DOI: 10.15587/978-617-8360-21-4.CH1

1 IMMUNOGENETIC ASPECTS OF THE PATHOGENESIS OF DISEASE IN CHILDREN WITH AUTISM SPECTRUM DISORDERS (REVIEW)

INTRODUCTION

Preservation of children's mental health is a priority task of modern medicine. A common and severe psychiatric pathology in the child population is the so-called autism spectrum disorders (ASD), the frequency of which has been rapidly increasing over the past decades. This determines the relevance of the problem and justifies the urgent need to develop effective methods of treatment and prevention of this mental illness, which is an unattainable goal without understanding the etiology and pathogenesis of the disease, which still remain insufficiently clarified. However, recent achievements in the field of immunogenetics, neuroimmunology and immunopsychiatry, at least partially, shed light on the mechanisms of encephalopathy development in children with ASD, which allows us to look with cautious optimism at the prospect of overcoming this severe pathology of the childhood psyche in the near future.

ASSOCIATION STUDY OF GENETIC DEFICIENCY OF THE FOLATE CYCLE (GDFC) AND ASD

One of the important achievements in psychiatry in recent years is the discovery of the association of GDFC and ASD in children. The data of the first ever meta-analysis of randomized controlled clinical trials by D. Pu et al. in 2013, which analyzed the results of 8 studies involving 1672 children with ASD and 6760 healthy children, demonstrated that the pathogenic polymorphic variant MTHFR C677T is associated with ASD in children [1]. Further, a meta-analysis of randomized controlled clinical trials by N. S. Mohammad et al. in 2016, which included data from 1361 children with autism spectrum disorders and 6591 healthy children, showed that MTHFR C677T and the associated hyperhomocysteinemia are associated with ASD in children. Additionally, synergism between MTHFR C677T and MTRR A66G in inducing hyperhomocysteinemia and increasing the risk of developing ASD in a carrier has been demonstrated [2]. The results of a subsequent meta-analysis of randomized controlled clinical trials by V. Rai in 2016, which included data from 13 studies involving 1978 children with ASD and 7257 healthy children, established an association between MTHFR C677T and ASD in children among both European and Asian individuals. MTHFR C677T increased the risk of ASD in all 4 genetic models used (ORT vs. C = 1.48; 95 % CI = 1.18–1.86; p = 0.0007; ORTT + CT vs. CC = 1.70, 95 % CI = 0.96–2.9, p = 0.05; ORTT vs. CC = 1.84, 95 % CI = 1.12–3.02, p = 0.02; % CI = 1.2–2.1, p = 0.003; ORTT vs. CT + CC = 1.5, 95 % CI = 1.02–2.2, p = 0.03) [3]. Data from a recent meta-analysis of randomized controlled clinical trials by T. Sadeghiyeh et al. 2019, which analyzed the results of 25 case-control clinical studies, found an association between MTHFR 677C > T and ASD in the general population and MTHFR 1298A > C and ASD in children only among Europeans. Specifically, MTHFR 677C > T increased the risk of ASD in children in 5 genetic models (T vs. C: OR = 1.483, 95 % CI = 1.188–1.850, $p \leq 0.001$; TT vs. CC: OR = 1.834, 95 % CI 1.155–2.913, p = 0.010; TC vs. CC: OR = 1.512, 95 % CI = 1.101–2.078, p = 0.011; TT + TC vs. CC: OR = 1.632, 95 % CI = 1.26; TT vs. TC + CC: OR = 1.427, 95 % CI = 1.002–2.032, p = 0.049) [4]. A recent meta-analysis of randomized

controlled clinical trials by Y. Li et al. 2020, covering the results of 15 studies, indicates an association of MTHFR C677T and ASD in children in 5 genetic models (viz, allelic, dominant, recessive, heterozygous, homozygous). Subgroup analysis showed an association of both MTHFR C677T and MTHFR A1298C with ASD in children [5].

The results of a controlled clinical trial by R. Haghiri et al. involving 103 children with ASD and 130 healthy control children showed a strong association of MTR A2756G and ASD in children. A 1.6-fold increased risk of ASD was demonstrated in carriers of MTR A2756G [6].

Thus, all 4 major polymorphic variants of folate cycle enzyme genes are associated with ASD in children, but the current evidence base for such an association is greater for MTHFR C677T and MTHFR A1298C and less for MTR A2756G and MTRR A66G (**Fig. 1.1**).

OXIDATIVE STRESS IN ASD

Biochemical abnormalities, including homocysteine cytotoxicity and disruption of gene censorship mechanisms via DNA methylation, induced by GDFC are thought to lead to a state of persistent oxidative stress in humans. There is now substantial evidence for the development of a state of oxidative stress in children with ASD, as summarized in several meta-analyses and systematic reviews.

The results of a meta-analysis and systematic review of randomized controlled trials by A. Frustaci et al. showed evidence of oxidative stress in children with ASD associated with GDFC. There were decreases in serum concentrations of the antioxidant compounds glutathione (27 %), glutathione peroxidase (18 %), methionine (13 %), and cysteine (14 %) and an abnormal increase in serum concentrations of oxidized glutathione (45 % of normal) [7]. These data indicate a serious disruption of the redox system in children with ASD, which is responsible for regulating the redox balance in the human body.

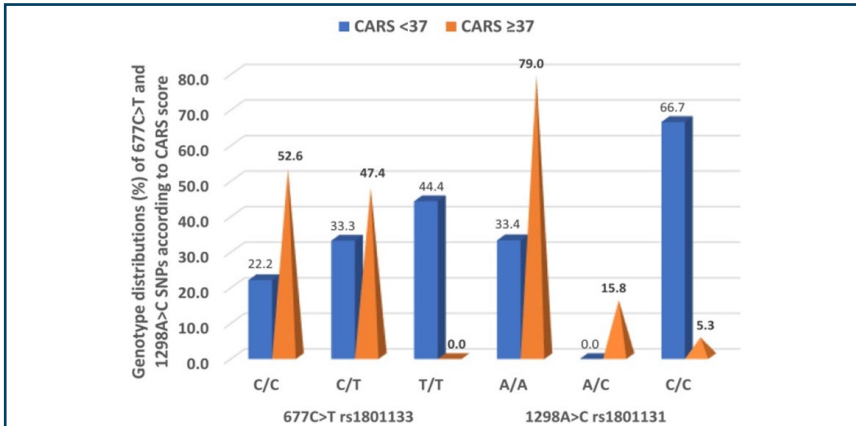

Fig. 1.1 Distribution of 677C > T rs1801133 and 1298A > C rs1801131 SNPs in CARS (childhood autism rating scale) < 37 and ≥ 37 cases. Source: [3]

The results of a meta-analysis of randomized controlled clinical trials conducted by L. Chen et al. in 2021, which included 87 studies involving 4928 children with ASD and 4181 healthy control children, demonstrate that in children with ASD, compared to healthy individuals, the serum concentration of such pro-oxidant agents as oxidized glutathione (GSSG), malondialdehyde, S-adenosylhomocysteine, nitric oxide, and copper is significantly increased, and, conversely, the serum concentration of known antioxidants glutathione (GSH), total glutathione (tgsh), methionine, cysteine, vitamins B9, D, B12, E, and calcium is significantly reduced, as well as the level of such indicators of the antioxidant system of the human body as GSH/GSSG, tgsh/GSSG, and S-Adenosylmethionine/S-Adenosylhomocysteine (**Fig. 1.2**) [8]. These results can be used when planning laboratory examinations of children with ASD to assess the current intensity of oxidative stress in the patient's body to determine the severity of their condition and the individual need for biochemical correction agents.

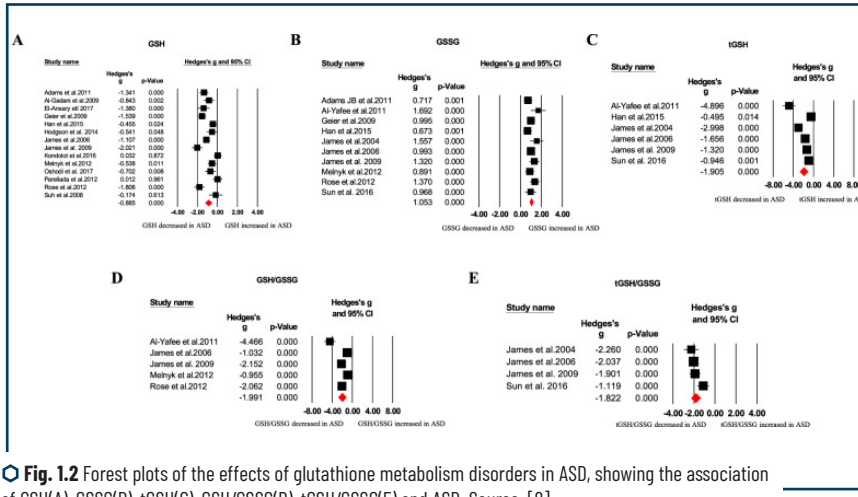

Fig. 1.2 Forest plots of the effects of glutathione metabolism disorders in ASD, showing the association of GSH(A), GSSG(B), tGSH(C), GSH/GSSG(D), tGSH/GSSG(E) and ASD. Source: [8]

IMMUNE SYSTEM STATUS IN ASD

Indeed, there is now accumulating evidence that the immune system plays an important role in the development of the human brain, participating in the regulation of neuronal proliferation and synapse formation, as well as influencing the processes of neuroplasticity, so disruption of its functioning may be important in the formation of encephalopathy in children with ASD.

There are indirect signs of compromised immune systems in children with ASD, including the following: abnormally high frequency of congenital cytomegalovirus infection, high microbial load on the body, frequent episodes of infections and antibiotic use, development of the ASD phenotype after neuroinfectious episodes, hyper-

production, production of anti-brain autoantibodies, association with some loci of the HLA major histocompatibility complex molecules, immunoinflammatory intestinal damage, hypersensitivity to food antigens and other forms of allergic reactions, predisposition to the formation of malignant neoplasms, poor tolerance of vaccines, clinical efficacy of a number of immunomodulatory, anti-inflammatory and immunotherapeutic interventions.

In particular, unclassified hypogammaglobulinemia, deficiency of CD4 + T-helper cells, complement component C4b, NK cells, IgA molecules, neutrophil myeloperoxidase, CD8 + cytotoxic T-lymphocytes, IgG subclasses, specific antibodies, and specific T-lymphocytes to certain infectious agents have been described in children with ASD [9–13].

Autistic features have been described in primary immunodeficiencies such as common variable immunodeficiency [14], type II adhesion molecule deficiency [15], ataxia telangiectasia [16], DiGeorge syndrome [17], CaV1.2 channelopathies [18], and hyper-IgE syndrome [19]. Results of a population-based national study by J. Isung et al. involving 8378 patients showed that humoral immunodeficiencies (common variable immunodeficiency, selective IgG subclass deficiency, and specific antibody deficiency) are associated with an increased risk of any mental disorder (adjusted odds ratio (AOR) = 1.91 = 18; 2.01), and the closest association among other mental illnesses was with ASD in children (AOR = 2.99, 95 % CI = 2.42–3.70) [20].

A systematic review by J. Mead et al. suggests evidence of immune dysregulation in children with ASD, including neuroinflammation, autoantibodies, enhanced T-cell responses, and abnormal natural killer and monocyte activity. These immune aberrations have been associated with worsening clinical features of ASD, including impaired social interaction, stereotyped behavior, and communication deficits. Furthermore, animal models have demonstrated resolution of ASD symptoms following removal of immune factors implicated in aberrant immune responses [21]. D. B. Noriega and H. F. Savelkoul in another systematic review on ASD in children, indicate signs of immune dysregulation in such patients, including hyperproduction of pro- and suppression of anti-inflammatory cytokines, increased permeability of the blood-brain barrier, abnormal synthesis of anti-brain autoantibodies, and modification of the functional activity of natural killer cells [22]. As noted by H. K. Hughes et al. 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, dysfunction of the adaptive and innate immune systems, and signs of autoimmunity are noted [23].

Experimental and clinical studies have already reported various immune status disorders in patients with both verified GDFC and folic acid deficiency. In particular, van der M. B. van der Weyden et al. established the inhibition of lymphoblast metabolism in folate deficiency, which includes disorders of deoxynucleotide metabolism and the thymidylate cycle [24]. T. Partearroyo et al. showed that the imbalance of folic acid and vitamin B12, typical of the GDFC phenotype, disrupts NK cell activity, B lymphocyte activity and lymphoproliferation [25]. C. Courtemanche et al. showed that folate deficiency leads to inhibition of proliferation of primary CD8 + cytotoxic T lymphocytes [26]. I. Abe et al. showed that folic acid deficiency leads to a decrease in the number of NK cells, T lymphocytes and B cells, but not basophils and granulocytes [27]. A. M. Troen et al. found that unmetabolized serum folate, which occurs in GDFC, causes suppression of NK cell cytotoxicity in postmenopausal women [28]. Accordingly, N. Bhatnagar et al. described pancytopenia in severe folate deficiency [29].

INFECTIOUS SYNDROME IN ASD

The presence of immune dysfunction implies a decrease in the host's resistance to microbial factors. Indeed, to date, there have been many reports of the abnormal development of opportunistic and conditionally pathogenic infections in children with ASD, which can be explained by the damage to the immune system induced by GDFC. Initially, a number of clinical reports of the development of the ASD phenotype in people after herpesvirus encephalitis were accumulated. Later, T. Binstock first pointed out selectively reduced immunoresistance in children with ASD, identifying a subgroup of patients with the so-called intramonocytic infectious pathogens – measles virus, cytomegalovirus, herpes virus type 6 and *Yersinia enterocolitica* [30]. Such children were characterized by suppression of hematopoiesis, impaired peripheral immunity, increased permeability of the blood-brain barrier and manifestations of demyelination in the white matter of the cerebral hemispheres – signs, as it turned out, typical of GDFC. G. L. Nicolson et al. in a controlled clinical study using blood PCR showed abnormally frequent detection of *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and herpes virus type 6 in children with ASD compared to healthy individuals [31]. A. Sakamoto et al. in a specially designed study found that congenital CMV infection with CNS involvement in children with ASD occurs probably more often (7.4 %) than in the general population (0.31 % of cases) ($p = 0.004$). CMV was identified by real-time PCR of dried newborn blood samples and umbilical cord blood samples obtained immediately after delivery [32]. S. Valayi et al. in a controlled clinical study demonstrated that specific IgM to EBV in the serum of children with ASD occurs probably more often than in healthy individuals ($p < 0.05$) [33]. H. Jyonouchi et al. in a specially designed study showed an association of ASD with a primary deficiency of specific antipolysaccharide antibodies, which may explain the known predisposition to the development of chronic streptococcal infection in such children [34]. H. K. Hughes and P. Ashwood in a controlled clinical study found that sulfur positivity for *Candida albicans* in children with ASD occurs in 36.5 % of cases, while in healthy children it occurs in only 14.3 % of cases (OR = 3.45, 95 % CI = 1.0409–11.4650, $p = 0.041$). Candida seropositivity has been shown to be associated with clinical manifestations of gastrointestinal dysfunction in children with ASD [35]. T. Nayeri et al. conducted a meta-analysis of randomized controlled clinical trials, in which they demonstrated the association of ASD with toxoplasmosis, and that the presence of toxoplasmosis infection increases the risk of developing ASD in a child by 1.93 times compared with uninfected individuals (95 % CI = 1.01–3.66) [36]. M. Kuhn et al. reported a series of clinical cases of the combination of chronic active borreliosis and ASD in children and a significant reduction in ASD manifestations following long-term therapy with ampicillin and azithromycin for borreliosis [37].

AUTOIMMUNE SYNDROME IN ASD

A special role in the pathogenesis of encephalopathy in children with ASD is attributed to autoimmune mechanisms, which are believed to develop as a result of impaired immune responses to maintain tolerance to self-antigens in conditions of immune dysfunction. Such ideas are based on a number of scientific evidences.

First, the results of a number of controlled clinical studies indicate the abnormal detection in patients with ASD of autoantibodies to CNS neurons, validated as markers of autoimmune encephalitis, which are not observed in healthy children. U. K. Rout et al. found autoantibodies to the brain autoantigen GAD65 (GADA) among children with autism in 15 % of cases, autism spectrum in 27 % of cases and in no healthy control children [38]. These autoantibodies are a recognized laboratory marker of autoimmune anti-GAD65 limbic encephalitis, which leads to the development of a number of severe mental disorders in children and adults. R. E. Frye et al. identified autoantibodies to folic acid receptors of brain neurons in children with ASD, indicating the heterogeneity of manifestations of anti-brain autoimmunity in such cases [39]. M. Cabanlit et al. established an association between ASD and the presence of autoantibodies to neurons of the hypothalamus and thalamus of the brain [40].

Secondly, experimental models have demonstrated the clinical significance of anti-brain autoantibodies in ASD, since the transfer of blood serum from children with ASD into the body of the tested animals led to the development of behavioral disorders similar to ASD in the latter. Thus, M. Gonzalez-Gronow et al. demonstrated that catalytic antibodies IgG and IgA isolated from the blood of patients with ASD disrupt the processes of hippocampal neuroplasticity in rats. The authors also demonstrated the ability of IgA to the myelin basic protein to act as a serine protease, cleaving the specified human autoantigen in vitro [41]. As noted by B. Gesundheit et al., experimental studies have shown that after the introduction of autoantibodies obtained from the blood serum of children with ASD, rhesus macaques develop specific behavioral disorders that closely resemble ASD in humans [42].

Third, four main pathways of migration of anti-brain autoantibodies from serum to CNS tissues are shown, including the transolfactory pathway, as well as penetration through the choroid plexus of the ventricles of the brain, damaged tight junctions between cells in the blood-brain barrier, and the endothelium of cerebral vessels via Fc-dependent transport (**Fig. 1.3**) [43].

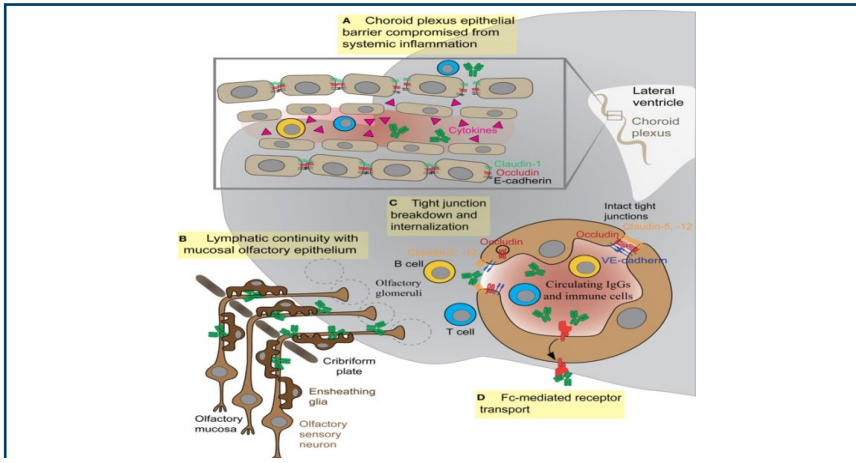

Fig. 1.3 Schematic diagram of migration of anti-brain autoantibodies from blood serum to the CNS in children with ASD. Source: [43]

Fourth, the molecular mechanisms of CNS tissue damage by anti-brain autoantibodies observed in children with ASD have now been discovered. In particular, both the specific stimulatory and inhibitory effects of autoantibodies on neurotransmitter receptors on the surface of neurons, which causes a clinically significant functional imbalance in the processes of neurotransmission, and the immune reactions of antibody-dependent cell-mediated cytotoxicity with the participation of natural killer cells and macrophages have been described. In particular, the cellular immune reaction leads to apoptotic and/or necrotic death of the attacked neurons with subsequent destruction of the CNS neuronal networks and the formation of aberrant interneuronal connections in the affected areas. These autoimmune anti-cerebral reactions ultimately lead to the development of a specific encephalopathy, which is characterized by disintegrative processes of mental activity, which are clinically manifested as symptoms of ASD (**Fig. 1.4**) [44].

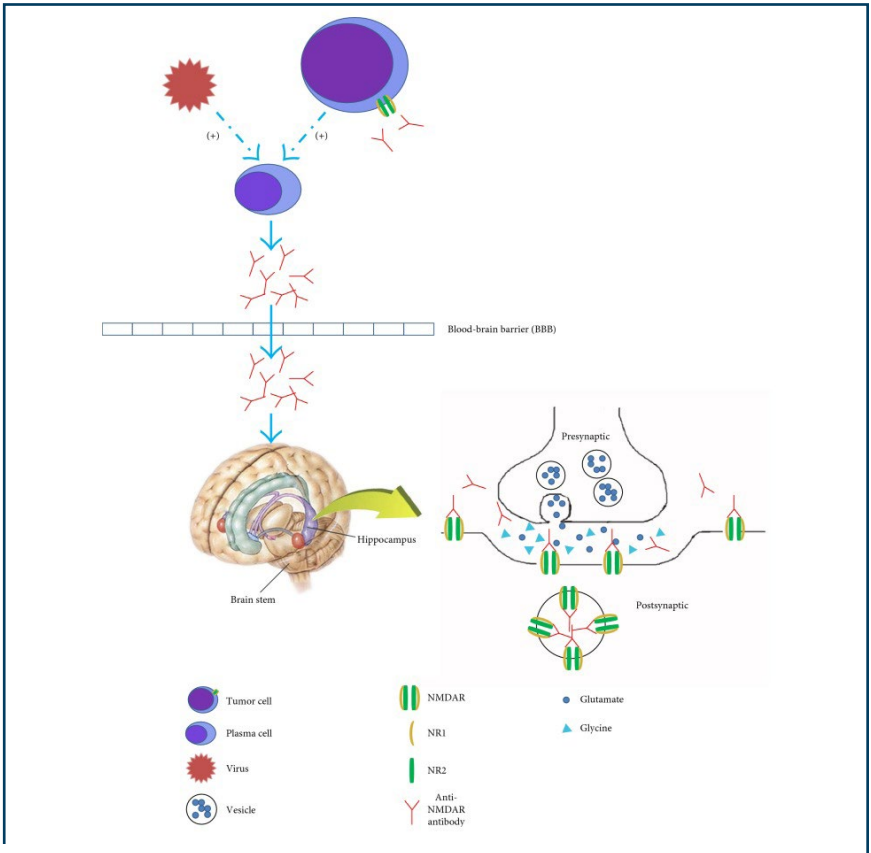

Fig. 1.4 Schematic diagram of CNS damage in autoimmune anti-NMDA receptor limbic encephalitis in humans. Source: [44]

Fifth, there are a number of described cases of the development of clinical manifestations of ASD after the onset of verified autoimmune limbic encephalitis in children and achieving clinical improvement with the treatment of autoimmune CNS disease. Thus, M. C. González-Toro et al. in 2013 reported two cases of autoimmune anti-NMDA limbic encephalitis in children, the clinical manifestations of which were consistent with symptoms of ASD [45]. R. Kiani et al. two years later also reported autistic regression of mental activity in the development of autoimmune anti-NMDA limbic encephalitis in a child [46]. D. U. Menon et al. described subacute autoimmune encephalitis caused by autoantibodies to the 3rd subunit of N-acetylcholine receptors of CNS neurons in a child with a clinical picture of ASD [47]. In all cases, at least partial recovery of mental status occurred after the administration of specific antirheumatic therapy.

Sixth, the results of a systematic review and meta-analysis of randomized controlled clinical trials conducted by S. Wu et al. indicate that a positive family history of autoimmune diseases is associated with a significant increase in the risk of ASD cases in children in the family [48].

And, finally, seventh, several drugs with anti-inflammatory and immunomodulatory therapeutic effects have demonstrated clinical efficacy in ASD, the mechanisms of which are associated with the inhibition of anti-neuronal autoimmunity and the associated intracerebral inflammation that underlies encephalopathy in children with ASD.

In addition to antineuronal, antimyelin autoimmunity has also been described in ASD. Thus, A. Vojdani et al. showed that in children with ASD, *Chlamydia pneumoniae* peptides, streptococcal M protein, and milk butyrophilin induce the production of defective specific antibodies with cross-reactivity, capable of recognizing not only microbial and food antigens, but also some molecules of nervous tissue, in particular, myelin basic protein, myelin-associated glycoprotein, myelin oligodendrocyte protein, neurofilament proteins, and tubulin [49].

A separate subtype of ASD by the autoimmune mechanism of cerebral damage is the so-called maternal-fetal immune conflict, in connection with which the fetal brain is damaged antenatally by allogeneic anticerebral autoantibodies of the mother, which migrate into the child's body through the fetoplacental barrier [50].

ALLERGIC SYNDROME IN ASD

A large population-based clinical study of 199,520 children by G. Xu et al. showed that food allergy, respiratory allergy, and skin allergy occurred in 11.25 %, 18.73 %, and 16.81 % of children with ASD, respectively, while these disorders were less common in mentally healthy children (4.25 %, 12.08 %, and 9.84 %, respectively) [51]. The odds ratios in children with ASD for different types of allergies were as follows: food allergy – OR = 2.29, 95 % CI95 % = 1.87–2.81; respiratory allergy – OR = 1.28, 95 % CI95 % = 1.10–1.50; and skin allergy – OR = 1.50, 95 % CI95 % = 1.28–1.77.

T. C. Theoharides et al. conducted a systematic review of experimental and clinical studies devoted to the study of the relationship between atopic allergic reactions and ASD in children, proposing a scientific concept that explains the mechanisms of allergy involvement in the pathogenesis of encephalopathy in ASD.

It has now been established that mast cells are in a hyperactivated state in children with ASD due to the presence of comorbid atopy. Activated mast cells have been found in the perivascular spaces of the thalamus and hypothalamus of the brain of patients with ASD. These cells, by releasing histamine and secreting a number of proinflammatory cytokines (IL-1beta, IL-6, IL-17, TNF-alpha), increase the permeability of the blood-brain barrier and cause intracerebral inflammation with predominant activation of Th17, which disrupts the formation of encephalopathy with the clinical picture of ASD (**Fig. 1.5**) [52].

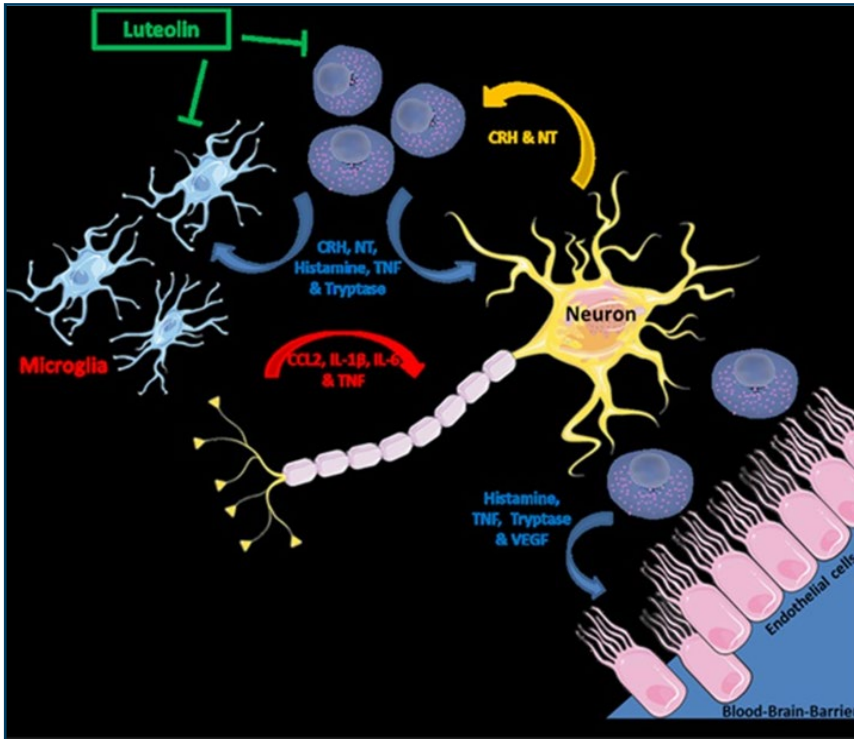

Fig. 1.5. Schematic diagram of the involvement of the atopic allergic mechanism in the pathogenesis of encephalopathy in ASD in children. Source: [52]

Thus, children with ASD are characterized by an allergic syndrome, but the real contribution of such immune-dependent disorders to the pathogenesis of encephalopathy in ASD remains unclear. It is necessary to study the relationship between the allergic syndrome and immune dysfunction observed in children with ASD in order to better understand the origin of allergies in such cases and to develop effective methods for assessing the severity of the patient's condition, predicting the further course of the disease, and treating and preventing the development of encephalopathy in ASD.

IMMUNOINFLAMMATORY SYNDROME IN ASD

Evidence for the development of a persistent systemic inflammatory response associated with immune dysregulation in children with ASD is based on the results of 2 meta-analyses of randomized controlled clinical trials. In particular, the first systematic review and meta-analysis of randomized controlled clinical trials showed increased serum concentrations of the pro-inflammatory mediators interleukin-1beta (IL-1beta) ($p < 0.001$), interleukin-6 (IL-6) ($p = 0.03$), interleukin-8 ($p = 0.04$), interferon-gamma (IFN-gamma) ($p = 0.02$), eotaxin ($p = 0.01$), and monocyte chemotactic factor 1 ($p < 0.05$) and decreased levels of the anti-inflammatory cytokine transforming growth factor beta 1 ($p < 0.001$) in children with ASD ($n = 743$) compared to healthy subjects ($n = 592$) [53]. The results of a meta-analysis of randomized controlled clinical trials prepared by A. Saghazadeh et al., which includes 38 studies involving 2487 children, show a significant 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 [54]. H. Jyonouchi et al. in a specially designed clinical study showed that increased serum concentrations of pro-inflammatory cytokines of monocyte origin, including TNF-alpha and IL-6, are 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 of the blood-brain barrier, and the associated induction of low-yielding intracerebral inflammation with dysfunction of neuronal networks of the CNS. The authors proposed to identify the immunoinflammatory mechanism as a separate link in the pathogenesis of encephalopathy in ASD, as well as a separate subgroup of children with ASD in whom the immunoinflammatory pathway of cerebral damage predominates [55].

IMMUNODEPENDENT TREATMENT APPROACHES FOR ASD

ASD is currently considered an incurable condition due to the lack of adequate evidence of the effectiveness of drugs in this pathology. Given the above data, therapeutic interventions have been repeatedly attempted to intervene in the biochemical and related immune-dependent mechanisms of encephalopathy formation in children with ASD to normalize the mental status of patients.

A systematic review devoted to the analysis of controlled studies on restrictive diets in autism recommends the use of a gluten-free and casein-free elimination diet only in laboratory-confirmed celiac disease and allergy to cow's milk casein to improve intestinal function and optimize the overall nutritional status of the child. However, no direct effect of the diet on the mental state of children with ASD has been demonstrated [56].

A systematic review of the results of 8 controlled clinical trials on the use of pre/probiotics in children with ASD, conducted by Q. X. Ng et al. in 2019, shows a small improvement in some ASD symptoms with the isolated use of pre/probiotics and a more significant positive dynamics in psychiatric manifestations with the combination of pre/probiotic therapy and an elimination gluten-free/casein-free diet, however, the data accumulated so far are insufficient for the routine use of these treatment strategies in children with ASD [57].

The results of the first open clinical trial conducted by D.-W. Kang et al. in 2017 demonstrated not only a reduction in gastrointestinal dysfunction (diarrhea, constipation, bloating, abdominal pain) but also ASD symptoms in children who received intestinal microbial transfer after a two-week course of antibiotic therapy, which justifies further research in this direction [58].

In 2018, Y.-J. Li et al. conducted a systematic review of the results of randomized controlled clinical trials devoted to the correction of micronutrient deficiencies observed in children with ASD. The results of 7 such studies indicate that vitamin B6 supplementation is ineffective in correcting mental status disorders in children with autism. The data of two other studies showed that the use of methyl forms of vitamin B12 leads to some improvement in mental status indicators in children with ASD. The results of three studies using vitamin D3 preparations indicate the insufficient effectiveness of this approach in correcting mental disorders in children with ASD. The data of another study showed the benefit of prescribing folic acid in ASD in children [59]. The obtained data indicate that the effectiveness of supplementation for correcting biochemical status abnormalities in GDFC in children with ASD is an insufficiently proven treatment strategy for routine use in clinical practice to improve mental functions, although they do not refute the need for further research in this direction.

As noted by J. Marchezan et al. in a systematic review devoted to the analysis of the limited evidence base of clinical studies of anti-inflammatory drugs in ASD, all drugs approved so far can be divided into two main groups:

a) drugs with primary anti-inflammatory and immunomodulatory effects, which include sulforaphane, celecoxib, lenalidomide, pentoxifylline, spironolactone, flavonoid luteolin, corticosteroids, oral and intravenous immunoglobulin, cell therapy, dialyzed blood lymphocyte extract, minocycline and pioglitazone;

b) other drugs prescribed for non-immunological indications, but providing additional immunomodulatory properties unrelated to the main mechanism of action, in particular, risperidone, vitamin D, omega-3 polyunsaturated fatty acids, ginkgo biloba, L-carnosine, N-acetylcysteine of intestinal microflora [60].

Positive results from individual clinical studies are not sufficient for the routine use of anti-inflammatory therapy in children with ASD in clinical practice, although these data may serve as the basis for further research in the outlined direction.

A recent controlled clinical trial of infliximab (a monoclonal antibody to TNF-alpha) in children with ASD associated with GDFC who had elevated serum TNF-alpha levels was conducted. Infliximab was shown to reduce hyperactivity and hyperexcitability, but not eye contact and language, by normalizing serum TNF-alpha levels, and to reduce PANDAS symptoms, intestinal dysfunction, and epileptiform activity on the EEG [61].

Another controlled clinical trial demonstrated the ability of rituximab (a monoclonal antibody to the CD20 molecule of B lymphocytes) to reduce ASD symptoms across all ABC scores in children with GDFC who had serological, neuroimaging, and neurophysiological features of autoimmune limbic encephalitis [62].

The results of clinical trials in the field of immunoglobulin therapy for ASD are now summarized in a systematic review and meta-analysis of clinical trials by D. A. Rossignol and R. E. Frye et al. 27 relevant studies 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 the trial of intravenous human normal immunoglobulin preparations according to this meta-analysis is improvement in communication, hyperexcitability, hyperactivity, cognition, attention, social interaction, eye contact, echolalia, language, response to commands, drowsiness, decreased activity, and in some cases, complete elimination of ASD symptoms [63]. Currently, intravenous immunoglobulin therapy is the treatment strategy with the largest evidence base of effectiveness among other considered therapeutic approaches for ASD, which indirectly indicates the priority of immune-dependent mechanisms of encephalopathy pathogenesis in children with ASD.

CONCLUSIONS TO THE SECTION 1

The accumulated evidence base indicates that immune dysfunction and the related immune-dependent mechanisms of cerebral damage are undoubtedly important components of the pathways of encephalopathy formation in children with ASD associated with GDFC. Subsequent clinical studies should focus on clarifying and expanding current ideas about the involvement of the immune system in the pathogenesis of ASD in humans. In particular, there is a lack of systematization of the accumulated data and the formulation of a single scientific concept of the scenario of pathological events, starting from the presence of pathogenic polymorphic nucleotide substitutions in the genes of folic acid cycle enzymes and ending with the clinical manifestations of ASD in a child. Such systematization and generalization would not only provide a coherent system of theoretical knowledge on the immune-dependent mechanisms of the pathogenesis of encephalopathy in ASD associated with GDFC for basic science, but would also help to create an effective diagnostic algorithm of medical care for clinical practice. Further clinical trials are also needed to test immunotropic treatments in patients with GDFC-associated ASD, given the encouraging results of previous trials in this direction. The results of recent genetic, biochemical, immunological, immunobiochemical, and neuroimmunological studies indicate new potentially useful points of application of immunotherapeutic interventions for the treatment of encephalopathy in children with ASD. There is reason to believe that the successful testing of such treatment strategies will allow for a breakthrough in the treatment of GDFC-associated ASD in children, which will not only ensure recovery from a severe and currently incurable neuropsychiatric disorder, but also contribute to stopping the large-scale threatening epidemic of autism worldwide.

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