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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**.

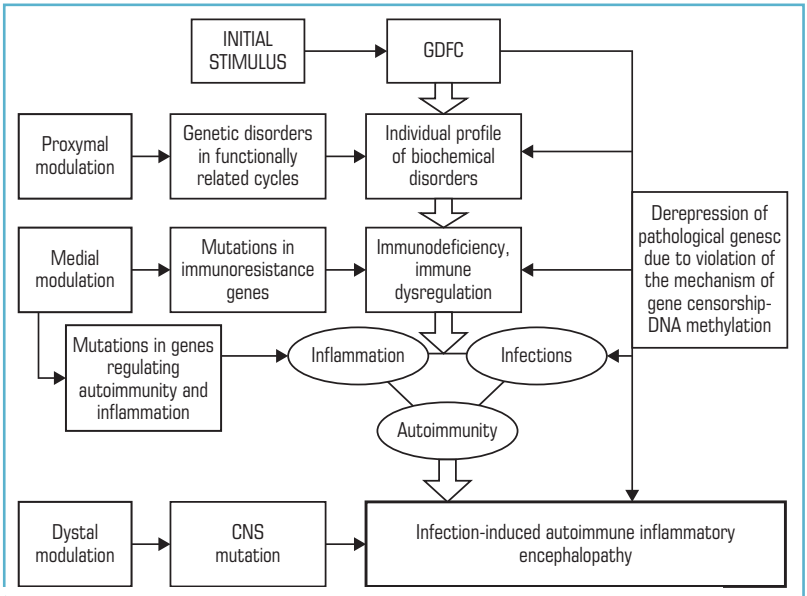

Fig. 4.1 The structure of individual pathological gene systems in the development of ASD and other neuropsychiatric syndromes in children in the context of the folate-centric concept of disease pathogenesis

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].

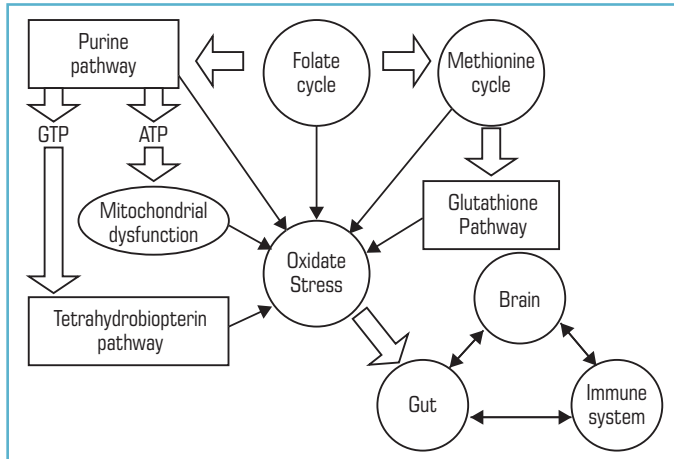

Fig. 4.2 Schematic diagram of the system of key functionally related biochemical cycles and pathways involved in the pathogenesis of neuropsychiatric diseases in children, according to the folate-centric concept

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**).

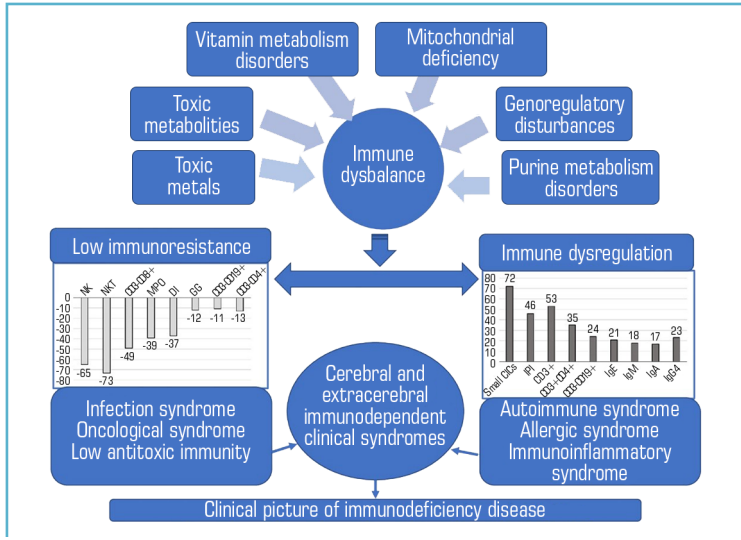

Fig. 4.3 Pathogenesis of a specific form of GDFC-induced immunodeficiency in children with neuropsychiatric syndromes and clinical consequences in the context of the folate-centric concept of disease pathogenesis

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].

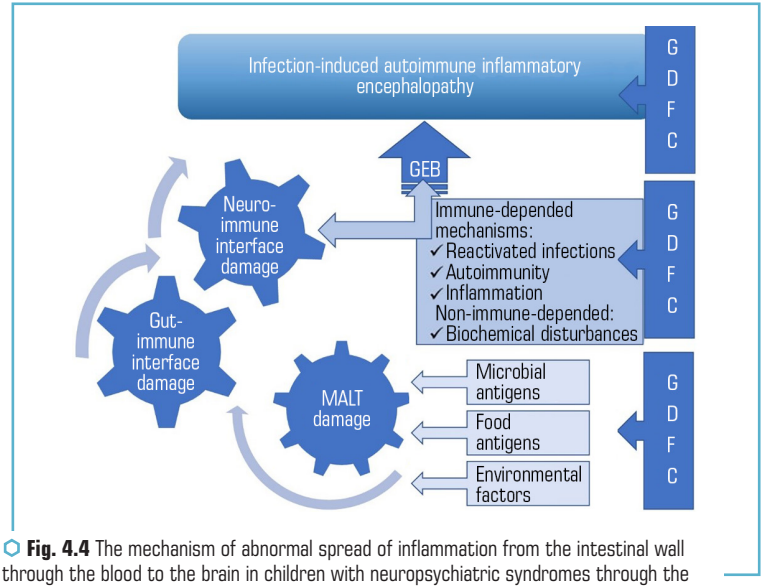

Fig. 4.4 The mechanism of abnormal spread of inflammation from the intestinal wall through the blood to the brain in children with neuropsychiatric syndromes through the functional microbiota-gut-brain axis within the framework of the folate-centric concept

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].

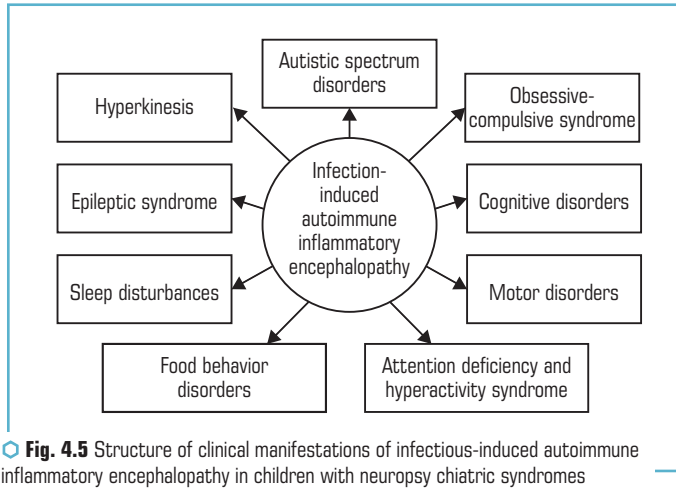

Fig. 4.5 Structure of clinical manifestations of infectious-induced autoimmune inflammatory encephalopathy in children with neuropsy chiatric syndromes

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**).

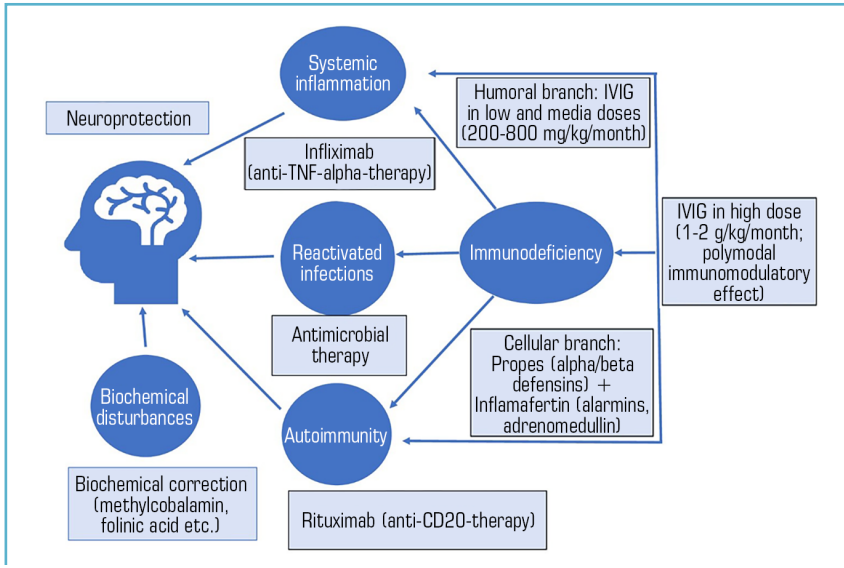

Fig. 4.6 Available means of neuroprotection in the implementation of immune-dependent mechanisms of cerebral damage in the development of infection-induced autoimmune inflammatory encephalopathy in children with neuropsychiatric syndromes in the context of the folate-centric concept

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**).

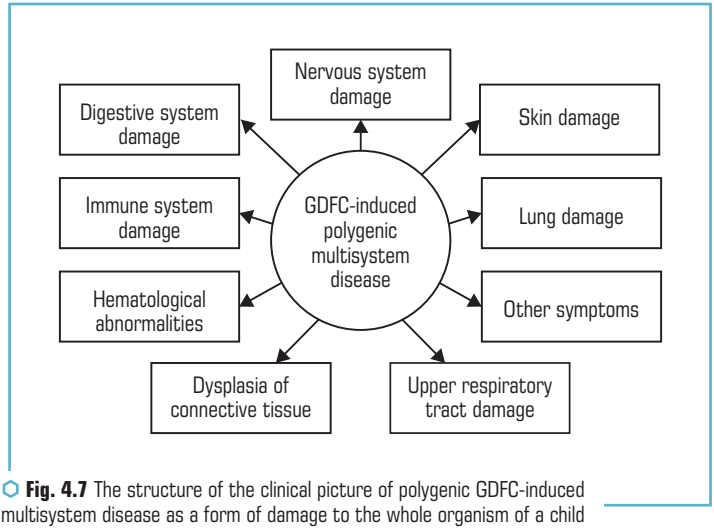

Fig. 4.7 The structure of the clinical picture of polygenic GDFC-induced multisystem disease as a form of damage to the whole organism of a child

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**.

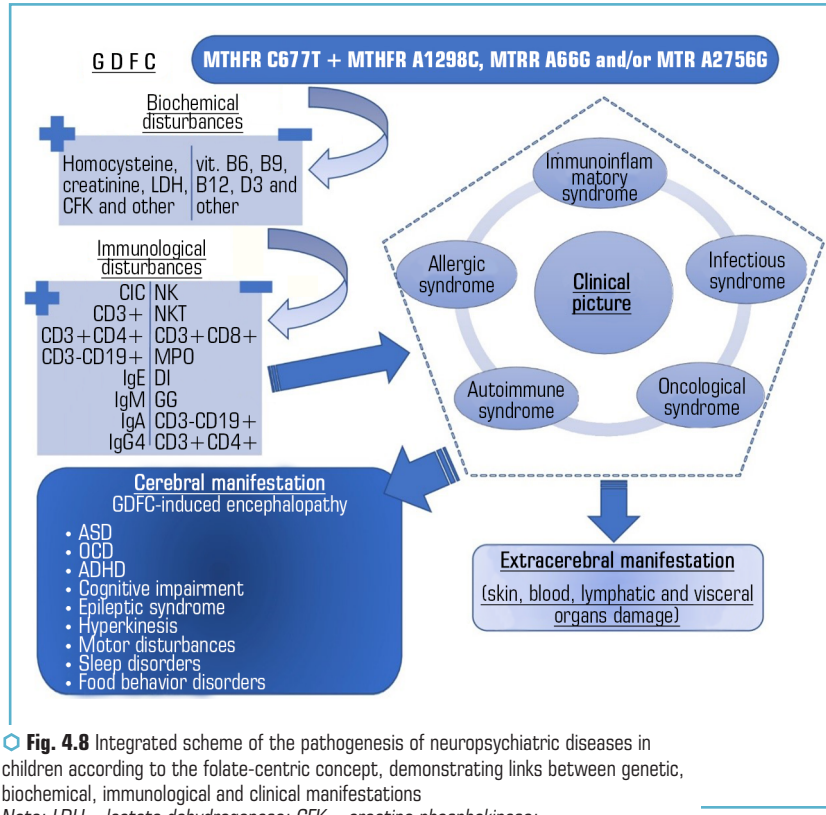

Fig. 4.8 Integrated scheme of the pathogenesis of neuropsychiatric diseases in children according to the folate-centric concept, demonstrating links between genetic, biochemical, immunological and clinical manifestations
Note: LDH – lactate dehydrogenase; CFK – creatine phosphokinase; DI – dysimmunoglobulinemia;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

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