapy with Propes and Inflamafertin to compensate for key disorders of cellular immunity [82] and normal intravenous human immunoglobulin in low and medium doses – to replace the deficiency of the humoral link of immunity [32] in GDFC-induced immunodeficiency, they provide practical medicine with effective means of preventing infections and manifestations of immune dysregulation associated with immunodeficiency, which are responsible for the development of immune-dependent pathways of encephalopathy in children with neuropsychiatric syndromes (**Fig. 4.6**).

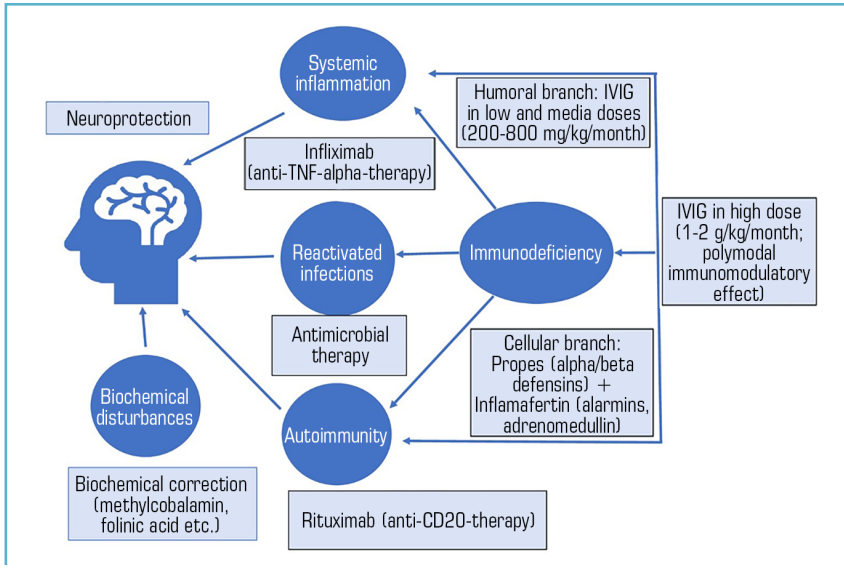


Fig. 4.6 Available means of neuroprotection in the implementation of immune-dependent mechanisms of cerebral damage in the development of infection-induced autoimmune inflammatory encephalopathy in children with neuropsychiatric syndromes in the context of the folate-centric concept

4.10 POLYGENIC GDFC-INDUCED MULTISYSTEM DISEASE AS A FORM OF DAMAGE TO THE WHOLE ORGANISM

Another significant drawback of a purely psychiatric approach to the management of children with neuropsychiatric diseases is insufficient attention to the damage to other organs and systems, except for the nervous system. Indeed, the biochemical and immune-dependent mechanisms of damage that develop in GDFC affect not only the CNS, but also other organs [130]. Such children have cerebral and extracerebral clinical manifestations of the disease. Extracerebral symptoms, although mostly related to damage to the immune system and intestines, in fact can involve all organs and systems in a variable manner [1, 37, 121], that is, there is a special form of damage to the whole body, which can be called as polygenic GDFC-induced multisystem disease (**Fig. 4.7**).

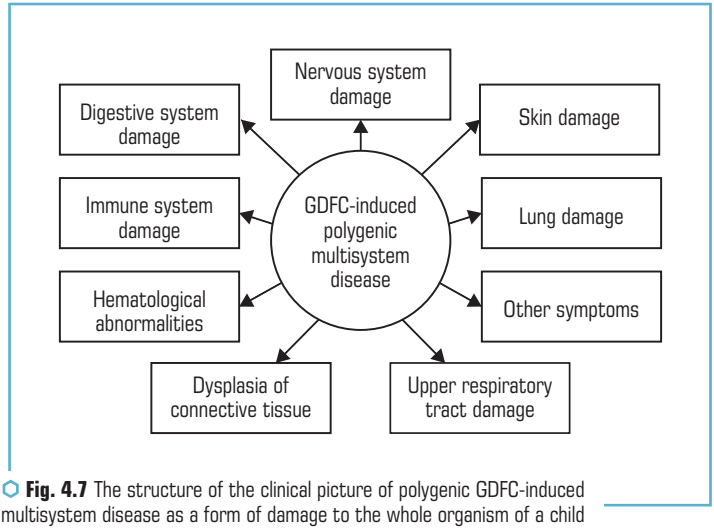


Fig. 4.7 The structure of the clinical picture of polygenic GDFC-induced multisystem disease as a form of damage to the whole organism of a child

Nancy J. Minshew and Diane L. Williams define autism as a polygenic neurobiological developmental disorder in a child with multiple organ damage, but with the leading involvement of the nervous system [121]. However, there is a systematic error in this definition. Indeed, the disease in such children has a polygenic inheritance, is accompanied by multiorgan damage and a violation of the neurobiological development of the child, however, autism as such is not the cause or essence of such a polysystemic disease, but only one of the clinical manifestations. It cannot be said that it is the psychiatric symptoms of the disease that are always leading, and the damage to other organs and systems is secondary, since the ratio of the severity of

syndromes in different children differs significantly. There are patients with GDFC who have severely affected intestines, but there are almost no psychiatric and neurological manifestations of the disease [37, 72]. In addition, it is the lesions of other organs, and not the central nervous system, that can determine the prognosis of the disease in some clinical cases. For example, the death of a child with ASD may occur due to pneumonia or sepsis due to the presence of immunodeficiency, or due to acute pancreatitis or appendicitis due to the development of severe immuno-inflammatory bowel disease [3].

An integrated diagram of the pathogenesis of neuropsychiatric diseases in children according to the folate-centric concept, which demonstrates the relationship between genetic, biochemical, immunological, and clinical manifestations, is shown in **Fig. 4.8**.

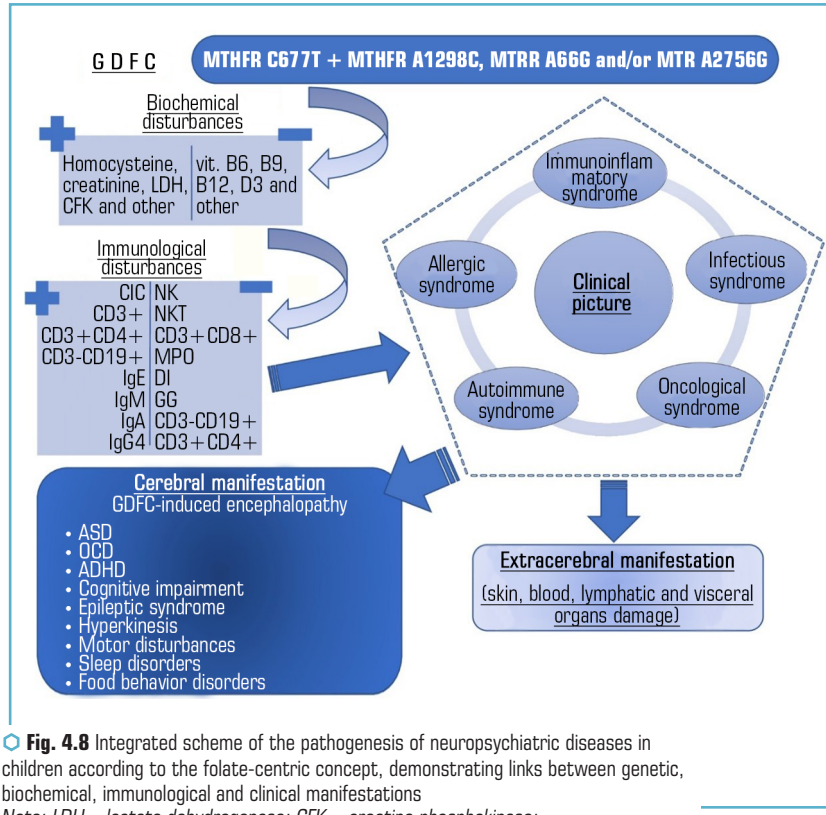


Fig. 4.8 Integrated scheme of the pathogenesis of neuropsychiatric diseases in children according to the folate-centric concept, demonstrating links between genetic, biochemical, immunological and clinical manifestations
Note: LDH – lactate dehydrogenase; CFK – creatine phosphokinase; DI – dysimmunoglobulinemia; GG – gypogammaglobulinemia; MPO – myeloperoxidase deficiency; CIC – circulating immune complexes

4.11 SCIENTIFIC CONCEPTS OF A PERSONALIZED MULTIDISCIPLINARY APPROACH TO PATIENT MANAGEMENT

Since the pathogenesis of the disease in children with neuropsychiatric syndromes involves interrelated lesions of the genome, metabolism, immune system, nervous system, and many organs and systems, a multidisciplinary approach to patient management is required, involving a medical geneticist, clinical immunologist, pediatric neurologist, and psychiatrists. Since each patient is characterized by a unique pathological gene system and associated biochemical and immunological disorders, it is impossible to strictly standardize approaches to diagnosis and treatment, which justifies a personalized approach based on the results of controlled clinical trials. At present, two personalized multidisciplinary approaches to the management of children with ASD and other neuropsychiatric syndromes have already been proposed and substantiated. Historically the first approach is James Jeffrey Bradstreet et al. (2010) is based on the analysis of a large group of laboratory biomarkers, the relevance of which has been demonstrated in clinical studies, and the subsequent targeted correction of the disorders that these biomarkers describe (the so-called biomarker-guided interventions) [131]. Although this approach is not holistic and systematized, but to a certain extent fragmented, mechanistic and empirical, biomarker-based diagnostics and therapy for the first time showed some success in the treatment of children with previously incurable neuropsychiatric diseases. Recently Hua Liu et al. demonstrated a wide range of possibilities for the practical application of the biomarker-guided strategy in children with ASD using sulfarofan as an example [132]. Subsequently, Richard E. Frye developed a more progressive multidisciplinary personalized approach called Bas-BISTOR (collect Baseline data, search by symptoms, Biomarkers, Select Treatment, Observe for Response methods), characterized by scientific validity, consistency, complexity, consistency and stage of the patient's condition and appointment corrective drugs [6, 133]. This protocol covers all forms of ASD in children in all their diversity, outlining only the general principles of diagnosis of the disease and clinical management of the patient. In order to improve existing recommendations on specific subtypes of neuropsychiatric syndromes in children, this article puts forward an improved personalized multidisciplinary approach to the clinical management of patients with ASD and neuropsychiatric manifestations associated with GDFC as GDINS (Genetic-Biochemical-Immunological-Neurological-Symptomatic evaluation). This approach shows the sequence of assessing the patient's condition and the subsequent prescription of corrective therapy according to the accumulated scientific evidence so far. According to this approach, an individual pathological system of genes (genetic status) is first studied, on the basis of which an individual volume of biochemical tests characterizing specific metabolic disorders induced by mutations/polymorphisms in the genome (biochemical status) is determined. Identification of the individual profile of biochemical disorders proves the need to assess the immune status for the diagnosis of GDFC-induced immunodeficiency and immune dysregulation with the study of the four main immune-dependent mechanisms of CNS damage (immunological status). The obtained genetic, biochemical, immunological, microbiological and rheumatological results facilitate the evaluation

of clinical and neuroimaging data in the diagnosis of infection-induced autoimmune inflammatory encephalopathy (neurological status). The last stage is going beyond the nervous system and a comprehensive assessment of the lesion of the whole organism with an analysis of all the symptoms of the disease associated with a multisystem lesion of the child's body (symptomatic status).

CONCLUSION

The results of recent genetic, biochemical, immunological, microbiological, immunobiochemical, neuroimmunological clinical studies allow to reconsider the established scientific views on the nature of neuropsychiatric syndromes in children and point to new potentially useful diagnostic biomarkers and points of application for therapeutic interventions. There is reason to believe that the successful testing in clinical practice of evidence-based personalized multidisciplinary diagnostic and treatment strategies will make it possible in the near future to make a breakthrough in the clinical management of children with severe mental disorders, which will provide not only the possibility of recovery from prognostically unfavorable and incurable neuropsychiatric disorder, but will also help stop the large-scale threatening epidemic of neuropsychiatric syndromes in the modern child population.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this paper.

REFERENCES

1. Hughes, H. K., Mills Ko, E., Rose, D., Ashwood, P. (2018). Immune Dysfunction and Autoimmunity as Pathological Mechanisms in Autism Spectrum Disorders. Frontiers in Cellular Neuroscience, 12. doi: https://doi.org/10.3389/fncel.2018.00405
2. Maenner, M. J., Shaw, K. A., Baio, J. et al. (2016). Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years – Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2016. Morbidity and Mortality Weekly Report, 69 (4). Available at: https://www.cdc.gov/mmwr/volumes/69/ss/ss6904a1.htm
3. Catalá-López, F., Hutton, B., Page, M. J., Driver, J. A., Ridao, M., Alonso-Arroyo, A. et al. (2022). Mortality in Persons With Autism Spectrum Disorder or Attention-Deficit/Hyperactivity Disorder. JAMA Pediatrics, 176 (4), e216401. doi: https://doi.org/10.1001/jamapediatrics.2021.6401

4. O'Halloran, L., Coey, P., Wilson, C. (2022). Suicidality in autistic youth: A systematic review and meta-analysis. Clinical Psychology Review, 93, 102144. doi: https://doi.org/10.1016/j.cpr.2022.102144
5. Zheng, Z., Zheng, P., Zou, X. (2018). Association between schizophrenia and autism spectrum disorder: A systematic review and meta-analysis. Autism Research, 11 (8), 1110–1119. doi: https://doi.org/10.1002/aur.1977
6. Frye, R. E. (2022). A Personalized Multidisciplinary Approach to Evaluating and Treating Autism Spectrum Disorder. Journal of Personalized Medicine, 12 (3), 464. doi: https://doi.org/10.3390/jpm12030464
7. Cakir, J., Frye, R. E., Walker, S. J. (2020). The lifetime social cost of autism: 1990–2029. Research in Autism Spectrum Disorders, 72, 101502. doi: https://doi.org/10.1016/j.rasd.2019.101502
8. Tick, B., Bolton, P., Happé, F., Rutter, M., Rijsdijk, F. (2015). Heritability of autism spectrum disorders: a meta-analysis of twin studies. Journal of Child Psychology and Psychiatry, 57 (5), 585–595. doi: https://doi.org/10.1111/jcpp.12499
9. Henske, E. P., Jóźwiak, S., Kingswood, J. C., Sampson, J. R., Thiele, E. A. (2016). Tuberous sclerosis complex. Nature Reviews Disease Primers, 2 (1). doi: https://doi.org/10.1038/rdp.2016.35
10. Mpoulimari, I., Zintzaras, E. (2022). Synthesis of genetic association studies on autism spectrum disorders using a genetic model-free approach. Psychiatric Genetics, 32 (3), 91–104. doi: https://doi.org/10.1097/ypg.0000000000000316
11. Li, Y., Qiu, S., Shi, J., Guo, Y., Li, Z., Cheng, Y., Liu, Y. (2020). Association between MTHFR C677T/A1298C and susceptibility to autism spectrum disorders: a meta-analysis. BMC Pediatrics, 20 (1). doi: https://doi.org/10.1186/s12887-020-02330-3
12. Shaik Mohammad, N., Sai Shruti, P., Bharathi, V., Krishna Prasad, C., Hussain, T., Alrokayan, S. A., Naik, U., Radha Rama Devi, A. (2016). Clinical utility of folate pathway genetic polymorphisms in the diagnosis of autism spectrum disorders. Psychiatric Genetics, 26 (6), 281–286. doi: https://doi.org/10.1097/ypg.0000000000000152
13. Pu, D., Shen, Y., Wu, J. (2013). Association between MTHFR Gene Polymorphisms and the Risk of Autism Spectrum Disorders: A Meta-Analysis. Autism Research, 6 (5), 384–392. doi: https://doi.org/10.1002/aur.1300
14. Rai, V. (2016). Association of methylenetetrahydrofolate reductase (MTHFR) gene C677T polymorphism with autism: evidence of genetic susceptibility. Metabolic Brain Disease, 31 (4), 727–735. doi: https://doi.org/10.1007/s11011-016-9815-0
15. Sadeghiyeh, T., Dastgheib, S. A., Mirzaee-Khoramabadi, K., Morovati-Sharifabad, M., Akbarian-Bafghi, M. J., Poursharif, Z. et al. (2019). Association of MTHFR 677C>T and 1298A>C polymorphisms with susceptibility to autism: A systematic review and meta-analysis. Asian Journal of Psychiatry, 46, 54–61. doi: https://doi.org/10.1016/j.ajp.2019.09.016
16. Haghiri, R., Mashayekhi, F., Bidabadi, E., Salehi, Z. (2016). Analysis of methionine synthase (rs1805087) gene polymorphism in autism patients in Northern Iran. Acta Neurobiologiae Experimentalis, 76 (4), 318–323. doi: https://doi.org/10.21307/ane-2017-030

17. Chen, L., Shi, X.-J., Liu, H., Mao, X., Gui, L.-N., Wang, H., Cheng, Y. (2021). Oxidative stress marker aberrations in children with autism spectrum disorder: a systematic review and meta-analysis of 87 studies (N = 9109). Translational Psychiatry, 11 (1). doi: https://doi.org/10.1038/s41398-020-01135-3
18. Frustaci, A., Neri, M., Cesario, A., Adams, J. B., Domenici, E., Dalla Bernardina, B., Bonassi, S. (2012). Oxidative stress-related biomarkers in autism: Systematic review and meta-analyses. Free Radical Biology and Medicine, 52 (10), 2128–2141. doi: https://doi.org/10.1016/j.freeradbiomed.2012.03.011
19. Guo, B.-Q., Li, H.-B., Ding, S.-B. (2020). Blood homocysteine levels in children with autism spectrum disorder: An updated systematic review and meta-analysis. Psychiatry Research, 291, 113283. doi: https://doi.org/10.1016/j.psychres.2020.113283
20. Wan, L., Li, Y., Zhang, Z., Sun, Z., He, Y., Li, R. (2018). Methylenetetrahydrofolate reductase and psychiatric diseases. Translational Psychiatry, 8 (1). doi: https://doi.org/10.1038/s41398-018-0276-6
21. Moll, S., Varga, E. A. (2015). Homocysteine and MTHFR Mutations. Circulation, 132 (1). doi: https://doi.org/10.1161/circulationaha.114.013311
22. James, S. J., Melnyk, S., Jernigan, S., Cleves, M. A., Halsted, C. H., Wong, D. H. et al. (2006). Metabolic endophenotype and related genotypes are associated with oxidative stress in children with autism. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 141B (8), 947–956. doi: https://doi.org/10.1002/ajmg.b.30366
23. Horiuchi, F., Yoshino, Y., Kumon, H., Hosokawa, R., Nakachi, K., Kawabe, K. et al. (2021). Identification of aberrant innate and adaptive immunity based on changes in global gene expression in the blood of adults with autism spectrum disorder. Journal of Neuroinflammation, 18 (1). doi: https://doi.org/10.1186/s12974-021-02154-7
24. Belardo, A., Gevi, F., Zolla, L. (2019). The concomitant lower concentrations of vitamins B6, B9 and B12 may cause methylation deficiency in autistic children. The Journal of Nutritional Biochemistry, 70, 38–46. doi: https://doi.org/10.1016/j.jnutbio.2019.04.004
25. Bjørklund, G., Doşa, M. D., Maes, M., Dadar, M., Frye, R. E., Peana, M., Chirumbolo, S. (2021). The impact of glutathione metabolism in autism spectrum disorder. Pharmacological Research, 166, 105437. doi: https://doi.org/10.1016/j.phrs.2021.105437
26. Frye, R. E. (2020). Mitochondrial Dysfunction in Autism Spectrum Disorder: Unique Abnormalities and Targeted Treatments. Seminars in Pediatric Neurology, 35, 100829. doi: https://doi.org/10.1016/j.spen.2020.100829
27. Frye, R. E., Rossignol, D. A. (2014). Treatments for Biomedical Abnormalities Associated with Autism Spectrum Disorder. Frontiers in Pediatrics, 2. doi: https://doi.org/10.3389/fped.2014.00066
28. Rossignol, D. A., Frye, R. E. (2021). The Effectiveness of Cobalamin (B12) Treatment for Autism Spectrum Disorder: A Systematic Review and Meta-Analysis. Journal of Personalized Medicine, 11 (8), 784. doi: https://doi.org/10.3390/jpm11080784

29. Rossignol, D. A., Frye, R. E. (2021). Cerebral Folate Deficiency, Folate Receptor Alpha Autoantibodies and Leucovorin (Folinic Acid) Treatment in Autism Spectrum Disorders: A Systematic Review and Meta-Analysis. Journal of Personalized Medicine, 11 (11), 1141. doi: https://doi.org/10.3390/jpm11111141
30. Heuer, L., Ashwood, P., Schauer, J., Goines, P., Krakowiak, P., Hertz-Picciotto, I. et al. (2008). Reduced levels of immunoglobulin in children with autism correlates with behavioral symptoms. Autism Research, 1 (5), 275–283. doi: https://doi.org/10.1002/aur.42
31. Jyonouchi, H., Geng, L., Streck, D. L., Toruner, G. A. (2012). Immunological characterization and transcription profiling of peripheral blood (PB) monocytes in children with autism spectrum disorders (ASD) and specific polysaccharide antibody deficiency (SPAD): case study. Journal of Neuroinflammation, 9 (1). doi: https://doi.org/10.1186/1742-2094-9-4
32. Rossignol, D. A., Frye, R. E. (2021). A Systematic Review and Meta-Analysis of Immunoglobulin G Abnormalities and the Therapeutic Use of Intravenous Immunoglobulins (IVIG) in Autism Spectrum Disorder. Journal of Personalized Medicine, 11 (6), 488. doi: https://doi.org/10.3390/jpm11060488
33. Baj, J., Sitarz, E., Forma, A., Wróblewska, K., Karakuła-Juchnowicz, H. (2020). Alterations in the Nervous System and Gut Microbiota after β-Hemolytic Streptococcus Group A Infection – Characteristics and Diagnostic Criteria of PANDAS Recognition. International Journal of Molecular Sciences, 21 (4), 1476. doi: https://doi.org/10.3390/ijms21041476
34. Luleyap, Hu., Onatoglu, D., Yilmaz, Mb., Alptekin, D., Tahiroglu, A., Cetiner, S. et al. (2013). Association between pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections disease and tumor necrosis factor-α gene−308 g/a, −850 c/t polymorphisms in 4-12-year-old children in Adana/Turkey. Indian Journal of Human Genetics, 19 (2), 196. doi: https://doi.org/10.4103/0971-6866.116116
35. Wang, Z., Ding, R., Wang, J. (2020). The Association between Vitamin D Status and Autism Spectrum Disorder (ASD): A Systematic Review and Meta-Analysis. Nutrients, 13 (1), 86. doi: https://doi.org/10.3390/nu13010086
36. Yektaş, Ç., Alpay, M., Tufan, A. E. (2019). Comparison of serum B12, folate and homocysteine concentrations in children with autism spectrum disorder or attention deficit hyperactivity disorder and healthy controls. Neuropsychiatric Disease and Treatment, 15, 2213–2219. doi: https://doi.org/10.2147/ndt.s212361
37. Furlano, R. I., Anthony, A., Day, R., Brown, A., McGarvey, L., Thomson, M. A. et al. (2001). Colonic CD8 and γδ T-cell infiltration with epithelial damage in children with autism. The Journal of Pediatrics, 138 (3), 366–372. doi: https://doi.org/10.1067/mpd.2001.111323
38. Deepmala, Slattery, J., Kumar, N., Delhey, L., Berk, M., Dean, O., Spielholz, C., Frye, R. (2015). Clinical trials of N-acetylcysteine in psychiatry and neurology: A systematic review. Neuroscience & Biobehavioral Reviews, 55, 294–321. doi: https://doi.org/10.1016/j.neubiorev.2015.04.015
39. Warren, R. P., Foster, A., Margaretten, N. C. (1987). Reduced Natural Killer Cell Activity in Autism. Journal of the American Academy of Child & Adolescent Psychiatry, 26 (3), 333–335. doi: https://doi.org/10.1097/00004583-198705000-00008

40. Warren, R. P., Yonk, L. J., Burger, R. A., Cole, P., Odell, J. D., Warren, W. L. et al. (1990). Deficiency of Suppressor-Inducer (Cd4+Cd45ra+) T Cells in Autism. Immunological Investigations, 19 (3), 245–251. doi: https://doi.org/10.3109/08820139009041839
41. Cabanlit, M., Wills, S., Goines, P., Ashwood, P., Van De Water, J. (2007). Brain-Specific Autoantibodies in the Plasma of Subjects with Autistic Spectrum Disorder. Annals of the New York Academy of Sciences, 1107 (1), 92–103. doi: https://doi.org/10.1196/annals.1381.010
42. Frye, R. E., Sequeira, J. M., Quadros, E. V., James, S. J., Rossignol, D. A. (2012). Cerebral folate receptor autoantibodies in autism spectrum disorder. Molecular Psychiatry, 18 (3), 369–381. doi: https://doi.org/10.1038/mp.2011.175
43. Binstock, T. (2001). Intra-monocyte pathogens delineate autism subgroups. Medical Hypotheses, 56 (4), 523–531. doi: https://doi.org/10.1054/mehy.2000.1247
44. Crawley, J. N., Heyer, W.-D., LaSalle, J. M. (2016). Autism and Cancer Share Risk Genes, Pathways, and Drug Targets. Trends in Genetics, 32 (3), 139–146. doi: https://doi.org/10.1016/j.tig.2016.01.001
45. McDougle, C. J., Landino, S. M., Vahabzadeh, A., O'Rourke, J., Zurcher, N. R., Finger, B. C. et al. (2015). Toward an immune-mediated subtype of autism spectrum disorder. Brain Research, 1617, 72–92. doi: https://doi.org/10.1016/j.brainres.2014.09.048
46. Maltsev, D. (2022). Rezultaty otsinky imunnoho statusu u ditei z ras: imunodefitsyt, asotsiiovanyi z henetychnym defitsytom folatnoho tsyklu. Immunology and Allergy: Science and Practice, 4, 5–22. doi: https://doi.org/10.37321/immunology.2021.4-01
47. Careaga, M., Rogers, S., Hansen, R. L., Amaral, D. G., Van de Water, J., Ashwood, P. (2017). Immune Endophenotypes in Children With Autism Spectrum Disorder. Biological Psychiatry, 81 (5), 434–441. doi: https://doi.org/10.1016/j.biopsych.2015.08.036
48. Maltsev, D. (2020). Features of folate cycle disorders in children with ASD. Bangladesh Journal of Medical Science, 19 (4), 737–742. doi: https://doi.org/10.3329/bjms.v19i4.46634
49. Mauracher, A. A., Gujer, E., Bachmann, L. M., Güsewell, S., Pachlopnik Schmid, J. (2021). Patterns of Immune Dysregulation in Primary Immunodeficiencies: A Systematic Review. The Journal of Allergy and Clinical Immunology: In Practice, 9 (2), 792-802.e10. doi: https://doi.org/10.1016/j.jaip.2020.10.057
50. Isung, J., Williams, K., Isomura, K., Gromark, C., Hesselmark, E., Lichtenstein, P. et al. (2020). Association of Primary Humoral Immunodeficiencies With Psychiatric Disorders and Suicidal Behavior and the Role of Autoimmune Diseases. JAMA Psychiatry, 77 (11), 1147. doi: https://doi.org/10.1001/jamapsychiatry.2020.1260
51. Maltsev, D. (2021). The results of the study of the microbial spectrum in children with autism spectrum disorders associated with genetic deficiency of the folate cycle. Men's Health, Gender and Psychosomatic Medicine, 1-2, 26–39. doi: https://doi.org/10.37321/ujmh.2021.1-2-04
52. Chen, N., Zhang, X., Zheng, K., Zhu, L., Zhang, N., Liu, L. et al. (2019). Increased risk of group B Streptococcus causing meningitis in infants with mannose-binding lectin deficiency.

Clinical Microbiology and Infection, 25 (3), 384.e1-384.e3. doi: https://doi.org/10.1016/j.cmi.2018.10.003

53. Asogwa, K., Buabeng, K., Kaur, A. (2017). Psychosis in a 15-Year-Old Female with Herpes Simplex Encephalitis in a Background of Mannose-Binding Lecithin Deficiency. Case Reports in Psychiatry, 2017, 1–5. doi: https://doi.org/10.1155/2017/1429847
54. Bagheri-Hosseinabadi, Z., Imani, D., Yousefi, H., Abbasifard, M. (2020). MTHFR gene polymorphisms and susceptibility to rheumatoid arthritis: a meta-analysis based on 16 studies. Clinical Rheumatology, 39 (8), 2267–2279. doi: https://doi.org/10.1007/s10067-020-05031-5
55. Maltsev, D. V. (2021). The results of the search for laboratory signs of autoimmune reactions to cerebral and extracerebral autoantigens in children with autism spectrum disorders associated with genetic deficiency of the folate cycle. Medical Science of Ukraine (MSU), 17 (3), 22–37. doi: https://doi.org/10.32345/2664-4738.3.2021.03
56. Carlus, S. J., Abdallah, A. M., Bhaskar, L. V. et al. (2016). The MTHFR C677T polymorphism is associated with mitral valve rheumatic heart disease. Eur. Rev. Med. Pharmacol Sci., 20 (1) 109–114.
57. Yigit, S., Inanir, A., Tural, S., Filiz, B., Tekcan, A. (2014). The effect of IL-4 and MTHFR gene variants in ankylosing spondylitis. Zeitschrift Für Rheumatologie, 74 (1), 60–66. doi: https://doi.org/10.1007/s00393-014-1403-2
58. Song, G. G., Bae, S.-C., Seo, Y. H., Kim, J.-H., Choi, S. J., Ji, J. D., Lee, Y. H. (2014). Meta-analysis of functional MBL polymorphisms. Zeitschrift Für Rheumatologie, 73 (7), 657–664. doi: https://doi.org/10.1007/s00393-014-1408-x
59. Glesse, N., Monticielo, O. A., Mattevi, V. S. et al. (2011). Association of mannose-binding lectin 2 gene polymorphic variants with susceptibility and clinical progression in systemic lupus erythematosus. Clin. Exp. Rheumatol, 29 (6), 983–990.
60. Schafranski, M. D., Stier, A., Nisihara, R., Messias-Reason, I. J. T. (2004). Significantly increased levels of mannose-binding lectin (MBL) in rheumatic heart disease: a beneficial role for MBL deficiency. Clinical and Experimental Immunology, 138 (3), 521–525. doi: https://doi.org/10.1111/j.1365-2249.2004.02645.x
61. Aydin, S. Z., Atagunduz, P., Inanc, N. et al. (2007). Mannose binding lectin levels in spondyloarthropathies. J. Rheumatol, 34 (10), 2075–2077.
62. Li, M., Tang, Y., Zhao, E. Y. et al. (2021). Relationship between MTHFR gene polymorphism and susceptibility to bronchial asthma and glucocorticoid efficacy in children. Zhongguo Dang Dai Er Ke Za Zhi, 23 (8), 802–808. doi: https://doi.org/10.7499/j.issn.1008-8830.2105035
63. Wang, T., Zhang, H.-P., Zhang, X., Liang, Z.-A., Ji, Y.-L., Wang, G. (2015). Is Folate Status a Risk Factor for Asthma or Other Allergic Diseases? Allergy, Asthma & Immunology Research, 7 (6), 538. doi: https://doi.org/10.4168/aair.2015.7.6.538
64. Birbian, N., Singh, J., Jindal, S. K., Joshi, A., Batra, N., Singla, N. (2012). Association of the Wild-Type A/A Genotype of MBL2 Codon 54 with Asthma in a North Indian Population. Disease Markers, 32 (5), 301–308. doi: https://doi.org/10.1155/2012/757302

65. El-Hadidy, M. A., Abdeen, H. M., Abd El-Aziz, S. M., Al-Harrass, M. (2014). MTHFR Gene Polymorphism and Age of Onset of Schizophrenia and Bipolar Disorder. BioMed Research International, 2014, 1–9. doi: https://doi.org/10.1155/2014/318483
66. Peerbooms, O. L. J., van Os, J., Drukker, M., Kenis, G., Hoogveld, L., de Hert, M. et al. (2011). Meta-analysis of MTHFR gene variants in schizophrenia, bipolar disorder and unipolar depressive disorder: Evidence for a common genetic vulnerability? Brain, Behavior, and Immunity, 25 (8), 1530–1543. doi: https://doi.org/10.1016/j.bbi.2010.12.006
67. Foldager, L., Köhler, O., Steffensen, R., Thiel, S., Kristensen, A. S., Jensenius, J. C., Mors, O. (2014). Bipolar and panic disorders may be associated with hereditary defects in the innate immune system. Journal of Affective Disorders, 164, 148–154. doi: https://doi.org/10.1016/j.jad.2014.04.017
68. Peng, Q., Lao, X., Huang, X., Qin, X., Li, S., Zeng, Z. (2015). The MTHFR C677T polymorphism contributes to increased risk of Alzheimer's Disease: Evidence based on 40 case-control studies. Neuroscience Letters, 586, 36–42. doi: https://doi.org/10.1016/j.neulet.2014.11.049
69. Sjölander, A., Minthon, L., Nuytinck, L., Vanmechelen, E., Blennow, K., Nilsson, S. (2013). Functional mannose-binding lectin haplotype variants are associated with Alzheimer's disease. Journal of Alzheimer's Disease, 35 (1), 121–127. doi: https://doi.org/10.3233/jad-122044
70. Chen, F., Wen, T., Lv, Q., Liu, F. (2019). Associations between Folate Metabolism Enzyme Polymorphisms and Lung Cancer: A Meta-Analysis. Nutrition and Cancer, 72 (7), 1211–1218. doi: https://doi.org/10.1080/01635581.2019.1677924
71. Pine, S. R., Mechanic, L. E., Ambs, S., Bowman, E. D., Chanock, S. J., Loffredo, C. et al. (2007). Lung Cancer Survival and Functional Polymorphisms in MBL2, an Innate-Immunity Gene. JNCI: Journal of the National Cancer Institute, 99 (18), 1401–1409. doi: https://doi.org/10.1093/jnci/djm128
72. Russo, A. (2009). Low serum myeloperoxidase in autistic children with gastrointestinal disease. Clinical and Experimental Gastroenterology, 85. doi: https://doi.org/10.2147/ceg.s6051
73. Kovacs, M., Papp, M., Lakatos, P. L., Jacobsen, S., Nemes, E., Polgar, M. et al. (2013). Low mannose-binding lectin (MBL) is associated with paediatric inflammatory bowel diseases and ileal involvement in patients with Crohn disease. Journal of Crohn's and Colitis, 7 (2), 134–141. doi: https://doi.org/10.1016/j.crohns.2012.03.008
74. Rai, V., Yadav, U., Kumar, P., Yadav, S. K., Mishra, O. P. (2014). Maternal Methylenetetrahydrofolate Reductase C677T Polymorphism and Down Syndrome Risk: A Meta-Analysis from 34 Studies. PLoS ONE, 9 (9), e108552. doi: https://doi.org/10.1371/journal.pone.0108552
75. Nisihara, R. M., Utiyama, S. R. R., Oliveira, N. P., Messias-Reason, I. J. (2010). Mannan-binding lectin deficiency increases the risk of recurrent infections in children with Down's syndrome. Human Immunology, 71 (1), 63–66. doi: https://doi.org/10.1016/j.humimm.2009.09.361
76. Borges, M. C., Hartwig, F. P., Oliveira, I. O., Horta, B. L. (2015). Is there a causal role for homocysteine concentration in blood pressure? A Mendelian randomization study. The American Journal of Clinical Nutrition, 103 (1), 39–49. doi: https://doi.org/10.3945/ajcn.115.116038

77. Madsen, H. O., Videm, V., Svejgaard, A., Svennevig, J. L., Garred, P. (1998). Association of mannose-binding-lectin deficiency with severe atherosclerosis. The Lancet, 352 (9132), 959–960. doi: https://doi.org/10.1016/s0140-6736(05)61513-9
78. Chen, H., Yang, X Lu, M. (2015). Methylenetetrahydrofolate reductase gene polymorphisms and recurrent pregnancy loss in China: a systematic review and meta-analysis. Archives of Gynecology and Obstetrics, 293 (2), 283–290. doi: https://doi.org/10.1007/s00404-015-3894-8
79. Christiansen, O. B., Kilpatrick, D. C., Souter, V. et al. (1999). Mannan-Binding Lectin Deficiency is Associated with Unexplained Recurrent Miscarriage. Scandinavian Journal of Immunology, 49 (2), 193–196. doi: https://doi.org/10.1046/j.1365-3083.1999.00473.x
80. Yang, Y., Luo, Y., Yuan, J., Tang, Y., Xiong, L., Xu, M. et al. (2015). Association between maternal, fetal and paternal MTHFR gene C677T and A1298C polymorphisms and risk of recurrent pregnancy loss: a comprehensive evaluation. Archives of Gynecology and Obstetrics, 293 (6), 1197–1211. doi: https://doi.org/10.1007/s00404-015-3944-2
81. Hultström, M., Frithiof, R., Eriksson, O., Persson, B., Lipcsey, M., Ekdahl, K. N., Nilsson, B. (2020). Mannose-Binding Lectin is Associated with Thrombosis and Coagulopathy in Critically Ill COVID-19 Patients. Thrombosis and Haemostasis, 120 (12), 1720–1724. doi: https://doi.org/10.1055/s-0040-1715835
82. Maltsev, D., Stefanyshyn, V. (2021). Efficacy of combined immunotherapy with propes and inflamafertin in selective deficiency of nk and nkt cells in children with autism spectrum disorders associated with genetic deficiency of the folate cycle. Romanian Journal of Neurology, 20 (2), 211–216. doi: https://doi.org/10.37897/rjn.2021.2.13
83. Nicolson, G. L., Gan, R., Nicolson, N. L., Haier, J. (2007). Evidence forMycoplasma ssp.,Chlamydia pneunomiae, and human herpes virus-6 coinfections in the blood of patients with autistic spectrum disorders. Journal of Neuroscience Research, 85 (5), 1143–1148. doi: https://doi.org/10.1002/jnr.21203
84. Valayi, S., Eftekharian, M. M., Taheri, M., Alikhani, M. Y. (2018). Evaluation of antibodies to cytomegalovirus and Epstein-Barr virus in patients with autism spectrum disorder. Human Antibodies, 26 (3), 165–169. doi: https://doi.org/10.3233/hab-180335
85. Kuhn, M., Grave, S., Bransfield, R., Harris, S. (2012). Long term antibiotic therapy may be an effective treatment for children co-morbid with Lyme disease and Autism Spectrum Disorder. Medical Hypotheses, 78 (5), 606–615. doi: https://doi.org/10.1016/j.mehy.2012.01.037
86. Hughes, H. K., Ashwood, P. (2018). Anti-Candida albicans IgG Antibodies in Children With Autism Spectrum Disorders. Frontiers in Psychiatry, 9. doi: https://doi.org/10.3389/fpsyt.2018.00627
87. Nayeri, T., Sarvi, S., Moosazadeh, M., Hosseininejad, Z., Sharif, M., Amouei, A., Daryani, A. (2020). Relationship between toxoplasmosis and autism: A systematic review and meta-analysis. Microbial Pathogenesis, 147, 104434. doi: https://doi.org/10.1016/j.micpath.2020.104434
88. Ghaziuddin, M., Al-Khouri, I., Ghaziuddin, N. (2002). Autistic symptoms following herpes encephalitis. European Child & Adolescent Psychiatry, 11 (3), 142–146. doi: https://doi.org/10.1007/s00787-002-0271-5

89. Sakamoto, A., Moriuchi, H., Matsuzaki, J., Motoyama, K., Moriuchi, M. (2015). Retrospective diagnosis of congenital cytomegalovirus infection in children with autism spectrum disorder but no other major neurologic deficit. Brain and Development, 37 (2), 200–205. doi: https://doi.org/10.1016/j.braindev.2014.03.016
90. Monge-Galindo, L., Pérez-Delgado, R., López-Pisón, J. et al. (2010). Mesial temporal sclerosis in paediatrics: its clinical spectrum. Our experience gained over a 19-year period. Rev. Neurol., 50 (6), 341–348.
91. Wipfler, P., Dunn, N., Beiki, O., Trinka, E., Fogdell-Hahn, A. (2018). The Viral Hypothesis of Mesial Temporal Lobe Epilepsy – Is Human Herpes Virus-6 the Missing Link? A systematic review and meta-analysis. Seizure, 54, 33–40. doi: https://doi.org/10.1016/j.seizure.2017.11.015
92. Harberts, E., Yao, K., Wohler, J. E., Maric, D., Ohayon, J., Henkin, R., Jacobson, S. (2011). Human herpesvirus-6 entry into the central nervous system through the olfactory pathway. Proceedings of the National Academy of Sciences, 108 (33), 13734–13739. doi: https://doi.org/10.1073/pnas.1105143108
93. Lecointe, D., Fabre, M., Habes, D. et al. (2000). Macrophage activation syndrome in primary human herpes virus-6 infection: a rare condition after liver transplantation in infants. Gastroenterol. Clin. Biol., 24 (12), 1227–1228.
94. Li, Y., Viscidi, R. P., Kannan, G., McFarland, R., Pletnikov, M. V., Severance, E. G. et al. (2018). Chronic Toxoplasma gondii Infection Induces Anti- N -Methyl- d -Aspartate Receptor Autoantibodies and Associated Behavioral Changes and Neuropathology. Infection and Immunity, 86 (10). doi: https://doi.org/10.1128/iai.00398-18
95. Venâncio, P., Brito, M. J., Pereira, G., Vieira, J. P. (2014). Anti-N-methyl-D-aspartate Receptor Encephalitis with Positive Serum Antithyroid Antibodies, IgM Antibodies Against Mycoplasma pneumoniae and Human Herpesvirus 7 PCR in the CSF. Pediatric Infectious Disease Journal, 33 (8), 882–883. doi: https://doi.org/10.1097/inf.0000000000000408
96. Singh, V. K., Warren, R. P., Odell, J. D., Warren, W. L., Cole, P. (1993). Antibodies to Myelin Basic Protein in Children with Autistic Behavior. Brain, Behavior, and Immunity, 7(1), 97–103. doi: https://doi.org/10.1006/brbi.1993.1010
97. Kong, X., Liu, J., Cetinbas, M., Sadreyev, R., Koh, M., Huang, H., et al. (2019). New and Preliminary Evidence on Altered Oral and Gut Microbiota in Individuals with Autism Spectrum Disorder (ASD): Implications for ASD Diagnosis and Subtyping Based on Microbial Biomarkers. Nutrients, 11 (9), 2128. doi: https://doi.org/10.3390/nu11092128
98. Snider, L. A., Lougee, L., Slattery, M., Grant, P., Swedo, S. E. (2005). Antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders. Biological Psychiatry, 57 (7), 788–792. doi: https://doi.org/10.1016/j.biopsych.2004.12.035
99. Brimberg, L., Sadiq, A., Gregersen, P. K., Diamond, B. (2013). Brain-reactive IgG correlates with autoimmunity in mothers of a child with an autism spectrum disorder. Molecular Psychiatry, 18 (11), 1171–1177. doi: https://doi.org/10.1038/mp.2013.101

100. Kern, J. K., Geier, D. A., Mehta, J. A., Homme, K. G., Geier, M. R. (2020). Mercury as a hapten: A review of the role of toxicant-induced brain autoantibodies in autism and possible treatment considerations. Journal of Trace Elements in Medicine and Biology, 62, 126504. doi: https://doi.org/10.1016/j.jtemb.2020.126504
101. Mostafa, G. A., El-Sherif, D. F., Al-Ayadhi, L. Y. (2014). Systemic auto-antibodies in children with autism. Journal of Neuroimmunology, 272 (1-2), 94–98. doi: https://doi.org/10.1016/j.jneuroim.2014.04.011
102. Whiteley, P., Marlow, B., Kapoor, R. R., Blagojevic-Stokic, N., Sala, R. (2021). Autoimmune Encephalitis and Autism Spectrum Disorder. Frontiers in Psychiatry, 12. doi: https://doi.org/10.3389/fpsyt.2021.775017
103. Maltsev, D. V. (2021). Efficacy of Rituximab in Autism Spectrum Disorders Associated with Genetic Folate Cycle Deficiency with Signs of Antineuronal Autoimmunity. Psychotherapy and Clinical Psychologythis, 12 (3), 472–486. doi: https://doi.org/10.34883/pi.2021.12.3.010
104. Masi, A., Quintana, D. S., Glozier, N., Lloyd, A. R., Hickie, I. B., Guastella, A. J. (2014). Cytokine aberrations in autism spectrum disorder: a systematic review and meta-analysis. Molecular Psychiatry, 20 (4), 440–446. doi: https://doi.org/10.1038/mp.2014.59
105. Saghazadeh, A., Ataeinia, B., Keynejad, K., Abdolalizadeh, A., Hirbod-Mobarakeh, A., Rezaei, N. (2019). A meta-analysis of pro-inflammatory cytokines in autism spectrum disorders: Effects of age, gender, and latitude. Journal of Psychiatric Research, 115, 90–102. doi: https://doi.org/10.1016/j.jpsychires.2019.05.019
106. Jyonouchi, H., Geng, L., Ruby, A., Zimmerman-Bier, B. (2005). Dysregulated Innate Immune Responses in Young Children with Autism Spectrum Disorders: Their Relationship to Gastrointestinal Symptoms and Dietary Intervention. Neuropsychobiology, 51 (2), 77–85. doi: https://doi.org/10.1159/000084164
107. Thom, R. P., Keary, C. J., Palumbo, M. L., Ravichandran, C. T., Mullett, J. E., Hazen, E. P. et al. (2019). Beyond the brain: A multi-system inflammatory subtype of autism spectrum disorder. Psychopharmacology, 236 (10), 3045–3061. doi: https://doi.org/10.1007/s00213-019-05280-6
108. Maltsev, D. (2021). Evaluation of markers of inflammation and neuronal damage in patients with autism spectrum disorders associated with genetic deficiency of the folate cycle. Immunology and Allergy: Science and Practice, 3, 31–39. doi: https://doi.org/10.37321/immunology.2021.3-04
109. Lv, M., Zhang, H., Shu, Y., Chen, S., Hu, Y., Zhou, M. (2016). The neonatal levels of TSB, NSE and CK-BB in autism spectrum disorder from Southern China. Translational Neuroscience, 7 (1), 6–11. doi: https://doi.org/10.1515/tnsci-2016-0002
110. Zheng, Z., Zheng, P., Zou, X. (2020). Peripheral Blood S100B Levels in Autism Spectrum Disorder: A Systematic Review and Meta-Analysis. Journal of Autism and Developmental Disorders, 51 (8), 2569–2577. doi: https://doi.org/10.1007/s10803-020-04710-1

111. Maltsev, D., Natrus, L. (2020). The effectiveness of infliximab in autism spectrum disorders associated with folate cycle genetic deficiency. Psychiatry, Psychotherapy and Clinical Psychologythis, 3, 583–594. doi: https://doi.org/10.34883/pi.2020.11.3.015
112. Xu, G., Snetselaar, L. G., Jing, J., Liu, B., Strathearn, L., Bao, W. (2018). Association of Food Allergy and Other Allergic Conditions With Autism Spectrum Disorder in Children. JAMA Network Open, 1 (2), e180279. doi: https://doi.org/10.1001/jamanetworkopen.2018.0279
113. Theoharides, T. C., Tsilioni, I., Patel, A. B., Doyle, R. (2016). Atopic diseases and inflammation of the brain in the pathogenesis of autism spectrum disorders. Translational Psychiatry, 6 (6), e844–e844. doi: https://doi.org/10.1038/tp.2016.77
114. Theoharides, T. C. (2013). Is a Subtype of Autism an Allergy of the Brain? Clinical Therapeutics, 35 (5), 584–591. doi: https://doi.org/10.1016/j.clinthera.2013.04.009
115. Cao, L.-H., He, H.-J., Zhao, Y.-Y., Wang, Z.-Z., Jia, X.-Y., Srivastava, K. et al. (2022). Food Allergy-Induced Autism-Like Behavior is Associated with Gut Microbiota and Brain mTOR Signaling. Journal of Asthma and Allergy, Volume 15, 645–664. doi: https://doi.org/10.2147/jaa.s348609
116. Yu, Y., Huang, J., Chen, X., Fu, J., Wang, X., Pu, L. et al. (2022). Efficacy and Safety of Diet Therapies in Children With Autism Spectrum Disorder: A Systematic Literature Review and Meta-Analysis. Frontiers in Neurology, 13. doi: https://doi.org/10.3389/fneur.2022.844117
117. Fiorentino, M., Sapone, A., Senger, S., Camhi, S. S., Kadzielski, S. M., Buie, T. M. et al. (2016). Blood–brain barrier and intestinal epithelial barrier alterations in autism spectrum disorders. Molecular Autism, 7 (1). doi: https://doi.org/10.1186/s13229-016-0110-z
118. Azhari, A., Azizan, F., Esposito, G. (2018). A systematic review of gut-immune-brain mechanisms in Autism Spectrum Disorder. Developmental Psychobiology, 61(5), 752–771. doi: https://doi.org/10.1002/dev.21803
119. Bouboulis, D., Mast, P. (2016). Infection-Induced Autoimmune Encephalopathy: Treatment with Intravenous Immune Globulin Therapy. A Report of Six Patients. International Journal of Neurology Research, 2 (1), 256–258. doi: https://doi.org/10.17554/j.issn.2313-5611.2016.02.44
120. Molina-López, J., Leiva-García, B., Planells, E., Planells, P. (2021). Food selectivity, nutritional inadequacies, and mealtime behavioral problems in children with autism spectrum disorder compared to neurotypical children. International Journal of Eating Disorders, 54 (12), 2155–2166. doi: https://doi.org/10.1002/eat.23631
121. Minshew, N. J., Williams, D. L. (2007). The New Neurobiology of Autism. Archives of Neurology, 64 (7), 945. doi: https://doi.org/10.1001/archneur.64.7.945
122. Hardan, A. Y., Fung, L. K., Frazier, T., Berquist, S. W., Minshew, N. J., Keshavan, M. S., Stanley, J. A. (2016). A proton spectroscopy study of white matter in children with autism. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 66, 48–53. doi: https://doi.org/10.1016/j.pnpbp.2015.11.005
123. Marseglia, L. M., Nicotera, A., Salpietro, V., Giaimo, E., Cardile, G., Bonsignore, M. et al. (2015). Hyperhomocysteinemia and MTHFR Polymorphisms as Antenatal Risk Factors

of White Matter Abnormalities in Two Cohorts of Late Preterm and Full Term Newborns. Oxidative Medicine and Cellular Longevity, 2015, 1–8. doi: https://doi.org/10.1155/2015/543134

124. Pavone, V., Praticò, A. D., Parano, E., Pavone, P., Verrotti, A., Falsaperla, R. (2012). Spine and brain malformations in a patient obligate carrier of MTHFR with autism and mental retardation. Clinical Neurology and Neurosurgery, 114 (9), 1280–1282. doi: https://doi.org/10.1016/j.clineuro.2012.03.008
125. Maltsev, D. V. (2021). Neuroradiological signs of encephalopathy in children with autism spectrum disorders associated with genetic folate deficiency. Ukrainian Neurological Journal, 3–4, 16–30. doi: https://doi.org/10.30978/unj2021-3-16
126. González Toro, M. C., Jadraque Rodríguez, R., Sempere Pérez, Á., Martínez Pastor, P., Jover Cerdá, J., Gómez Gosálvez, F. A. (2013). Encefalitis antirreceptor de NMDA: dos casos pediátricos. Revista de Neurología, 57 (11), 504. doi: https://doi.org/10.33588/rn.5711.2013272
127. Pinillos Pisón, R., Llorente Cereza, M. T., López Pisón, J., Pérez Delgado, R., Lafuente Hidalgo, M., Martínez Sapiñá, A., Peña Segura, J. L. (2009). Infección congénita por citomegalovirus. Revisión de nuestra experiencia diagnóstica de 18 años. Revista de Neurología, 48 (07), 349. doi: https://doi.org/10.33588/rn.4807.2008391
128. Maltsev, D. V. (2022). The results of a retrospective analysis of the use of normal intravenous human immunoglobulin in high dose for the treatment of immune-dependent encephalopathy with a clinical picture of autism spectrum disorders in children with genetic deficiency of the folate cycle. International Neurological Journal, 17 (8), 26–38. doi: https://doi.org/10.22141/2224-0713.17.8.2021.250818
129. Perlmutter, S. J., Leitman, S. F., Garvey, M. A., Hamburger, S., Feldman, E., Leonard, H. L., Swedo, S. E. (1999). Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. The Lancet, 354 (9185), 1153–1158. doi: https://doi.org/10.1016/s0140-6736(98)12297-3
130. Slingsby, B., Yatchmink, Y., Goldberg, A. (2017). Typical Skin Injuries in Children With Autism Spectrum Disorder. Clinical Pediatrics, 56 (10), 942–946. doi: https://doi.org/10.1177/0009922817705187
131. Bradstreet, J. J., Smith, S., Baral, M., Rossignol, D. A. (2010). Biomarker-guided interventions of clinically relevant conditions associated with autism spectrum disorders and attention deficit hyperactivity disorder. Altern Med Rev., 15 (1), 15–32.
132. Liu, H., Talalay, P., W. Fahey, J. (2016). Biomarker-Guided Strategy for Treatment of Autism Spectrum Disorder (ASD). CNS & Neurological Disorders - Drug Targets, 15 (5), 602–613. doi: https://doi.org/10.2174/1871527315666160413120414
133. Frye, R. E., Rose, S., Boles, R. G., Rossignol, D. A. (2022). A Personalized Approach to Evaluating and Treating Autism Spectrum Disorder. Journal of Personalized Medicine, 12 (2), 147. doi: https://doi.org/10.3390/jpm12020147

DOI: 10.15587/978-617-7319-65-7.CH5

Lyudmyla Yuryeva, Andrii Shornikov

CHAPTER 5

CYBER ADDICTION: A NEW VIEW AND APPROACHES TO DIAGNOSTICS

ABSTRACT

The evolution of views on the problem of Internet addiction is presented, information is given on its prevalence and comorbidity with mental disorders, and an overview of modern clinical classifications and psychometric tools for its diagnosis is done.

According to modern scientific research, conceptual developments and the I-PACE model, the authors propose to single out a single definition of "cyber addiction" to combine all variants of Internet addiction. The selection of a single definition of "cyber addiction" is based on the fact that the object of addiction is interacting with various information resources and technical means.

For the phenomenon of cyber addiction, the authors proposed clinical diagnostic criteria, which are based on the criteria for diagnosing mental and behavioural disorders due to the use of psychoactive substances of ICD-11 and provided characteristics of the boundary with normative behaviour when using various information resources and technical means. They developed and validated a new psychodiagnostic screening tool based on the proposed cyber addiction paradigm – the YSCAS scale (Yuryeva – Shornikov Cyber Addiction Scale).

KEYWORDS

Internet addiction, cyber addiction, diagnosis, YSCAS scale, computer addiction, mental health problem.

Internet addiction has become a new mental health problem in the 21st century. From 2001 to 2016 the number of Internet users increased by 1000 % [1].

As of January 2023, there were 5.16 billion Internet users worldwide, representing 64.4 % of the world's population. Out of these, 4.76 billion, or 59.4 % of the world's population, were users of social networks [2]. The global internet penetration rate is 62.5 %, with Northern Europe leading the way with 98 % internet penetration among the population. In fact, more than 80 % of adults in the United States state that they go online every day.

In the UNESCO program document "Towards Knowledge Societies" (2005), modern society is defined as a society based on knowledge [3]. New information technologies are an integral part of this society. In just a few decades, a cyber culture with its virtual worldview, various social networks and lifestyle has formed. People spend a lot of time in the virtual world and are largely dependent on it. The average global Internet user spends an average of about 7 hours a day using the Internet on all devices. Gradually, the information environment acquires the character of basic, and interpersonal and social relations acquire the character of secondary [4, 5].

In a society based on knowledge, the system "man-man" is gradually replaced by the system "man-machine", and Homo Faber turns into Homo Informaticus. The environment of modern man is changing from purely social to informational, which is accompanied by mental changes: the transformation of mental activity, emotional alienation, desocialization and destructive changes in the psyche [6].

The question of whether the Internet has a positive or negative effect on people has been debated for more than 25 years. Back in 1999, Kimberly Young et al. described cyber disorders and related mental health problems [7], and Maressa Hecht Orzack described a new generation of children – cyber kids [8]. With the advent of the Internet came the problem of Internet addiction. Currently, the Internet plays an increasingly important role in people's lives, and the line between the Internet and real life is becoming more blurred.

Data on the prevalence of cyber addictions are very variable, as different diagnostic tools are used, and different ages, gender, place of residence and mentality of population groups are studied. In addition, various types of addictive Internet use (addiction to Internet games, social networks, cybersex, and other types) are investigated, which narrows the diagnostic range. When using a descriptive review using electronic databases, as well as a hand search of relevant publications or cross-references from 1970 to 2010, Kaustav Chakraborty et al. concluded that the prevalence of Internet addiction among users ranges from 0.3 to 38 %, with a predominance of young men [9].

According to Aviv Weinstein, the prevalence of IA ranges from 1.5–8.2 % in the USA and Europe [10]. In the developed countries of the East, this indicator ranges from 4 to 18 % [11].

Among teenagers, cyber addiction rates are also very variable and range from 0.8 % in Italy [12] and 1 % in Korea [13] to 8.8 % among Chinese teenagers [14].

With the development of technologies and the appearance of virtual reality, augmented reality, and the widespread use of social networks and online games, the idea of the genesis of Internet addiction is changing, and the use of the term Internet addiction is becoming less accurate to describe the negative phenomena that occur when these technologies are abused [15]. In this regard, the definition, clinical diagnostic criteria and tools for the diagnosis of this disorder need to be modified. The analysis of the current state of the study of this problem and the results of our own research allowed us to consider the addiction that occurs when using the Internet, accompanied by mental problems and the lack of harmonious integration, as cyber addiction [16]. Based on this paradigm, we developed clinical diagnostic criteria and a psychometric screening tool for the diagnosis of this disorder, which is the basis for their successful prevention, correction and treatment.

5.1 EVOLUTION OF IDEAS ABOUT CYBER ADDICTION

Until the 1980s, computer networks were mainly used only by employees of special institutions. Since the 1980s, the distribution of personal computers and communication on the Internet among the population began. In 1990, Isaac Marks wrote that excessive use of the Internet could be considered a form of technological addiction that affects a wide range of behavioural reactions [17].

The Internet officially became publicly available in 1991, and the existence of computer addiction among Internet users was recognized in the United States as early as 1995. The definition of Internet addiction as a behavioural disorder due to Internet and computer use was given by Ivan Goldberg in 1996 [18].

Kimberly Young presented the second concept – problem Internet use (PIU). Using criteria similar to pathological gambling, she suggested that problematic Internet use is closer to impulse control disorder than to addictive conditions. She considered the term "Internet addiction" as a broad concept that means a large number of behavioural and impulse control problems [19].

She identified and described 5 types of internet addiction: computer addiction, net compulsions, information overload, cyber-relational addiction and cybersexual addiction.

Richard A. Davis supplemented Young's definition, highlighted comorbidity, and showed that pathological use of the Internet could activate existing pathology or act as a separate type of addiction. Davis proposes a theoretical cognitive and behavioural model of pathological Internet use (PIU) [20].

He distinguished two categories of Internet use:

– Generalized Problematic Internet Use (GPIU) – a multidimensional overuse of the Internet itself not concerned with any specific online activity;

– Specific Problematic Internet Use (SPIU) – pathological indulgence into an online behaviour through a specific function and/or application.

Alex S. Hall and Jeffrey Parsons introduced a third term, Internet Addictive Behaviour (IAB). They agree that excessive use of the Internet can harm cognitive, behavioural and affective spheres, that is, affect a person's health, but they do not support a pathological aetiology of this problem [21]. Scientists present excessive use of the Internet as a "benign" disorder, which is seen as compensation for behavioural deficiencies in real life. It is believed that this pathology can be compensated due to cognitive-behavioural relationships. In the 21st century, the relevance of research on disorders associated with the excessive use of information resources and technical means is increasing, which is confirmed by the increase in the number of publications on these topics, which were indexed in PubMed (**Fig. 5.1**).

It is worth noting that since 2008, publications devoted to cyber addiction have constantly been appearing in the scientific literature. Cyber addiction is a new phenomenon that is more common among young people due to their high curiosity and frequent lack of time limit in the use of new technologies [22].

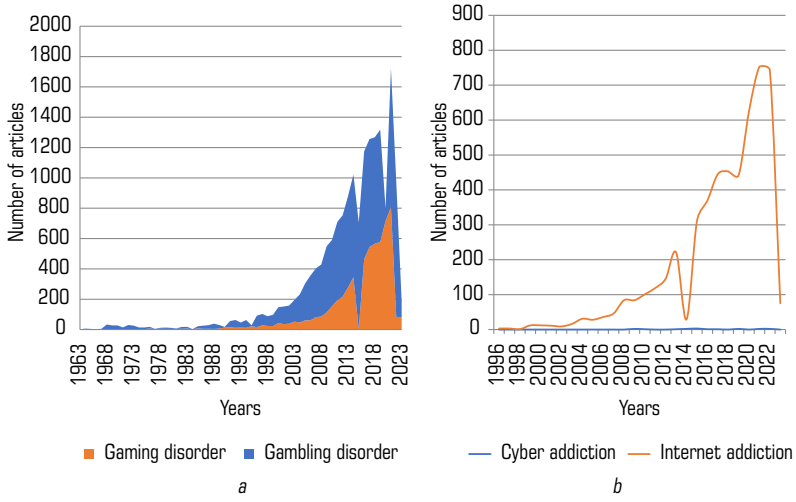


Fig. 5.1 Number of articles in PubMed about: *a* – Gaming disorder and Gambling disorder; *b* – Internet addiction and Cyber addiction

There are several common reasons that can lead to cyber addiction:

1. The need to escape from the real world: the Internet can become a way of avoiding real problems and responsibilities, which can lead to increased degradation of social and interpersonal skills.

2. Availability: the Internet is available to users anytime and anywhere. Unlimited access to a variety of content can lead to unhealthy addiction.

3. Social interaction: the Internet provides an opportunity to easily communicate with other people through social networks, forums and chat rooms. For some people, it becomes the main form of social interaction and sometimes even replaces normal communication in real life. This factor has become more relevant during the restrictive measures due to the COVID-19 pandemic.

4. A sense of success: the Internet can become a means of achieving success through virtual games, virtual communities, and entertainment. For some people, this becomes a motivation to continue spending a lot of time online.

5. Psychological factors: some people may use the Internet to avoid problems in real life and reduce anxiety, depression, loneliness or insecurity.

6. Information factors: the Internet is a limitless source of information, and some people may spend an inordinate amount of time searching for and consuming this information.

When analyzing research topics devoted to IA, it was found that the problem of pathogenesis and diagnosis is constantly being investigated by scientists, and the number of publications on this topic is constantly growing (**Fig. 5.2**). It is these studies that underlie the creation of various conceptual models of pathogenesis and the development of therapeutic strategies for IA.

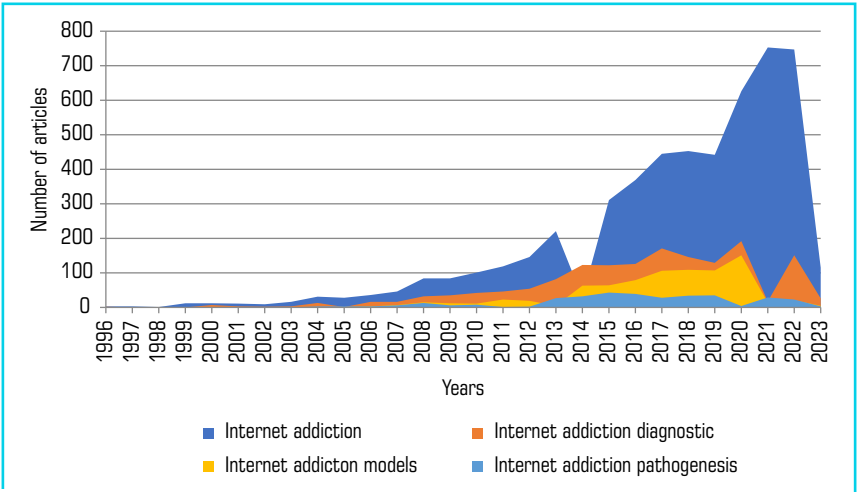


Fig. 5.2 Number of articles in PubMed devoted to Internet addiction and Internet addiction diagnosis

At the beginning of research into the phenomenon of Internet addiction, psychological models explaining their occurrence dominated. The cognitive-behavioural model of pathological use of the Internet by Richard A. Davis became the basis of cognitive-behavioural therapy for patients with IA [20].

The theoretical foundation for the pharmacological treatment of IA became the medical-biological concepts based on biological and psychopathological studies. Three models have been described in which IA is viewed as an obsessive-compulsive disorder [23], an impulse control disorder [24], and/or an addictive disorder [25]. The most evident is the hypothesis according to which IA is considered a non-chemical addiction.

In pilot studies, it was established that pathological addiction to gambling (Gambling disorder) has similar biochemical features to addiction to psychoactive substances and other disorders characterized by impulsive features. According to the available data, norepinephrine is believed to be associated with arousal, dopamine with reward and reinforcing behaviour, serotonin with behavioural initiation and termination (or impulse control), and opioids with pleasure and urges.

The central place in disorders characterized by impaired impulse control is occupied by motivational neural pathways. A central component of motivational neural pathways is cortico-striatal-thalamo-cortical circuits, with more ventral components particularly important for impulsive and reward-oriented behaviours.

The biological hypothesis is confirmed by the revealed neurobiological correlates. The serotonin transporter gene (SS-5HTTLPR) polymorphism was found in Internet addicts [26]. Modern morphometric studies have revealed abnormalities of the white and grey matter of the brain in Internet addicts compared to the control group [27, 28].

In 2016, Matthias Brand et al. proposed An Interaction of the Person-Affect-Cognition-Execution (I-PACE) model [29]. This model is based on the integration of data from psychological, psychopathological and neurobiological studies of pathological disorders related to the use of the Internet. Disorders related to the use of the Internet, without division into separate clinical variants, can be explained by the I-PACE (interaction of person-affect-cognition-performance) model. An example of such a disorder can be cyberbullying. The authors of this model proposed to describe the processes that underlie addiction when using certain Internet applications or sites, Internet games, in particular gambling, watching pornography, shopping, or communicating on the Internet (**Fig. 5.3**).

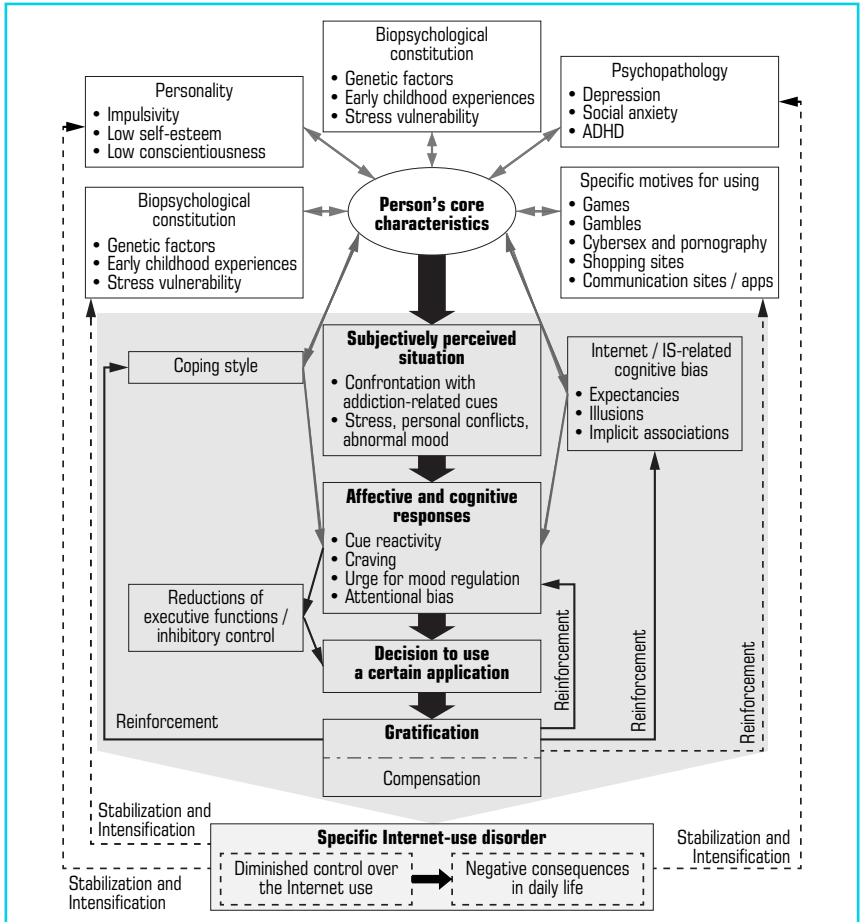


Fig. 5.3 Model I-PACE [29]

Motivation, satisfaction, achievement, and exploration are some of the psychological needs that drive video game addiction. These needs rely on other factors, such as competition, competence, persistence, creativity, and risk management, to keep a loyal game customer as long as possible, even with the potential for addiction [30].

There is currently a discussion on the formation of terminology to describe new non-chemical addictions associated with the use of computers/smartphones and the Internet.

Different types of Internet addiction are often distinguished and studied: compulsive web surfing; excessive virtual communication; gaming addiction (online or offline) – related and not related to gambling; compulsive shopping using the Internet; excessive watching of movies or listening to music; cybersexual addiction, phubbing, or "phone snubbing (insult)", i.e. using the phone during face-to-face communication, pathological upgrading of computers/smartphones. These options are not permanently reflected in modern classifications and are considered separately.

According to modern scientific research, conceptual developments and the I-PACE model, we propose to combine all the above-mentioned disorders into a single diagnostic taxon associated with the excessive use of modern communication technologies – cyber addiction. Our proposed diagnostic criteria for cyber addiction and a new tool for diagnosing cyber addiction – the Yuryeva-Shornikov Cyber Addiction Scale (YSCAS) will be described below.

5.2 MENTAL HEALTH PROBLEMS IN CYBER ADDICTION

Computer addicts experience distress in at least one of five areas: social, professional, educational, financial, and psychophysical. Mental health problems arise as a result of computer addiction and neglect of various aspects of life in exchange for virtual reality.

Among the negative consequences of human interaction with gadgets, socio-psychological and medical negative effects are distinguished. Among the social consequences, pronounced social, family, professional and educational maladjustment, financial problems and deviant forms of behaviour are most common. Among psychological problems, there are problems associated with deformations of the user's personal structure, a decrease in his intellectual abilities and a reduction in elementary school knowledge (use of functions "Spelling check", "mathematical operations"), a decrease in the flexibility of cognitive processes and clip thinking. But the most pathogenic are the medical consequences. Migraine-type headaches, back pain, conjunctivitis, numbness and pain in the fingers of the hand (carpal tunnel syndrome) are the most common among somato-neurological ones, and among psychiatric ones – cyber addiction, sleep disorders, depression and suicidal behaviour.

Cross-sectional studies indicate high comorbidity of Internet addiction and mental disorders [31].

A review of 20 studies correlating problematic internet use (PIU) and mental disorders found that 75 % reported significant correlations of PIU with depression, 57 % with anxiety, 100 % with symptoms of attention-deficit hyperactivity disorder (ADHD), 60 % with obsessive – compulsive symptoms, and 66 % with hostility or aggression. Comorbidity with Borderline personality disorder,

hypomania, and binge eating disorder is less common. People with internet video game addiction are especially likely to have underlying mental health disorders, such as depressive disorder, antisocial personality disorder, other addictions, ADHD and social phobia (agoraphobia).

With Internet addiction, there is a higher risk of addiction to psychoactive substances in adolescents. A significantly higher risk of drug addiction and alcoholism was revealed in young Internet addicts compared to healthy peers. Addicted users of online video games are more likely to use tobacco, alcohol, and cannabis [33]. It has been proven that the presence of Internet addiction can be a predictor of further use of psychoactive substances in adolescents [34].

In a representative sample of 4,957 10th-grade pupils in Istanbul, Turkey, it was found that male gender, substance use, depression, symptoms of attention deficit hyperactivity disorder, and lack of self-confidence predicted an increased risk of Internet addiction among 10th-grades Turkish pupils [35].

According to research data in Asia, among 2,500 college students, Internet addiction was found in 12.3 %, and alcohol addiction in 6.6 %. Often these addictions were combined, and in these cases, depression was most often diagnosed [36].

Adolescents with IA are also prone to suicidal thoughts, self-harm and delinquent behaviour [35]. A study by Patricia R. Recupero et al. proved that 11 % of suicides are the result of visiting pro-suicide sites. The risk group includes patients prone to depression and suicidal behaviour which use the Internet [37].

In patients with IA, short-term psychotic episodes during the period of abstinence have been described. In addition to the usual withdrawal symptoms such as agitation and irritability, the clinical presentation included persecutory delusions and disorganized behaviour. Psychosis was quickly stopped with atypical antipsychotics [38].

The issue of the relationship between cyber addiction and mental and behavioural disorders remains debatable. Do pathological disorders precede or result from IA? To clarify this question, Dong et al. examined the mental state of 59 students by Symptom Checklist-90 before and after the development of addiction [39].

They found that OCD symptoms were present in the study participants even before they became addicted to the Internet. After their addiction, significantly higher scores were observed for dimensions of depression, anxiety, hostility, interpersonal sensitivity, and psychoticism, suggesting that these were outcomes of Internet addiction disorder. An association between withdrawal syndrome, anxiety-depressive disorder, and future Internet addiction was found among South Korean men [40].

The presence of IA may predict a more successful treatment outcome in adults with depression, as IA may slow the process of symptom reduction and correlate with relapse [41].

Anxiety was found to be a predictor of Internet addiction, and Internet addiction was a significant predictor of depression. The results also showed that the relationship between Internet addiction and anxiety depends on gender. Male gender was found to be a significant predictor of Internet addiction [42].

Based on the research of children aged 12–14 with mental disorders and computer addiction, Lyudmyla Yuryeva and Tetiana Bolbot identified primary and symptomatic computer addiction. They described the 3-stage clinical and psychopathological dynamics of the formation of computer addiction [43]. Their research shows symptomatic computer addiction occurs much more often than primary addiction. Based on the conducted clinical-psychopathological examination of patients with computer addiction, it was found that in 55 % of cases, symptomatic computer addiction in children was comorbid with socialized and non-socialized behaviour disorders, in 16 % – with organic anxiety disorder and organic personality disorder, in 11 % – with mild mental retardation. Before the formation of computer addiction, 8 % of the subjects were treated by a psychiatrist and 8 % by a neurologist. These children belong to the risk group of the formation of cyber addiction, and it is advisable for them to carry out screening diagnostics for the purpose of prevention and correction [44].

When carrying out preventive and corrective work among children and young people, it is important to convey information about the phenomenon of codependency to their loved ones and relatives.

Codependency is a psychological concept that describes the relationship between two people, one of whom has an addiction problem, and the other is trying to help him. In the case of cyber addiction, co-dependency may occur in family members or friends of a person with a cyber addiction problem.

In the case of cyber addiction, this can manifest itself in the fact that loved ones try to control the time a person spends on the Internet, forbid him to use a computer or mobile phone, and force him to go to therapy. However, such actions are not always beneficial, as they can make a person suffering from cyber addiction even more dependent on loved ones, reduce their independence and can reduce their motivation to fight addiction on their own.

To prevent codependency, it is important for the loved ones of a person with cyber addiction to maintain a balance between help and independence. They must provide assistance but must also take care of their own needs and health.

5.3 PROBLEMS OF CLINICAL DIAGNOSIS OF CYBER ADDICTION

The issue of recognizing IA as a nosological unit and including it in the classifications of mental disorders remains debatable.

In 2008, Jerald J. Block proposed to include Internet addiction in DSM-V [45]. He identified three subtypes of internet addiction (excessive gaming, sex addiction, email/texting addiction) and computer game addiction.

For all selected subtypes of IA, he proposed the following 4 criteria:

– excessive use of the Internet, often with a loss of sense of time or disregard for basic needs;

– withdrawal syndrome, including aggression, tension, and/or depression when the computer is unavailable;

– tolerance, including the need for better computer equipment, more computer programs, and increased time spent at the computer;

– negative consequences including arguments, lying, problems with learning and recreation, social isolation and fatigue.

Diagnostic criteria also include symptomatic criteria (seven clinical symptoms of Internet addiction), criteria for clinically significant disorders (functional and psychosocial), course criteria (duration of addiction for at least three months and use of the Internet for at least 6 hours a day, while the person is completely could do without it) and exclusion criteria (exclusion of addiction caused by mental disorders).

In 2010, Chinese researchers led by Ran Tao proposed their criteria for the diagnosis of Internet addiction, which are based on the DSM-5 criteria for chemical dependence [46].

Diagnostic criteria for Internet addiction:

1. Symptomatic criteria.

Both criteria must be present:

1) preoccupation with the Internet: the person constantly remembers previous Internet activity or anticipates the next Internet session;

2) withdrawal symptoms, as evidenced by dysphoria, anxiety, irritability, and boredom after several days without Internet use.

At least one (or more) of the following symptoms:

1) tolerance: the increase in time spent online that is necessary to achieve satisfaction;

2) persistent desire and/or unsuccessful attempts to control, reduce, or stop Internet use;

3) continued excessive use of the Internet despite knowledge of ongoing or recurrent physical or psychological problems that have been caused or exacerbated by Internet use;

4) loss of interest in previous hobbies and pastimes, with the exception of Internet use, as a direct result;

5) a person uses the Internet to avoid or relieve a bad mood (e.g., dysphoria, feelings of helplessness, guilt, anxiety);

6) exclusion criterion: excessive Internet use associated with psychiatric disorder or type I bipolar disorder.

2. Clinically significant criteria for violations: functional violations (reduction in social, scientific, educational, industrial activity), including loss of significant relationships, work, educational or career opportunities.

3. Temporal criteria: the duration of Internet addiction should be more than 3 months when using the Internet for 6 or more hours a day.

Korean experts also proposed diagnostic criteria for detecting IA in adolescents and college students [47, 48].

But due to the fact that the number of studies based on the standards of evidence-based medicine turned out to be insufficient, experts concluded that there are currently no grounds for including IA as a classification of mental disorders [33].

In 2013, IA was not included in DSM-5, and in 2019 in ICD-11. Internet addiction was mentioned in the DSM-5 as a condition requiring further study, but it is not considered a mental disorder.

Modern classifications of disorders associated with excessive use of information resources and technical means are given in **Table 5.1** [49–51]. Among the disorders associated with excessive use of information resources and technical means, only two diagnostic taxon have been identified: Gambling disorder and Gaming disorder.

It should be noted that a new disease appears in ICD-11 – Gaming disorder, which is characterized by dependence on the process of games and not on excitement, as in Gambling disorder.

There are two variants of Gaming disorder: mainly online and mainly offline. This division significantly narrows the diagnosis of disorders related to the use of technical means and the Internet.

Proposed diagnostic criteria for cyber addiction.

To improve and unify the diagnosis of cyber addiction based on a single addictive theory, we propose the following diagnostic criteria, which are based on the criteria for the diagnosis of mental and behavioural disorders due to the use of psychoactive substances ICD-11 [49].

We see interaction with various information resources and technical means as the object of dependence. It is this approach that will not divide the single phenomenon of cyber addiction into dozens of sub-variants.

The main criteria for the diagnosis of cyber addiction include a model of repeated episodic or constant interaction with various information resources and technical means with signs of dysregulation of interaction with various information resources and technical means, which is manifested by one or more of the following signs:

– violation of control over interaction with various information resources and technical means (i.e., start, frequency, intensity, duration, termination, context of interaction);

– increasing the priority of interaction with various information resources and technical means over other aspects of life, including health maintenance, daily activities and responsibilities, so much so that interaction with various information resources and technical means continues or increases, despite causing harm or negative consequences (for example, repeated violations of relationships, especially family ones, professional or school consequences, negative effects on health).

Additional clinical characteristics:

– a subjective feeling of urge or desire (craving) to interact with various information resources and technical means often, but not always, accompanies the main signs of cyber addiction;

– tolerance (measured by the minimally comfortable duration or amount of time per day of interaction with various information resources and technical means) varies depending on individual factors (for example, history of use of psychoactive substances, genetics). With abstinence, the effects of tolerance diminish over time;

– individuals with certain co-occurring disorders or conditions (e.g., substance abuse, personality disorders) usually have reduced tolerance;

Table 5.1 Diagnostic criteria

Disease	ICD-10	DSM-5	ICD-11
Gambling disorder	The disorder consists of frequent, repeated episodes of gambling that dominate the patient's life to the detriment of social, occupational, material, and family values and commitments	A persistent pattern of gambling behaviour, which may be predominantly online (i.e., over the Internet or similar electronic networks) or offline, manifested by all of the following: – impaired control over gambling behaviour (e.g., onset, frequency, intensity, duration, termination, context); – increasing priority is given to gambling behaviour to the extent that gambling takes precedence over other life interests and daily activities; – continuation or escalation of gambling behaviour despite negative consequences (e.g., marital conflict due to gambling behaviour, repeated and substantial financial losses, negative impact on health). The pattern of gambling behaviour may be continuous or episodic and recurrent but is manifested over an extended period of time (e.g., 12 months). The gambling behaviour is not better accounted for by another mental disorder (e.g., Manic Episode) and is not due to the effects of a substance or medication. The pattern of gambling behaviour results in significant distress or impairment in personal, family, social, educational, occupational, or other important areas of functioning	A. Persistent and recurrent problematic gambling behaviour leading to clinically significant impairment or distress, as indicated by the individual exhibiting four (or more) of the following in a 12-month period: 1. Needs to gamble with increasing amounts of money in order to achieve the desired excitement. 2. Is restless or irritable when attempting to cut down or stop gambling. 3. Has made repeated unsuccessful efforts to control, cut back, or stop gambling. 4. Is often preoccupied with gambling (e.g., having persistent thoughts of reliving past gambling experiences, handicapping or planning the next venture, thinking of ways to get money with which to gamble). 5. Often gambles when feeling distressed (e.g., helpless, guilty, anxious, depressed). 6. After losing money gambling often returns another day to get even ("chasing" one's losses). 7. Lies to conceal the extent of involvement with gambling. 8. Has jeopardized or lost a significant relationship, job, or educational or career opportunity because of gambling. 9. Relies on others to provide money to relieve desperate financial situations caused by gambling. B. The gambling behavior is not better explained by a manic episode
Gaming disorder	–	–	A persistent pattern of gaming behaviour ("digital gaming" or "video-gaming"), which may be predominantly online (i.e., over the Internet or similar electronic networks) or offline, manifested by all of the following: – impaired control over gaming behaviour (e.g., onset, frequency, intensity, duration, termination, context); – increasing priority is given to gaming behaviour to the extent that gaming takes precedence over other life interests and daily activities; – continuation or escalation of gaming behaviour despite negative consequences (e.g., family conflict due to gaming behaviour, poor scholastic performance, negative impact on health). The pattern of gaming behaviour may be continuous or episodic and recurrent but is manifested over an extended period of time (e.g., 12 months). The gaming behaviour is not better accounted for by another mental disorder (e.g., Manic Episode) and is not due to the effects of a substance or medication. The pattern of gaming behaviour results in significant distress or impairment in personal, family, social, educational, occupational, or other important areas of functioning

– physical or mental health consequences (other than the core characteristics of cyber addiction) are commonly present in individuals with cyber addiction but are not required for the diagnosis. Similarly, functional impairment in one or more areas of life (e.g., work, household responsibilities, parenting) is commonly observed in individuals with cyber addiction but is not required for the diagnosis;

– individuals with cyber addiction have elevated rates of many other mental disorders, particularly those associated with high levels of anxiety. The specific pattern of combined occurrence depends on the characteristics of the patient's personality and reflects common risk factors and general cause-and-effect relationships;

– a model of interaction with various information resources and technical means, which includes frequent repetitions or a long time of interaction, is more common among certain subgroups (for example, teenagers). In such cases, peer group dynamics may contribute to the maintenance of cyber addiction. Regardless of the social contribution to behaviour, a pattern of interaction with various informational resources and technical means that conforms to subgroup norms should not be considered presumptive evidence of cyber addiction unless all diagnostic requirements for the disorder are met.

Limit with the norm (threshold):

– frequent interaction with various information resources and technical means does not automatically mean a diagnosis of cyber addiction. There should be evidence of signs of cyber addiction, such as a violation of control over the time of interaction with various information resources and technical means, an increased priority of interaction with various information resources and technical means over other life priorities or physiological features.

5.4 INSTRUMENTS FOR INTERNET ADDICTION EVALUATION

Over 30 years of studying IA in different countries of the world, many tools for its assessment have been developed, but the "gold standard" for the diagnosis and assessment of IA has not yet been created. In a large literature review of IA measurement tools, Stéphanie Laconi et al. identified 45 instruments that measure and assess IA through scales, interviews, or diagnostic criteria [52].

Among these instruments, not all have been properly validated, and their psychometric properties have not been investigated among different groups of users. Of the 45 instruments, only 17 had their psychometric characteristics evaluated more than once, and 10 had three or more evaluations. Other scales require further study before they can be used by researchers and clinicians as a tool to assess IA. According to Keith W. Beard and Aviv Weinstein and Michel Lejoyeux, the validity of these scales is questionable mainly due to the lack of definition for IA and its current grounding in multiple theoretical frameworks [53, 54].

Among the well-studied diagnostic tools used in scientific and practical activities, the following scales are most often used [55, 56].

The most frequently used is the Internet Addiction Test – IAT is based on the Internet Addiction Diagnostic Questionnaire – IADQ and assesses IA based on criteria for the diagnosis of pathological gambling. The IADQ is based on diagnostic criteria for compulsive gambling and alcoholism [19, 57].

The Internet Addiction Scale (IAS), which was created by Griffiths and validated by Laura A. Nichols and Richard Nicki and Fatih Canan et al. [58].

The Compulsive Internet Use Scale – CIUS was developed primarily on criteria for pathological gambling [59]. The Chen Internet Addiction Scale – CIAS is another questionnaire developed on criteria for pathological gambling and substance dependence [60]. The Online Cognition Scale – OCS is a questionnaire based on cognitive-behavioural theory [61]. The Generalized Problematic Internet Use Scale – GPIUS is another questionnaire based on cognitive-behavioural theory [62]. Examples of other IA instruments include the Problematic Internet Use Questionnaire – PIUQ [63], Problematic Internet Use Scale – PIUS [64], Computer and Internet Use – CIU [65], Problematic Internet Use Diagnostic-Interview – PIUD-I [24] and others.

In 2005, Ukrainian researchers Lyudmyla Yuryeva and Tetiana Bolbot had created a "Method of screening diagnostics of computer addiction". This method, unlike others, allows not only to diagnose of the state of addiction but also to identify a "risk group" with signs of computer addiction to apply effective preventive programs aimed at preventing the development of mental and behavioural disorders. The questionnaire consists of 11 questions. The answer is evaluated on a 4-point scale: 1 – never, 2 – rarely, 3 – often and 4 – very often [66] (**Table 5.2**).

Evaluation of the emotional state, volitional qualities, consumer aspects, abilities to control behaviour, and physical and psychological influences on the user, which are reflected in the questions using an extended range of adapted indicators of the symptoms of computer addiction, allows you to differentiate the initial data between the stages of "addiction", "hobbies" and "risk of occurrence" [43].

The results are evaluated based on the sum of points:

– up to 15 points – 0 % risk of developing computer addiction;

– 16–22 points – the stage of enthusiasm;

– 23–37 points – the risk of developing computer addiction (the need for preventive programs in the future);

– more than 38 points – presence of computer addiction.

The use of this method allows for effective screening and diagnostics of computer addiction both among individuals and in a group of gadget users, as well as at the same time assessing the emotional state of the individual, his volitional characteristics, the ability to self-control behavior, physical and psychological state.

In 2013–2015, an international study was conducted to compare the results of using three survey methods that are designed to diagnose Internet addiction: the Young's Internet Addiction Scale [19], Chen Internet Addiction Scale [60] and the method of screening diagnostics of computer addiction Lyudmyla Yuryeva and Tetiana Bolbot [66]. The results of the study showed that all correlations between respondents' answers are high, the scales are comparable, and the results obtained on any of the three scales can be compared [67].

Table 5.2 Screening diagnostic scale of computer addiction by Lyudmyla Yuryeva and Tetiana Bolbot

№	Question	Never	Rarely	Often	Very often
1	How often do you feel invigorated, satisfied, or relieved when you are at the computer (being online)?				
2	How often do you foresee being at the computer (being online), thinking and reflecting on how you will find yourself at the computer, opening a certain site, finding certain information, and making new acquaintances?				
3	How often do you need to spend more and more time at the computer (being online) or spend more and more money in order to get the same sensations?				
4	How often do you manage to independently stop working at the computer (being online)?				
5	How often do you feel nervous, depressed, irritable, or empty when away from the computer (being offline)?				
6	How often do you feel the need to go back to the computer (being online) to improve your mood or get away from life's problems?				
7	How often do you neglect family, social responsibilities and studies due to frequent computer work (being online)?				
8	How often do you have to lie and hide from parents or teachers the amount of time spent on the computer (being online)?				
9	How often is there an actualization or threat of loss of friendly and/or family relationships, changes in financial stability, and academic success in connection with frequent work at the computer (being online)?				
10	How often do you notice physical symptoms, such as numbness and pain in your hand, back pain, dry eyes, headaches, neglect of personal hygiene, and eating near the computer?				
11	How often do you notice sleep disturbances or changes in sleep patterns in connection with frequent work at the computer (being online)?				

5.5 YSCAS SCALE. A NEW INSTRUMENT FOR THE CYBER ADDICTION DIAGNOSIS

Existing tools for diagnosing Internet addiction no longer meet the times in their theoretical approaches, and do not fully reflect the problems of addicts. Between general Internet addiction and specific types of addictive Internet use (addiction to Internet games, social networks, cybersex, etc.) there are not only general features but also psychological and psychopathological differences.

The use of diagnostic methods focused on certain types of non-chemical addictions significantly narrows the diagnostic corridor and distorts statistical data on the prevalence of IA.

Based on these considerations, we developed a new psychodiagnostic tool based on the modern paradigm of cyber addiction. The YSCAS scale (Yuryeva-Shornikov Cyber Addiction Scale) can be a tool for diagnosing various types of Internet addiction. It is an 18-item self-report scale, each rated on a 5-point Likert scale from 1 (very rarely) to 5 (very often) [68]. The proposed scale allows you to detect cyber addiction and can be used as a screening method, after which you still need to consult a specialist in non-chemical addictions. High prognostic characteristics make it possible to detect addictive behaviour with a high degree of probability when interacting with various information resources and technical means.

When developing the YSCAS scale in 2020–2021, we conducted an assessment of the reliability of the questionnaire (psychometric reliability) and an assessment of validity. Psychometric reliability is based on two main criteria: internal consistency criteria of scale items and stability criteria (test-retest reliability). To determine the validity of the test, we investigated external, content, construct and criterion validity. In the first stage, we evaluated the internal consistency of the YSCAS scale, and external and content validity, at the second stage – stability, construct and criterion validity. To characterize the criterion validity of the YSCAS, we used the Chen Internet Addiction Scale (CIAS) and its subscales [60].

A study by Chih-Hung Ko et al. showed that the Chen Internet Addiction Scale has high predictive qualities in the diagnosis of gaming disorder according to the DSM-5 criteria: the optimal points for screening and diagnosis were 68 or more (sensitivity – 97.1 %; specificity – 76.8 %) and 72 or more (sensitivity – 85.5 %; specificity – 87.0 %) [69].

At the pilot testing stage, 116 people (39 men and 77 women) who were students at the Dnipro State Medical University (Ukraine) took part in the study. Age range – from 19 to 69 years. The main sample of respondents was represented by 101 people, of which 60 people participated in the study of the retest reliability of the questionnaire. In **Table 5.3** the general characteristics of the studied persons are shown.

Table 5.3 General characteristics of participants (Me[Q1;Q3])

Indicator	**Value**		
Study	**Primary**	**Repeated**	**Total**
Participants number	116	101	217
Proportion of men/women	39/77	27/74	66/151
Age	21 [20;34]	21 [20;45]	21 [20;40]
YSCAS	34 [28.5;41.5]	35 [30;40]	34 [29;42]
CIAS	–	44 [37;53]	44 [37;53]

The normality of the distribution of features was assessed using the Shapiro-Wilk test. Internal consistency and homogeneity of the YSCAS scale were assessed using Cronbach's α coefficient and average correlation coefficients between scale items. The coefficient of internal consistency of the split test was also studied. A value of ≥ 0.70 was taken as the cut-off point of Cronbach's α coefficient, and 0.20 to 0.40 was considered an acceptable range of average correlation coefficients between items. Possible gender differences in the YSCAS total score were assessed using the Mann-Whitney test for unrelated groups. When assessing the stability (sensitivity) of the test, its repeatability was studied using the "test-retest" method with an interval of two weeks using the Wilcoxon W-test.

Since external and content validity were considered by the authors at the stage of question preparation, the validity analysis included an assessment of construct and criterion validity. The construct validity of the YSCAS questionnaire was tested by studying its structure using factor analysis. To characterize the criterion validity of the YSCAS, Spearman's correlation coefficients were calculated between the total score of this scale and the total score of the Chen Internet Addiction Scale (CIAS) and its subscales [60, 70].

In order to determine the diagnostic significance of the proposed test, a characteristic curve (ROC-curve) was constructed based on the values of sensitivity and specificity, which shows the dependence of the number of correctly diagnosed positive cases on the number of incorrectly diagnosed negative cases (X axis = specificity, Y axis = sensitivity) and is one of the methods of assessing model quality. To obtain the numerical value of the clinical significance of the test, the AUC (Area Under Curve) indicator was used – the area under the curve, which evaluates the quality of the model as follows: 0.9–1.0 – excellent, 0.8–0.9 – very good, 0.7–0.8 – good, 0.6–0.7 – average, 0.5–0.6 – unsatisfactory [71].

In all cases of hypothesis testing, $p < 0.05$ was considered a significant level of differences.

When assessing the internal consistency and homogeneity of the YSCAS scale using the α-Cronbach coefficient and the average correlation coefficients between the items of the scale as a whole. The average Cronbach's α was 0.840953, standardized – 0.855660, and the average correlation coefficient between scale items – 0.253627. Detailed Cronbach's α values for individual questions and the correlation between the question and the total score are given in the **Table 5.4**.

Also, in order to assess the internal consistency of the test, the test was evaluated using the splitting method (Split half reliability). The indicator of the coefficient of internal consistency of the test was obtained at the level of 0.8719 with a strong correlation between equal halves ($r_s = 0.7730$).

Evaluating the gender difference of the YSCAS scale using the Mann-Whitney test, the following results were obtained: U = 4865.00, z = –0.2761 with $p = 0.7823$, which indicates the absence of a gender difference in the total score of the YSCAS scale.

As shown in **Fig. 5.4**, the frequency distribution of answers to the questions corresponds to the expected results, with the exception of questions 5 and 9, however, according to the analysis of Cronbach's alpha (**Table 5.4**), the exclusion of these questions will not lead to a significant increase in the quality of the questionnaire.

Table 5.4 Evaluation of the internal consistency of the YSCAS scale

Question №	Correlation between question and total score	Alpha if removed
1	0.473534	0.831469
2	0.498949	0.830008
3	0.422908	0.833743
4	0.437342	0.833102
5	–0.050315	0.867160
6	0.474572	0.831420
7	0.619197	0.824429
8	0.646118	0.822805
9	0.450731	0.834427
10	0.403059	0.834673
11	0.336436	0.838198
12	0.311800	0.840688
13	0.625457	0.822149
14	0.492079	0.830451
15	0.591625	0.825526
16	0.676506	0.820607
17	0.498346	0.831753
18	0.324345	0.837966

The obtained data together indicate a high internal consistency and homogeneity of the questions of the proposed YSCAS scale.

To determine the stability of the indicators of the YSCAS scale, the assessment of the subjects was carried out twice with an interval of two weeks. The sums of points obtained with the help of the YSCAS scale decreased, which can be explained by the fact that certain respondents paid attention to the amount of time they spend using various gadgets and reduced it. To check the statistical reliability of these changes, the scores on the YSCAS questionnaire (test-retest) were compared with each other using the non-parametric Wilcoxon W-test, the calculation of which revealed a high reliability of differences ($p = 0.0061$) (**Fig. 5.5**). However, the calculation of Cohen's d revealed that the obtained effect of changes is small ($d = –0.248$ (95 % CI 0.683, –0.038)), which allows us to ignore the decrease in the total score after two weeks. Spearman's correlation coefficient, which reflects the retest reliability of the YSCAS was $r_s = 0.7464$ ($p < 0.001$), which indicates a very strong relationship between the results of repeated assessments of the examined.

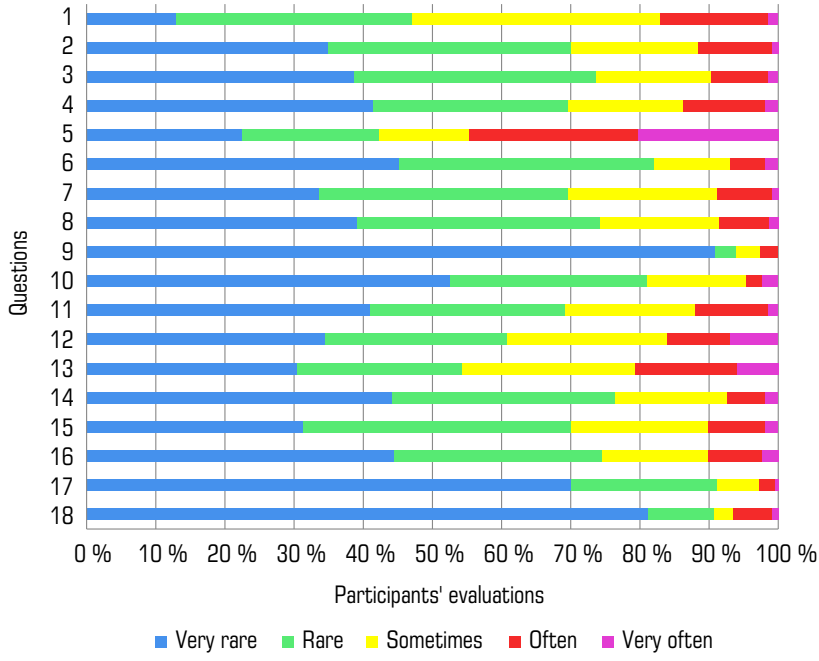


Fig. 5.4 Participants' evaluations of YSCAS questions

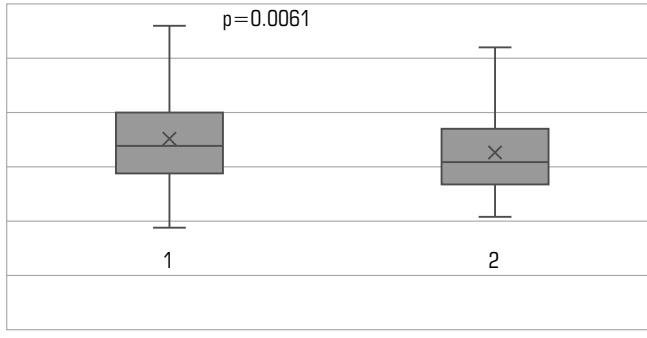


Fig. 5.5 YSCAS value at time: 1 – test; 2 – retest
Note: *p = 0.0061 according to the Wilcoxon test (T = 462, Z = 2.74078037)*

Criterion validity was assessed using Spearman's correlation coefficient between YSCAS and Chen's Internet Addiction Scale (CIAS), which was $r_s = 0.8044$ ($p < 0.001$). The limit value of this parameter is most often considered $r_s = 0.8$ [72].

The obtained results indicate high criterion validity, that is, both the proposed scale and the CIAS test measure the same phenomena.

From the data given in **Table 5.5**, it follows that the YSCAS total score among the subscales of the CIAS test correlates more strongly with the core symptoms of Internet addiction than with problems related to Internet addiction. The data of the study of construct validity explain this. Using factor analysis, we did not find internal factors that would act as subscales. According to the rocky embankment criterion (**Fig. 5.6**), a sufficient number of factors in the YSCAS scale is 2, but **Table 5.6** shows that even using a four-factor model will explain only 53.8 % of the variance. None of the orthogonal rotations of the factors led to an increase in the cumulative percentage. Thus, the proposed YSCAS scale should be considered as a single factor, which does not have subscales in its structure.

Table 5.5 Rank correlation coefficients of the YSCAS scale with CIAS subscales

Symptom	Com	Wit	Tol	IH	TM	IA-Sym	IA-RP
YSCAS	0.687	0.732	0.587	0.652	0.607	0.800	0.686

Note: *Com – compulsive symptoms; Wit – withdrawal symptoms; Tol – symptoms of tolerance; IH – intrapersonal problems and health problems; TM – problems with time management; IA-Sym – key symptoms of Internet addiction, IA-RP – problems related to Internet addiction*

Table 5.6 Variance analysis of the YSCAS scale

Factors	Dispersions	% of the total variance	Cumulative variance	Cumulative %
1	5.719459	31.77477	5.719459	31.77477
2	1.474328	8.19071	7.193787	39.96548
3	1.312862	7.29368	8.506649	47.25916
4	1.180317	6.55732	9.686966	53.81648

The quality of the YSCAS model was analyzed using ROC analysis. The resulting area under the curve (AUC) was 0.971 (95 % CI 0.88, 1.0), which characterizes the excellent quality of the model (**Fig. 5.7**). In our work, the threshold value of the total risk scale (cut off) was 47 points. The studied indicator had a sensitivity (Se) of 100.0 % and a specificity (Sp) of 90.4 %.

Since the obtained results indicate the presence of cyber addiction with a YSCAS test result of 47 or more points, we offer the following gradation of results: 18–33 points – no addiction, 33–46 points – a tendency to addiction, and 47 or more points – present cyber addiction.

As a result of the approbation of the proposed psychodiagnostic technique "Yuryeva-Shornikov Cyber Addiction Scale" (**Table 5.7**), it was established that this psychodiagnostic tool is a reliable and valid method of diagnosing cyber addiction. The results of our work confirm the psychometric reliability of the proposed YSCAS test, high construct and criterion validity.

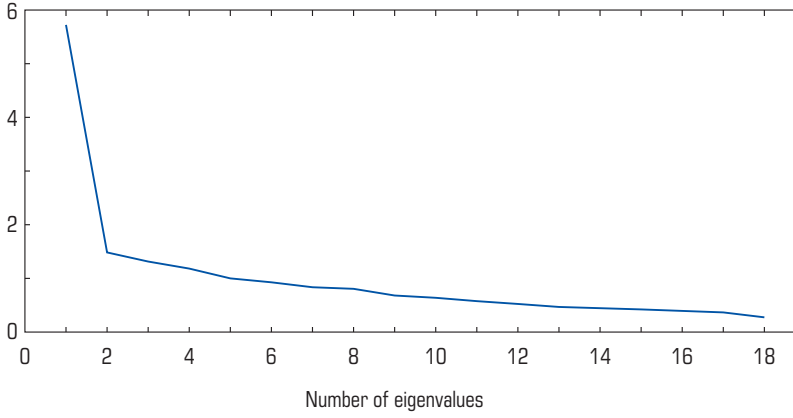


Fig. 5.6 Stone embankment criterion for YSCAS

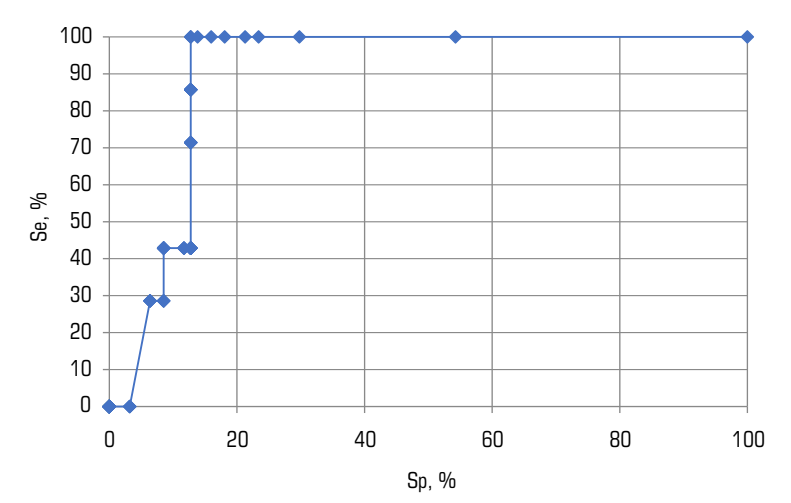


Fig. 5.7 ROC curve for the YSCAS test

Table 5.7 Yuryeva-Shornikov Cyber Addiction Scale – YSCAS

№	Statement	Very rarely	Rarely	Regularly / from time to time	Often	Very often
1	How often do you feel invigorated, satisfied, or relieved when you are online?					
2	How often do you anticipate being online when you are offline?					
3	How often do you notice that you need to spend more and more time online?					
4	How often do you spend time online instead of sleeping?					
5	How often do you manage to stop your online activity on your own?					
6	How often do you feel irritable, depressed, and empty when offline or without gadgets?					
7	How often do you feel the need to go online to improve your mood or get away from problems?					
8	How often do you neglect family, community responsibilities and studies due to frequent online presence?					
9	How often do you have to lie to family members or others about the amount of time you spend online?					
10	How often do people say that you spend too much time online?					
11	How often do you notice physical symptoms, such as numbness and pain in the wrists, pain in the back and neck, dry eyes?					
12	How often do you notice sleep disturbances or changes in sleep patterns?					
13	When online, how often do you find yourself saying, "Just a few more minutes, and that is it"?					
14	How often do you choose the Internet over face-to-face communication?					
15	How often does using the Internet decrease your ability to work and/or your efficiency?					
16	How often does it happen to you that you want to reduce the amount of time you spend online, but nothing works?					
17	How often do you try to hide the amount of time you spend online?					
18	How often do you think you should get help for coping with the Internet?					

Calculation of points.

For questions 1–4 and 6–18: very rarely – 1 point, rarely – 2 points, regularly / from time to time – 3 points, often – 4 points, very often – 5 points.

In question 5 – reverse calculation of points: very rarely – 5 points, rarely – 4 points, regularly / from time to time – 3 points, often – 2 points, very often – 1 point.

Results:

– 18–32 points – no addiction;

– 33–46 points – a tendency towards addiction;

– 47 or more points – cyber addiction is present.

In a clinical study of the YSCAS scale, it was established that the Spearman correlation coefficient between the YSCAS indicators and Chen's Internet addiction scale was $r_s = 0.8044$ ($p < 0.001$), which indicates high criterion validity. Evaluating the construct validity, it was established that the YSCAS scale should be considered as a single factor, which does not have subscales in its structure. The proposed method of diagnosing cyber addiction showed a high quality of the predictive model using ROC analysis: the area under the curve (AUC) was 0.971 (95 % CI 0.88, 1.0). The sensitivity of the scale was 100.0 % with a specificity of 90.4 %.

Analyzing our own data, we note that among 217 examined persons aged 19 to 69, the median score on the scale was 34 (29; 42) points. The prevalence of cyber addiction was 14.3 %, while 45.6 % of respondents were in the risk zone (**Fig. 5.8**). The obtained indicators are significantly higher than the results of the meta-analysis by Yuan-Chien Pan et al., according to which the prevalence of Internet addiction is 7.02 % (95 % CI 6.09–8.08 %), and the prevalence of Internet gaming is 2.47 % (95 % CI 1.46–4.16 %). This is explained by excellent approaches in diagnostics: Yuan-Chien Pan et al. separate Internet Gaming disorder from Internet addiction, then the proposed scale distinguishes all manifestations of addictive behaviour associated with interaction with various information resources and technical means [73].

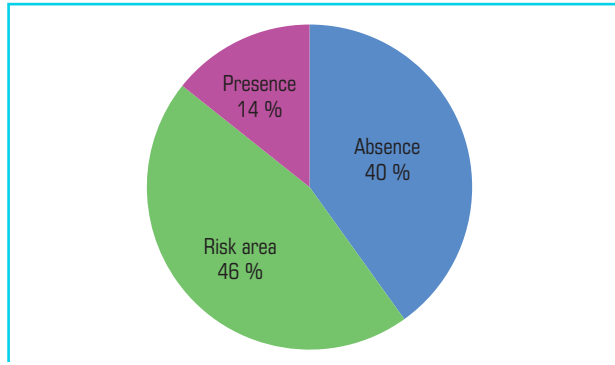


Fig. 5.8 Prevalence of cyber addiction according to the YSCAS scale

Comparing our data with the results of the study by Ameena M. Al Mukhaini et al., who investigated Internet addiction among those who studied at a residency in Oman, it is possible to assert the similarity of the obtained data. Thus, in Oman, 37.3 % of residents were addicted to the Internet; moreover, among those addicted, 36.2 % had depression [74].

As a perspective for further research, it is possible to conduct additional studies to assess the factorial validity of the scale in samples of conditionally healthy individuals and in heterogeneous clinical samples using factor analysis.

CONCLUSION

Analysis of the dynamics of the study of the problem of cyber addiction and a review of modern research on this topic shows that in recent decades, the efforts of researchers have been directed to the study of its genesis, the creation of conceptual models, and the search for effective methods of diagnosis and treatment. However, it should be noted that despite the 30-year history of research into this phenomenon, scientists have not been able to reach a consensus on definitions, clinical and psychometric tools for the diagnosis and classification of Internet addiction behaviour. To date, only Gambling Disorder and Gaming Disorder are represented as diagnostic taxa in mental disorder classifications. This significantly narrows the diagnostic possibilities of detecting Internet risky behaviour, especially at the first stages of its development, which is very important not only for its timely prevention and correction, but also for the prevention of mental and behavioural disorders comorbid with it.

According to modern scientific studies, conceptual developments and the I-PACE model, we propose to combine all variants of Internet addiction, which are not consistently reflected in modern classifications and are considered separately (phubbing, obsessive web surfing; telephone snubbing, excessive virtual communication; cybersexual addiction and others) into a single diagnostic taxon associated with excessive use of modern communication technologies and call it cyber addiction. The selection of a single definition of "cyber addiction" is based on the fact that we see interaction with various information resources and technical means as the object of addiction. It is this approach that will not divide the single phenomenon of cyber addiction into dozens of sub-variants.

In order to improve and unify the diagnosis of cyber addiction and based on a single addictive theory, we proposed clinical diagnostic criteria based on the criteria for the diagnosis of mental and behavioural disorders due to the use of psychoactive substances ICD-11. We have highlighted and described the main and additional clinical characteristics of cyber addiction and provided characteristics of the boundary with normative behaviour when using various information resources and technical means.

Due to the fact that the existing tools for diagnosing various variants of Internet addiction do not fully correspond to our proposed definition of cyber addiction and cannot be used for its screen-

ing, we developed a new psychodiagnostic tool based on the modern paradigm of cyber addiction. The YSCAS (Yuryeva-Shornikov Cyber Addiction Scale) is an 18-item self-report scale, each rated on a 5-point Likert scale from 1 (very rarely) to 5 (very often). The proposed scale allows detecting cyber addiction and can be used as a screening method.

In a clinical study of the YSCAS scale, it was established that the Spearman correlation coefficient between the YSCAS indicators and Chen's Internet addiction scale was $r_s = 0.8044$ ($p < 0.001$), which indicates high criterion validity. Evaluating the construct validity, it was established that the YSCAS scale should be considered as a single factor, which does not have subscales in its structure. The proposed method of diagnosing cyber addiction showed a high quality of the predictive model using ROC analysis: the area under the curve (AUC) was 0.971 (95 % CI 0.88, 1.0). The sensitivity of the scale was 100.0 % with a specificity of 90.4 %.

High prognostic characteristics make it possible to detect addictive behaviour with a high degree of probability when interacting with various information resources and technical means.

Our proposed new approach to the phenomenon of cyber addiction, clinical diagnostic criteria for cyber addiction and the new screening psychometric tool in the diagnosis of cyber addiction YSCAS will allow to unify the diagnosis of various variants of addiction states, carry out their early screening diagnosis, identify risk groups and carry out timely preventive and corrective work.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this paper.

REFERENCES

1. Kuss, D. J., Lopez-Fernandez, O. (2016). Internet addiction and problematic Internet use: A systematic review of clinical research. World Journal of Psychiatry, 6 (1), 143–176. doi: https://doi.org/10.5498/wjp.v6.i1.143
2. Petrosyan, A. (2023). Internet and social media users in the world 2023. Statista. Available at: https://www.statista.com/statistics/617136/digital-population-worldwide/
3. Bindé, J., Matsuura, K. (Eds.) (2005). Towards knowledge societies. UNESCO Pub, 237.
4. Yuryeva, L. N. (2014). Kompiuternaia zavisimost-addiktciia obshchestva, osnovannogo na znaniiakh. Tiumenskii Meditcinskii Zhurnal, 16 (1), 54–55.
5. Yuryeva, L. N. (2015). Formirovanie kiberkultury: Ot klinopisi k Internetu. Novosti Meditciny i Farmatcii, 15 (558), 20–21.
6. Maruta, N. O., Yuryeva, L. M. (Ed.) (2022). Okhorona psykhichnoho zdorov'ia. Strokov D. V.

7. Young, K., Pistner, M., O'Mara, J., Buchanan, J. (1999). Cyber Disorders: The Mental Health Concern for the New Millennium. CyberPsychology & Behavior, 2 (5), 475–479. doi: https://doi.org/10.1089/cpb.1999.2.475
8. Orzack, M. H. (1999). Cyberkids: Overdosing on computers? FCD Update, 4, 1.
9. Chakraborty, K., Basu, D., Vijaya Kumar, K. G. (2010). Internet addiction: Consensus, controversies, and the way ahead. East Asian Archives of Psychiatry, 20 (3), 123–132.
10. Weinstein, A. (2015). Comorbidity of Internet addiction with other psychiatric conditions. Journal of Behavioral Addictions, 4 (S1), 43–44.
11. Christakis, D. A., Moreno, M. M., Jelenchick, L., Myaing, M. T., Zhou, C. (2011). Problematic internet usage in US college students: a pilot study. BMC Medicine, 9 (1). doi: https://doi.org/10.1186/1741-7015-9-77
12. Poli, R., Agrimi, E. (2011). Internet addiction disorder: Prevalence in an Italian student population. Nordic Journal of Psychiatry, 66 (1), 55–59. doi: https://doi.org/10.3109/08039488.2011.605169
13. Park, S., Jeon, H. J., Bae, J. N., Seong, S. J., Hong, J. P. (2017). Prevalence and Psychiatric Comorbidities of Internet Addiction in a Nationwide Sample of Korean Adults. Psychiatry Investigation, 14 (6), 879–882. doi: https://doi.org/10.4306/pi.2017.14.6.879
14. Xu, J., Shen, L., Yan, C., Hu, H., Yang, F., Wang, L. et al. (2012). Personal characteristics related to the risk of adolescent internet addiction: a survey in Shanghai, China. BMC Public Health, 12 (1). doi: https://doi.org/10.1186/1471-2458-12-1106
15. Starcevic, V. (2013). Is Internet addiction a useful concept? Australian & New Zealand Journal of Psychiatry, 47 (1), 16–19. doi: https://doi.org/10.1177/0004867412461693
16. Lin, X., Su, W., Potenza, M. N. (2018). Development of an Online and Offline Integration Hypothesis for Healthy Internet Use: Theory and Preliminary Evidence. Frontiers in Psychology, 9. doi: https://doi.org/10.3389/fpsyg.2018.00492
17. Marks, I. (1990). Behavioural (non-chemical) addictions. Addiction, 85 (11), 1389–1394. doi: https://doi.org/10.1111/j.1360-0443.1990.tb01618.x
18. Goldberg, I. (1996). Internet addiction disorder. CyberPsychol. Behavior, 3 (4), 403–412.
19. Young, K. S. (1998). Internet Addiction: The Emergence of a New Clinical Disorder. CyberPsychology & Behavior, 1 (3), 237–244. doi: https://doi.org/10.1089/cpb.1998.1.237
20. Davis, R. A. (2001). A cognitive-behavioral model of pathological Internet use. Computers in Human Behavior, 17 (2), 187–195. doi: https://doi.org/10.1016/s0747-5632(00)00041-8
21. Hall, A. S., Parsons, J. (2001). Internet addiction: College student case study using best practices in cognitive behavior therapy. Journal of Mental Health Counseling, 23 (4), 312–328.
22. Sánchez Palacios, B. I., Zambrano Vera, G. (2020). La ciberadicción en el rendimiento académico de los estudiantes de educación básica superior de la escuela Cicerón Robles Velásquez, 2019. Caribeña de Ciencias Sociales, agosto, Article agosto. Available at: https://www.eumed.net/rev/caribe/2020/08/ciberadiccion.html

23. Grant, J. E., Potenza, M. N., Weinstein, A., Gorelick, D. A. (2010). Introduction to Behavioral Addictions. The American Journal of Drug and Alcohol Abuse, 36 (5), 233–241. doi: https://doi.org/10.3109/00952990.2010.491884
24. Beard, K. W., Wolf, E. M. (2001). Modification in the Proposed Diagnostic Criteria for Internet Addiction. CyberPsychology & Behavior, 4 (3), 377–383. doi: https://doi.org/10.1089/109493101300210286
25. Fisoun, V., Floros, G., Siomos, K., Geroukalis, D., Navridis, K. (2012). Internet Addiction as an Important Predictor in Early Detection of Adolescent Drug Use Experience – Implications for Research and Practice. Journal of Addiction Medicine, 6 (1), 77–84. doi: https://doi.org/10.1097/adm.0b013e318233d637
26. Lee, Y. S., Han, D. H., Yang, K. C., Daniels, M. A., Na, C., Kee, B. S., Renshaw, P. F. (2008). Depression like characteristics of 5HTTLPR polymorphism and temperament in excessive internet users. Journal of Affective Disorders, 109 (1-2), 165–169. doi: https://doi.org/10.1016/j.jad.2007.10.020
27. Lin, F., Zhou, Y., Du, Y., Qin, L., Zhao, Z., Xu, J., Lei, H. (2012). Abnormal White Matter Integrity in Adolescents with Internet Addiction Disorder: A Tract-Based Spatial Statistics Study. PLoS ONE, 7 (1), e30253. doi: https://doi.org/10.1371/journal.pone.0030253
28. Zhou, Y., Lin, F., Du, Y., Qin, L., Zhao, Z., Xu, J., Lei, H. (2011). Gray matter abnormalities in Internet addiction: A voxel-based morphometry study. European Journal of Radiology, 79 (1), 92–95. doi: https://doi.org/10.1016/j.ejrad.2009.10.025
29. Brand, M., Young, K. S., Laier, C., Wölfling, K., Potenza, M. N. (2016). Integrating psychological and neurobiological considerations regarding the development and maintenance of specific Internet-use disorders: An Interaction of Person-Affect-Cognition-Execution (I-PACE) model. Neuroscience & Biobehavioral Reviews, 71, 252–266. doi: https://doi.org/10.1016/j.neubiorev.2016.08.033
30. Shaikh, B., Jumain, R. S. A. (2014). Grounded Theory of Consumer Loyalty, a Perspective through Video Game Addiction. International Journal of Economics and Management Engineering, 8 (5), 1542–1544.
31. Weinstein, A., Curtiss Feder, L., Rosenberg, K. P., Dannon, P.; Rosenberg, K. P., Feder, L. C. (Eds.) (2014). Chapter 5 – Internet Addiction Disorder: Overview and Controversies. Behavioral Addictions. Academic Press, 99–117. doi: https://doi.org/10.1016/B978-0-12-407724-9.00005-7
32. Carli, V., Durkee, T., Wasserman, D., Hadlaczky, G., Despalins, R., Kramarz, E. et al. (2012). The Association between Pathological Internet Use and Comorbid Psychopathology: A Systematic Review. Psychopathology, 46 (1), 1–13. doi: https://doi.org/10.1159/000337971
33. Van Rooij, A. J., Kuss, D. J., Griffiths, M. D., Shorter, G. W., Schoenmakers, T. M., van de Mheen, D. (2014). The (co-)occurrence of problematic video gaming, substance use, and psychosocial problems in adolescents. Journal of Behavioral Addictions, 3 (3), 157–165. doi: https://doi.org/10.1556/jba.3.2014.013

34. Rücker, J., Akre, C., Berchtold, A., Suris, J.-C. (2015). Problematic Internet use is associated with substance use in young adolescents. Acta Paediatrica, 104 (5), 504–507. doi: https://doi.org/10.1111/apa.12971
35. Evren, C., Dalbudak, E., Evren, B., Demirci, A. C. (2014). High risk of Internet addiction and its relationship with lifetime substance use, psychological and behavioral problems among 10(th) grade adolescents. Psychiatria Danubina, 26 (4), 330–339.
36. Yen, C., Tang, T., Yen, J., Lin, H., Huang, C., Liu, S., Ko, C. (2008). Symptoms of problematic cellular phone use, functional impairment and its association with depression among adolescents in Southern Taiwan. Journal of Adolescence, 32 (4), 863–873. doi: https://doi.org/10.1016/j.adolescence.2008.10.006
37. Recupero, P. R., Harms, S. E., Noble, J. M. (2008). Googling Suicide. The Journal of Clinical Psychiatry, 69 (6), 878–888. doi: https://doi.org/10.4088/jcp.v69n0601
38. Paik, A., Oh, D., Kim, D. (2014). A Case of Withdrawal Psychosis from Internet Addiction Disorder. Psychiatry Investigation, 11 (2), 207. doi: https://doi.org/10.4306/pi.2014.11.2.207
39. Dong, G., Lu, Q., Zhou, H., Zhao, X. (2011). Precursor or Sequela: Pathological Disorders in People with Internet Addiction Disorder. PLoS ONE, 6 (2), e14703. doi: https://doi.org/10.1371/journal.pone.0014703
40. Cho, S.-M., Sung, M.-J., Shin, K.-M., Lim, K. Y., Shin, Y.-M. (2012). Does Psychopathology in Childhood Predict Internet Addiction in Male Adolescents? Child Psychiatry & Human Development, 44 (4), 549–555. doi: https://doi.org/10.1007/s10578-012-0348-4
41. Zhou, J., Friedel, M., Rosmarin, D. H., Pirutinsky, S. (2023). Internet Addiction and the Treatment of Depression? A Prospective Naturalistic Outcome Study. Cyberpsychology, Behavior, and Social Networking, 26 (2), 121–126. doi: https://doi.org/10.1089/cyber.2022.0184
42. Xie, X., Cheng, H., Chen, Z. (2023). Anxiety predicts internet addiction, which predicts depression among male college students: A cross-lagged comparison by sex. Frontiers in Psychology, 13. doi: https://doi.org/10.3389/fpsyg.2022.1102066
43. Yuryeva, L. N., Bolbot, T. Yu. (2006). Kompiuternaia zavisimost: Formirovanie, diagnostika, kor rektciia i profilaktika. Porogi, 196.
44. Yuryeva, L. N., Bolbot, T. Yu., Nosov, S. H. (2004). Sluchai symptomatycheskoi kompiuternoi zavysymosty u patsyenta s orhanycheskym porazhenyem tsentralnoi nervnoi systemi. Arkhiv Psykhiatrii, 10 (3 (38)), 134–138.
45. Block, J. J. (2008). Issues for DSM-V: Internet Addiction. American Journal of Psychiatry, 165 (3), 306–307. doi: https://doi.org/10.1176/appi.ajp.2007.07101556
46. Tao, R., Huang, X., Wang, J., Zhang, H., Zhang, Y., Li, M. (2010). Proposed diagnostic criteria for internet addiction. Addiction, 105 (3), 556–564. doi: https://doi.org/10.1111/j.1360-0443.2009.02828.x
47. Ko, C.-H., Yen, J.-Y., Chen, S.-H., Yang, M.-J., Lin, H.-C., Yen, C.-F. (2009). Proposed diagnostic criteria and the screening and diagnosing tool of Internet addiction in college students. Comprehensive Psychiatry, 50 (4), 378–384. https://doi.org/10.1016/j.comppsych.2007.05.019

48. Ko, C.-H., Yen, J.-Y., Chen, C.-C., Chen, S.-H., Yen, C.-F. (2005). Proposed Diagnostic Criteria of Internet Addiction for Adolescents. The Journal of Nervous and Mental Disease, 193 (11), 728–733. doi: https://doi.org/10.1097/01.nmd.0000185891.13719.54
49. ICD-11 for Mortality and Morbidity Statistics (2021). WHO. International classification of diseases. Available at: https://icd.who.int/browse11/l-m/en#/http%3a%2f%2fid.who.int%2ficd%2fentity%2f499894965
50. Nuller, Yu. L., Tsyrkyn, S. Yu. (Eds.) (1994). Mezhdunarodnaia klassyfykatsyia boleznei (10-i peresmotr). Klassyfykatsyia psykhycheskykh y povedencheskykh rasstroistv. Klynycheskye opysanyia y ukazanyia po dyahnostyke. Adys.
51. Diagnostic and Statistical Manual of Mental Disorders (2013). American Psychiatric Association. doi: https://doi.org/10.1176/appi.books.9780890425596
52. Laconi, S., Rodgers, R. F., Chabrol, H. (2014). The measurement of Internet addiction: A critical review of existing scales and their psychometric properties. Computers in Human Behavior, 41, 190–202. doi: https://doi.org/10.1016/j.chb.2014.09.026
53. Beard, K. W. (2005). Internet Addiction: A Review of Current Assessment Techniques and Potential Assessment Questions. CyberPsychology & Behavior, 8 (1), 7–14. doi: https://doi.org/10.1089/cpb.2005.8.7
54. Weinstein, A., Lejoyeux, M. (2010). Internet Addiction or Excessive Internet Use. The American Journal of Drug and Alcohol Abuse, 36 (5), 277–283. doi: https://doi.org/10.3109/00952990.2010.491880
55. Mihajlov, M., Vejmelka, L. (2017). Internet addiction: a review of the first twenty years. Psychiatria Danubina, 29 (3), 260–272. doi: https://doi.org/10.24869/psyd.2017.260
56. Weinstein, A. (2015). Internet Addiction: Diagnosis, comorbidity and treatment. Meditsinskaya psikhologiya v Rossi, 4 (33), 3.
57. Young, K. S. (1998). Caught in the net: How to recognize the signs of Internet addiction--and a winning strategy for recovery. J. Wiley.
58. Nichols, L. A., Nicki, R. (2004). Development of a Psychometrically Sound Internet Addiction Scale: A Preliminary Step. Psychology of Addictive Behaviors, 18 (4), 381–384. doi: https://doi.org/10.1037/0893-164x.18.4.381
59. Meerkerk, G.-J., Van Den Eijnden, R. J. J. M., Vermulst, A. A., Garretsen, H. F. L. (2009). The Compulsive Internet Use Scale (CIUS): Some Psychometric Properties. CyberPsychology & Behavior, 12 (1), 1–6. doi: https://doi.org/10.1089/cpb.2008.0181
60. Chen, S.-H., Weng, L.-J., Su, Y.-J., Wu, H.-M., Yang, P.-F. (2003). Development of a Chinese Internet Addiction Scale and Its Psychometric Study. Chinese Journal of Psychology, 45 (3), 279–294.
61. Davis, R. A., Flett, G. L., Besser, A. (2002). Validation of a New Scale for Measuring Problematic Internet Use: Implications for Pre-employment Screening. CyberPsychology & Behavior, 5 (4), 331–345. doi: https://doi.org/10.1089/109493102760275581

62. Caplan, S. E. (2002). Problematic Internet use and psychosocial well-being: development of a theory-based cognitive-behavioral measurement instrument. Computers in Human Behavior, 18 (5), 553–575. doi: https://doi.org/10.1016/s0747-5632(02)00004-3
63. Demetrovics, Z., Szeredi, B., Rózsa, S. (2008). The three-factor model of Internet addiction: The development of the Problematic Internet Use Questionnaire. Behavior Research Methods, 40 (2), 563–574. doi: https://doi.org/10.3758/brm.40.2.563
64. Morahan-Martin, J., Schumacher, P. (2000). Incidence and correlates of pathological Internet use among college students. Computers in Human Behavior, 16 (1), 13–29. doi: https://doi.org/10.1016/s0747-5632(99)00049-7
65. Pratarelli, M. E., Browne, B. L. (2002). Confirmatory Factor Analysis of Internet Use and Addiction. CyberPsychology & Behavior, 5 (1), 53–64. doi: https://doi.org/10.1089/109493102753685881
66. Yuryeva, L. M., Bolbot, T. Yu. (2005). Pat. No. 72366. Method of screening diagnostics for detecting computer dependence. MPK: G09B 3/00. published: 15.02.2005. Available at: https://uapatents.com/3-72366-sposib-skriningovo-diagnostiki-kompyuterno-zalezhnosti.html
67. Voiskunskii, A., Mitina, O., Guseinova, A., Rustamova, N. (2015). Measurement of Internet addiction: Comparison of diagnostic methods. Meditsinskaya psikhologiya v Rossi, 4 (33), 11.
68. Yuryeva, L., Shornikov, A. (2021). A new instrument for the cyberaddiction diagnosis. Ukrains'kyi Visnyk Psykhonevrolohii, 29 (3 (108)), 57–62. doi: https://doi.org/10.36927/2079-0325-v29-is3-2021-11
69. Ko, C.-H., Chen, S.-H., Wang, C.-H., Tsai, W.-X., Yen, J.-Y. (2019). The Clinical Utility of the Chen Internet Addiction Scale – Gaming Version, for Internet Gaming Disorder in the DSM-5 among Young Adults. International Journal of Environmental Research and Public Health, 16 (21), 4141. doi: https://doi.org/10.3390/ijerph16214141
70. Malygin, V. L., Feklisov, K. A., Iskandirova, A. B., Antonenko, A. A. (2011). Metodologicheskie podkhody k rannemu vyiavleniiu Internet-zavisimogo povedeniia. Meditcinskaia Psikhologiia v Rossii, 6.
71. Grigoryev, S. G., Lobzin, Yu. V., Skripchenko, N. V. (2016). The role and place of logistic regression and roc analysis in solving medical diagnostic task. Journal Infectology, 8 (4), 36–45. doi: https://doi.org/10.22625/2072-6732-2016-8-4-36-45
72. Boateng, G. O., Neilands, T. B., Frongillo, E. A., Melgar-Quiñonez, H. R., Young, S. L. (2018). Best Practices for Developing and Validating Scales for Health, Social, and Behavioral Research: A Primer. Frontiers in Public Health, 6. doi: https://doi.org/10.3389/fpubh.2018.00149
73. Pan, Y.-C., Chiu, Y.-C., Lin, Y.-H. (2020). Systematic review and meta-analysis of epidemiology of internet addiction. Neuroscience & Biobehavioral Reviews, 118, 612–622. doi: https://doi.org/10.1016/j.neubiorev.2020.08.013
74. Al Mukhaini, A. M., Al Houqani, F. A., Al Kindi, R. M. (2021). Internet Addiction and Depression Among Postgraduate Residents. Sultan Qaboos University Medical Journal, 21 (3), 408–415. doi: https://doi.org/10.18295/squmj.4.2021.008

MODERN METHODS OF DIAGNOSING DISEASES

Ivan Mamontov, Kostyantin Kramarenko, Tamara Tamm, Valentin Nepomniashchyi,
Olena Shakalova, Dmytro Rjabushhenko, Olha Yuryk, Lukyan Anatychuk,
Roman Kobylianskyi, Nadiia Yuryk, Liliia Yukhymenko, Sergii Khomenko, Lidiia Iliukha,
Dmytro Maltsev, Lyudmyla Yuryeva, Andrii Shornikov

Collective monograph

Technical editor I. Prudius
Desktop publishing T. Serhiienko

PC TECHNOLOGY CENTER
Published in March 2023
Enlisting the subject of publishing No. 4452 – 10.12.2012
Address: Shatylova dacha str., 4, Kharkiv, Ukraine, 61165
