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Review

Integrative concept of pathogenesis and GBINS personalized multidisciplinary approach to clinical management of children with neuropsychiatric syndromes, associated with genetic deficiency of folate cycle

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Abstract. *Background and aim:* The problem of children's neuropsychiatric diseases is a priority task of modern medicine to resolve. Scientific achievements in genetics, molecular biology, and immunology shed light on the mechanisms of brain damage in children with ASD. *Results:* Today, the folate-centric concept of polygenic inheritance of predisposition to the development of neuropsychiatric syndromes in children with multisystem body lesions has been established. Biochemical and immune-dependent ways of formation of microbe-induced autoimmune inflammatory encephalopathy with neuropsychiatric clinical manifestations in the context of a folate-centric concept are discussed. Considering the new data, two personalized multidisciplinary approaches to managing children with ASD and other neuropsychiatric syndromes are proposed. The first approach of Bradstreet et al (2010) is based on an empirical analysis of a large group of laboratory biomarkers. In 2022 Frye R. developed a multidisciplinary personalized approach called Bas-VISTOR. It systematizes and stratifies diagnostic and therapeutic interventions according to biomarkers assessment. *Conclusions:* This article puts forward an improved personalized multidisciplinary approach to clinical management of patients with ASD and neuropsychiatric manifestations associated with genetic folate cycle deficiency - Genetic-Biochemical-Immunological-Neurological-Symptomatic. The successful testing of evidence-based personalized multidisciplinary diagnostic and treatment strategies in clinical practice will make it possible to make a breakthrough in the clinical management of children with severe mental disorders. This will provide not only the possibility of recovery from the prognostically unfavorable and currently non-curable neuropsychiatric disorder but will also contribute to stop the large-scale threatening epidemic of neuropsychiatric syndromes in the modern pediatric population. (www.actabiomedica.it)

Key words: autism spectrum disorders, attention deficit hyperactivity disorder, obsessive-compulsive syndrome, immunodiagnostics, biochemical correction, immunotherapy

Introduction

Solving the problem of children's neuropsychiatric diseases is a priority task of modern medicine. The greatest attention among the diverse pathology of the mental sphere is now focused on the study of the etiology and pathogenesis of autism spectrum disorders (ASD) in children.

According to DSM-5 (APA) ASD is a neurodevelopmental disorder characterized by deficits in social communication and the presence of restricted interests and repetitive behaviors. According to a systematic review by Hughes et al. in the USA, during the period from 1972 to 2014, the frequency of reported cases of ASD increased from a case per 10 thousand people (0.01%) to a single case per 57 children (2%),

that is, 200 times, which cannot be explained only by improving 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 incidence of ASD in the modern child population has reached 1 case per 44 children, which indicates the persistence 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 determines the social maladaptation of a child due to communication disorders, but is also accompanied by a variety of comorbid pathology, including obsessive-compulsive syndrome, attention deficit hyperactivity disorder, cognitive impairment and other forms of psychiatric syndromes, which deepens the severity of the patient's clinical condition and worsens the quality of life of both the child and all members of the family. Based on the results of a recent systematic review and meta-analysis of Catalá-López et al., which covers the results of 27 controlled clinical trials with a total participation of 642,260 children, it is indicated on an increase of at least 3.8 times in mortality from natural causes and 2.5 times in mortality from unnatural causes in children with ASD compared with healthy peers (3). According to systematic review and methaanalysis by O'Halloran et al., including data from 47 controlled studies, it is indicated on the presence of suicidal ideation in children with ASD in at least 25.2%. Suicide attempts were recorded in 8.3% of cases, and suicidal acts were commited in 0.2% of cases (4). The results of a systematic review and meta-analysis by Zheng et al., covering data from epidemiological studies involving 1,950,113 participants, indicate a 3.55-fold increase in the number of cases of schizophrenia in children suffering from ASD compared to individuals in the general population. In addition, 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 Food and Drug Administration has not yet registered a single medication that would modify the course of the disease and/or ensure the patient's recovery. As Frye rightly points out, specialized educational programs and behavioral therapy, which are traditionally used for children with ASD for at least partial adaptation to social conditions, have not passed the appropriate number, volume and design of clinical trials according to the requirements of evidence-based medicine, thus, their effectiveness has not yet been properly confirmed (6).

The economic burden that the ASD creates in connection with intensive and long-term educational, social and rehabilitation programs for sick children in the United States exceeds $7 trillion per year, but the results obtained in many cases remain unsatisfactory (7). Nevertheless, the latest scientific achievements in the field of genetics, molecular biology and immunology, which demonstrate biochemical and immune dependent ways of forming neuropsychiatric disorders of a person, shed light on the mechanisms of brain dysfunction and nontypical neurodevelopmental trajectory in children with ASD, which allows looking with restrained optimism at the prospect of overcoming this severe psychiatric pathology in the foreseeable future through the introduction of genetic, biochemical and immunodiagnostic approaches, as well as metabolic and immunotherapeutic interventions with neuroprotective effects.

Materials and methods

The purpose of this critical review is to analyze and systematize the accumulated evidence of immunogenetic, immunobiochemical and immunopathological aspects of the pathogenesis of neuropsychiatric syndromes in children with the formation of a modern scientific concept of clinical management of patients. To achieve this goal, a search was carried out for scientific articles in the international scientometric electronic database of peer-reviewed medical periodicals PubMed by the keywords "autism spectrum disorders", "obsessive-compulsive syndrome" and "attention deficit hyperactivity disorder" in combination with one of such keywords as "folate cycle genetic deficiency", "immunogenetic aspects", "biochemical anomalies", "immunodeficiency", "immune dysregulation", "immunopathogenesis", "infections", "autoimmunity", "allergy", "immune inflammation", "biochemical correction", "immunotherapy". The results of original research from the author's published scientific articles were also used. Preference for scientific research in

the preparation of this systematic analysis was given to meta-analyses published over the past decade systematic reviews double-blind placebo-controlled randomized clinical trials, as well as articles where original scientific concepts based on evidence were put forward. Interim results of clinical trials, letters to the editor, comments on scientific papers, articles with signs of advertising, chapters of monographs as well as publications were not taken into account they did not contain a detailed summary. When selecting articles for the final list, the quality of the study was taken into account, namely the presence of randomization, the use of adequate methods of statistical analysis, a sufficient number of participants in observation groups, and the absence of methodological errors. At the initial stage, 215 publications were selected that met the criteria for inclusion in the review, where 141 works were subsequently left after the exclusion criteria were applied, which served as the basis for this review.

Results and discussion

Genetic factors

The scientific evidence accumulated so far allows considering genetic factors as key in the development of ASD and other neuropsychiatric disorders in children, however, the penetrance of pathological genes varies depending on the influence of environmental factors, as shown, in particular, by the results of systematic examination and meta-analysis of twin studies covering clinical data of 6,413 pairs of mono- and dizygotic twins (8). Only 4% of children with ASD have classic genetic diseases, isolated as separate nosological units, which are characterized by only one genetic disorder and for which the clinical phenotype of the disease can be fully explained (fragile X syndrome, tuberous sclerosis complex, Rett syndrome, and etc.) (9). In the vast majority of the studied cases of ASD, the 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 many cases of ASD, we can speak not about strict determinism with high penetrance of the pathogenic gene, but about polygenic inheritance with a certain susceptibility risk of developing the disease, given the low penetrance of pathogenic genes polymorphisms/mutations.

The study of genetic associations by Mpoulimari and Zintzaras, which studied 57 candidate genes and 128 related polymorphisms according to 159 articles on the electronic scientometric database PubMed, showed a statistically significant association of the phenotype of ASD with the pathology of genes adenosine deaminase (*ADA*), bone marrow stromal cell antigen-1 (*CD157/BST1*), dopamine receptor D1 (*DRD1*), engrailed homolog 2 (*EN2*), met proto-oncogene (*MET*), methylenetetrahydrofolate 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 significant association of the phenotype of ASD and nucleotide substitutions in the genes of 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 these data, genetic pathology associated with ASD can be combined into 3 main groups – metabolic, immunological and neurological disorders, which will include disorders of metabolism, functioning of the immune system, as well as neurogenesis, synaptic plasticity and neurotransmitter metabolism in the central nervous system (CNS).

It is important to clarify the role and place of each of the many genetic disorders associated with ASD that are contained in the genome of a child with neuropsychiatric disorders. The results of at least 5 systematic reviews and meta-analyses of RCTs (2013-2021), covering data from 8 to 25 trials, indicate an association of *MTHFR* C677T and the phenotype of ASD in children (11-15). Data from 2 meta-analyses of RCTs confirm the association of ASD manifestations with *MTHFR A1298C* (11,12), and one more study – with *MTRR A66G* (13). Results of a controlled clinical trial by Haghiri et al. 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 carriers of *MTR A2756G* (16). In addition, the results of at least 4 systemic reviews and meta-analysis of RCT indicate an association of the phenomenon of hyperhomocysteinemia, specific disorder of one-carbon metabolism in *MTHFR C677T* and similar genetic disorders, with the phenotype of ASD in children (13,17-19).

These data allow advancing the folate-centric concept of the development of ASD and other related neuropsychiatric syndromes in children with polygenic inheritance of the disease (20). Moll and Varga named nucleotide substitutions in folate cycle genes not as polymorphisms, but as mutations (21). It may be a good idea for scientific discussion despite the severe clinical consequences that may be associated with their presence in the patient's genome.

The folic acid cycle functions in close connection with other biochemical cycles and pathways, which genetic damage can lead to similar clinical consequences. James et al. in a controlled clinical study involving 360 children with ASD and 250 control group healthy individuals studied mutations/polymorphisms in the folate cycle and functionally related metabolic pathways, establishing associations of ASD and lesions of 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).

Folate cycle genetic deficiency (GDFC) is believed to lead to the development of ASD in at least three ways. Biochemical way is due to the induction of hyperhomocysteinemia and other related manifestations of oxidative stress. Genoregulatory influences by epigenetic modifications of gene expression is the second way that due to the changes in the expression of various pathogenic and normal genes for violating the universal mechanism of gene censorship by DNA methylation. Epigenetic regulation at the posttranslational stage is the third way that is due to the methylation of proteins, nucleoproteins, and lipids, which affects their functional activity.

It has been established that the addition of methyl groups to a pathological gene reduces its expression, and vice versa, the 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 polymorphisms of *MTHFR*. In this case, there is a multiple activation of the expression of undesirable genes that should normally be repressed, and hypermethylation with a predominant polymorphisms of *MTRR* and *MTR*, when a number of normal functionally important genes are detected mistakenly turned off, without the participation of which the proper implementation of key biochemical processes in the human body is impossible (21,23).

It is possible talking on the biochemical-genoregulatory dualism of the influence of GDFC on the human body. It should be noted that genoregulatory disorders may be stronger than direct GDFC-induced biochemical effects in many children with ASD. Thus, Horiuchi et al. studying the global gene expression in the blood of children with ASD (analysis of 11,617 genes), identified 117 abnormally hyperactive and 83 pathologically suppressed genes of innate and adaptive immunity. This created an aberrant pattern of functioning of the immune system with the formation of related pathological conditions of reduced immunoresistance and immune dysregulation, important in the pathogenesis of ASD (24).

GDFC-induced biochemical disorders probably create an initial pathological stimulus, which is subsequently transformed many times under the influence of other genes, which expression is pathologically altered due to a violation of their methylation, as well as due to multiple epigenetic disorders. These modular 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 into proximal, medial and distal. Additional mutations in the adjacent folate cycle biochemical pathways (methionine cycle, thiol transulforation pathway, purine metabolism, biopterin-neopterin pathway, mitochondrial dysfunction, etc.) (25-27) create proximal or biochemical modulus effects, weakening or strengthening the initial GDFC-induced metabolic disorders immediately after their origin (28). The complex of biochemical disorders formed at this stage of pathogenesis forms the so-called biochemical pathway of

central nervous system damage. The relevance of identifying a separate biochemical pathway of brain damage in children with ASD is confirmed by the proven clinical effectiveness of a number of specific therapeutic interventions aimed at compensating for specific biochemical disorders (29,30). Additionally to neurotoxic, GDFC-induced biochemical disorders have an imunotoxic effect, leading to the development of immunodeficiency and related immune dysregulation, however, mutations in genes encoding individual immune factors (so-called immunoresistance genes, for instance, *ADA*, *CD157/BST1*, *C4B* genes) and mutations in immunoregulatory genes affect the final state of the immune system contributing to the development of a certain form of immune pathology in conditions of immunodeficiency (22). These genetically mediated effects can be considered medial or immunogenic modulation. They are important in the formation of immune-dependent CNS pathways in children with ASD and other neuropsychiatric syndromes. There are four known such pathways so far: infectious, autoimmune, allergic and inflammatory. It is possible that one patient may have a combination of mutations in immunoresistance genes, which predisposes to infections, and mutations in genes that regulate the immune response, which predisposes to the development of immune-related complications - autoimmune, immunoinflammatory, allergic, in which the role of microbial factors as triggers for the breakdown of immune tolerance is studied. racesAn instance may be deletions in the genes of the lower regions of immunoglobulins, which contribute to the formation of deficits of various classes of immunoglobulins, IgG subclasses and specific antibodies (31-33), which, in turn, among other consequences contributes to the development of chronic infection caused by beta-hemolytic streptococcus group A (34). 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 autoantigens of the subcortical ganglia of the cerebral hemispheres induced by rheumatogenic streptococcus and the formation of autoimmune subcortical encephalitis, which is indicated by the acronym PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections) (35).

Related biochemical and immune pathological mechanisms lead to damage to the central nervous system, 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 exchange (distal or neurogenic modulation, for instance, *NLGN4*, *SNAP-25*, *DRD1* genes) (22).

Thus, it may be discussed on an individual pathological system of genes that form a picture of ASD and other neuropsychiatric syndromes in each case, since the affected genes do not function in isolation, but, on the contrary, interact with each other in various ways at different stages of pathogenesis, significantly transforming the initial pathological signal. When analyzing such individual pathological systems of genes that determine the polygenic nature of the inheritance of ASD, it should be borne in mind that they lead to a qualitatively greater clinical result than the simple sum of their parts. This justifies the expediency of a comprehensive, rather than a separate analysis of genetic models in patients with ASD. For clinical practice, it is important to create specialized diagnostic genetic panels that would allow routine identification 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 in the form of a genetic tree, as shown by Figure 1.

Biochemical disorders

The functioning of the pathological gene system leads to the formation of multiple metabolic anomalies that concern both the central nervous system in particular and the child's body as a whole (36,37). The most vulnerable are the brain, immune system and digestive organs, which constitute a kind of pathological organ triad in children with ASD (1,38,39). The clinical picture of the disease is largely due to the defeat of this particular organ triad, however, without a doubt, it is not limited only hereby.

In general, diverse biochemical disorders in the folic acid cycle and functionally related metabolic pathways (methionine cycle, thiol transulforate pathway, purine metabolism, the biopterin-neopterin

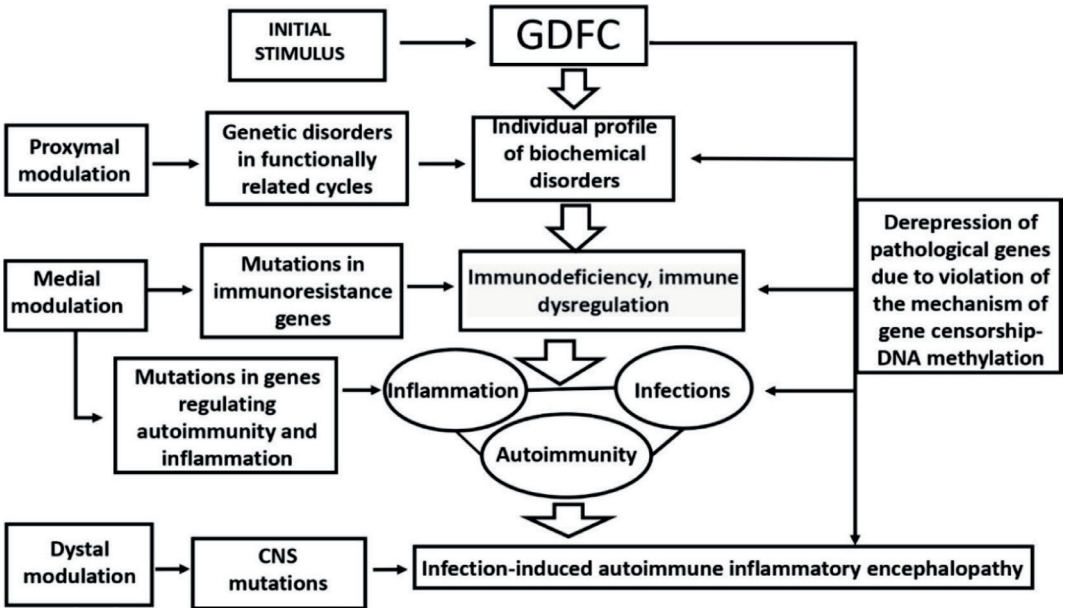

Figure 1. Structure of individual pathological gene systems in the development of ASD and other neuropsychiatric syndromes in children in the context of the folate-centric concept of the disease pathogenesis.

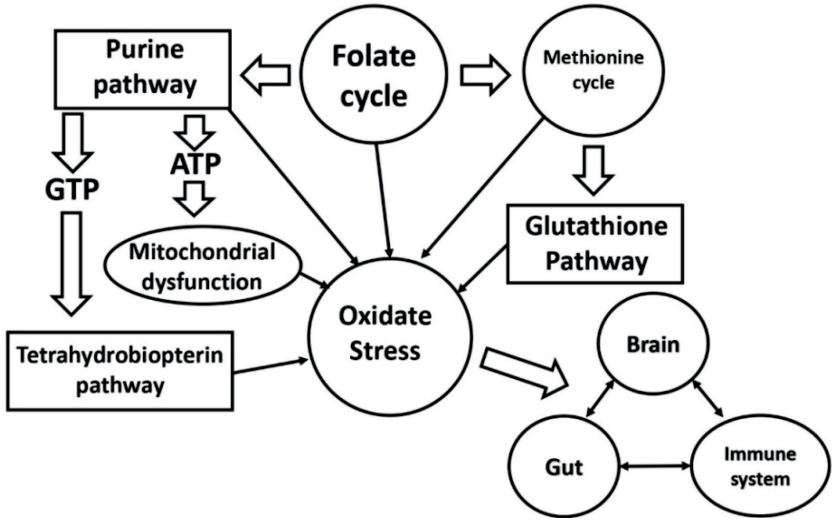

Figure 2. Schematic diagram of the system of key functionally related biochemical cycles and pathways involved in the pathogenesis of neuropsychiatric diseases in children, in connection with folate-centric concept.

pathway, mitochondrial dysfunction, etc.) (25-27) in the context of the folate-centric concept of the pathogenesis of the disease can be characterized as a state of persistent oxidative stress (17,18) (Figure 2).

The results of a meta-analysis and a systematic review of RCTs prepared by Frustaci et al. in 2012 show signs of oxidative stress in children with ASD. A decrease in serum concentrations of antioxidant compounds glutathione (27%), glutathione peroxidase (18%), methionine (13%) and cysteine (14%) and an abnormal increase in the concentration of oxidized glutathione in blood serum (by 45% of the normal level)

was found (1). Results of meta-analysis of RCT by Chen et al. of 2021, which covers 87 clinical trials involving 4,928 children with ASD and 4,181 healthy control group peers, demonstrate that in children with ASD, compared with healthy individuals, the serum concentration of such pro-oxidant agents as oxylene glutathione (GSSG), malondialdehyde, homocysteine, S-adenosylhomocysteine, nitric oxide and copper, and, conversely, significantly reduced serum concentrations of known antioxidants glutathione (GSH), total glutathione (tGSH), methionine, cysteine, vitamins B9, D, B12, E and calcium, as well as the level of such laboratory indicators for assessing the antioxidant system of the human body as GSH/GSSG, tGSH/GSSG and S-adenosyl methionine/S-adenosylhomocysteine have been reduced (17).

The data of these RCTs meta-analyses provide clinical practice with a number of informative laboratory biomarkers for assessing the individual pattern of biochemical disorders and associated oxidative stress. James et al. in 2006 identified genetically induced metabolic endophenotypes in children with ASD caused by damage to the folate cycle and functionally related metabolic pathways that lead to oxidative stress in the child's body (22). In regard to 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, folic acid and tetrahydrofolate, and with the involvement of the methionine cycle – homocysteine, methionine, S-adenosylhomocysteine and S-adenosylmethionine. At the same time, the thiol transsulforization system or glutathione pathway is evaluated by the glutathione, cysteine, cystathionine, and choline concentrations in the blood serum, and 4-tetrahydrobiopterine metabolism – by the cluster of neopterin, monapterin, isoxanthopterin, biopterin, primapterin, and pterin in the urine (28). It should be emphasized that laboratory biomarkers are not associated with Asd itself, but with those genetic abnormalities that, as research results show, are associated with the ASD phenotype in children.

Genetically induced multiple metabolic disorders in children with neuropsychiatric syndromes form individual patterns of pathological biochemical disorders, or metabolic endophenotypes, for which evaluation in clinical practice it is necessary to develop specialized laboratory diagnostic panels for the analysis of specific metabolic disorders in the context of the folate-centric concept of the pathogenesis of the disease. Identification of an individual pattern of pathological biochemical disorders in each case is an important clinical task, since it allows selecting an individual program of biochemical correction to weaken the biochemical pathway of central nervous system damage, so that neuropsychiatric manifestations can be weakened. 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 of clinical manifestations of ASD in children (29). The results of another systematic examination and meta-analysis of RCT 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 insufficiency caused by autoantibodies to folic acid receptors in the central nervous system in children with ASD (30). For the time being, numerous results of controlled clinical trials have been published, which indicate the successful use of many other key metabolites for specific biochemical correction, including N-acetylcysteine, L-carnitine and resveratrol (40). Key biochemical disorders and means of their correction in children with ASD are considered in detail in the systematic review of Frye and Rossignol (28). Surely the list of recommended means of biochemical correction in children with ASD will expand each year based on new results receipt of controlled clinical trials.

Immunological disorders

By inducing biochemical, genoregulatory and epigenetic disorders, GDFC and disorders in functionally related cycles damage the maturation and functioning of the child's immune system. As noted by Hughes et al. in a systematic review devoted to the phenomenon of disruption of the immune system in children with ASD, in such cases there is an aberrant cytokine profile, a deviation in the absolute and relative number of immunocompetent cells and their subpopulations,

signs of neuro-inflammation, disruption of the adaptive and innate immunity system, an imbalance of immunoglobulins of different classes and signs of autoimmunity (1). According to the results of few studies, the depth of immune factor deficiency correlates with the severity of clinical manifestations of neuropsychiatric disorders in children (31).

Ambivalent disorders of the immune status are formed in children with neuropsychiatric syndromes, including simultaneous coexistence of deficiency/suppression of some immune defense factors (41,42) and excess/hypeactivation of others (43,44). Among other reasons, this may be due to reciprocal connections between various components of the immune system capable of self-regulation. The consequences of the imbalance in the immune status are the phenomenon of decreased immune resistance due to the lack of certain immune factors protecting against infectious agents (45) and tumors (46), and the phenomenon of immune dysregulation with the development of immuno-inflammatory, allergic and autoimmune reactions due to violations of endogenous mechanisms of immune inflammation regulation and maintenance of immune tolerance to a number of antigens (1). In fact, it is referred to an immune-mediated subtype of ASD in children isolated by McDougle et al. in 2015 (47).

Multidirectional changes in the immune status were demonstrated in a controlled clinical study, which showed in children with ASD a decrease in the amount of NK, NKT, CD8+ cytotoxic T-lymphocytes in the blood, serum concentrations of some classes of immunoglobulins, IgG subclasses and a weakening of the functional activity of neutrophil myeloperoxidase in parallel with an abnormal increase in the number of circulating immune complexes, CD3+ and CD3+CD4+ T-lymphocytes, CD3-CD19+ B cells, and variable serum concentrations of antibodies of E, M, A, and G4 classes (48). Despite the known variability of pathological changes in the immune status in different children with ASD, Careaga et al. proposed to isolate the so-called immune endophenotypes, which can lead to various immunosuppressive complications and require various immunotherapeutic interventions to carry out of immune correction (49).

A specific form of primary immunodeficiency associated with GDFC has now been isolated (50). Clinically, immunodeficiency in children with ASD manifests itself in the form of a pentad of syndromes, including infectious, allergic, immunosuppressive, autoimmune and oncological manifestations, which are components of primary immunodeficiency phenotype accordanly with the postulates of clinical immunology (Figure 3).

Mauracher et al. in the systematic review, which covers the results of 186 scientific publications, identified a pattern of immune dysregulation characteristic of primary immunodeficiency, which includes autoimmunity (64%), intestinal syndrome (38%), lymphoproliferation (36%) and allergy (34% of cases) (51). In patients with GDFC the indicated pattern of immune dysregulation is fully reproduced. Results of a large population study by Isung et al., which examined the medical data of 14 million Swedish residents, indicate in 2020 that children with primary immunodeficiency risk of developing ASD increases at least 3.2 times compared to peers who have not been diagnosed with diseases of the immune system. The authors indicate the close involvement of immune mechanisms in the pathogenesis of neuropsychiatric disorders in such cases (18).

According presented data, an unprecedented correspondence of clinical phenotypes of GDFC looks obvious, it is widespread in the population and affects mainly the system of innate immunity and primary deficiency of mannose-binding lectin, which is common in the population of genetically determined immunodeficiency with predominant damage to the immunity of innate components of immune protection (Table 1).

In clinical practice, it is necessary to group children with neuropsychiatric syndromes by the nature of immunological disorders to identify the individual immune endophenotype of GDFC-induced immunodeficiency. This is due to the fact that various disorders in the immune status can be associated with various infectious factors, external complications and related clinical results, and also require different approaches to immunotherapy. Thus, deficits of NK, NKT, CD8+ cytotoxic T-lymphocytes are associated with reactivated herpes virus infections, deficits of classes and subclasses of immunoglobulins are associated with streptococcal infection, and myeloperoxidase deficiency is associated with candidiasis, which affects the nature of the infectious syndrome and related immune-dependent manifestations (52).

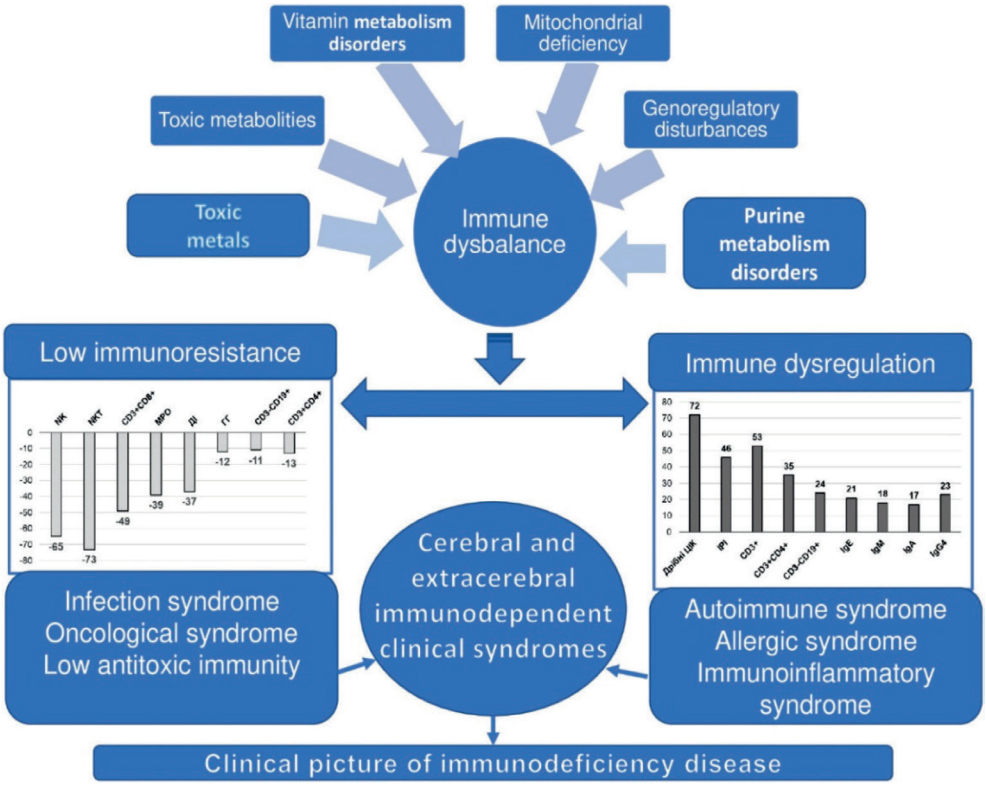

Figure 3. Pathogenesis of a specific form of GDFC-induced immunodeficiency in children with neuropsychiatric syndromes and clinical consequences in the context of folate-centric concept of disease pathogenesis.

Indeed, immunodeficiency in children with GDFC requires immunocorrection, and the benefit of combined immunotherapy with Propes and Inflamafertin in a controlled clinical trial has recently been demonstrated to be the first step towards developing effective immunotherapeutic approaches to eliminate disorders in cellular immunity in children with ASD, whereas manifestations of hypo-immunoglobulinemia, deficits of IgG subclasses and specific antibodies in such cases can be effectively compensated by using low- and medium-dose intravenous immunoglobulin therapy, as shown by the results of a systematic review and meta-analysis of clinical studies by Frye and Rossignol in 2021 (33).

Infectious factors

Due to the immunocompromised condition, children with ASD and other neuropsychiatric syndromes are characterized by reduced immune resistance, which implies an increased predisposition to a number of infectious agents, which are the first immune-dependent factor of damage to the nervous system in such cases. Today, it is believed that not all children with ASD have an increased susceptibility to infections, but such a phenomenon is real in those patients who show signs of reduced immunoresistance and related immune dysregulation.

Now the ideas on the dualism of microbe-induced pathways of central nervous system damage in children with ASD have become established. It is possible to distinguish a direct pathway of damage when a microbe causes acute or chronic neuroinfection, and indirect pathways associated with brain damage by microbe-induced autoimmune and immune-related reactions.

Binstock T. in 2001 for the first time identified a subgroup of children from ASD with abnormally reduced immunoresistance to a number of intracellular

Table 1. Comparative characteristics of clinical phenotypes of GDFC and primary deficiency of mannose binding protein in humans.

Sign	GDFC	Deficiency of a mannose-binding protein
Infectious syndrome	Reduced resistance to streptococci and herpesviruses (52,53)	Propensity to streptococcal (54), herpesvirus infection (55)
Autoimmune syndrome	Rheumatoid arthritis (56-58), systemic lupus erythematosus (58), rheumatic heart disease (60), spondyloarthritis (61,62) and others (63).	Rheumatoid arthritis (64), systemic lupus erythematosus (65), rheumatic heart disease (66), spondyloarthritis [61]
Allergic syndrome	Bronchial asthma (67), atopy (68).	Bronchial asthma, atopy (69).
Psychiatric pathology	Bipolar disorder, depression, schizophrenia (70,71).	Bipolar disorder, panic attacks, schizophrenia (72).
Neurodegenerative pathology	Alzheimer's disease (72).	Alzheimer's disease (73).
Oncological syndrome	Acute lymphocytic leukemia, ovarian cancer, hepatocellular carcinoma and others (74-79).	Acute lymphocytic leukemia, ovarian cancer, hepatocellular carcinoma and others (80).
Immune inflammatory lesions	Nonspecific ulcerative colitis (81).	Nonspecific ulcerative colitis (82).
Aggravation of other genetic pathologies	Increased risk of development and aggravation of Down's disease (83).	Aggravation of Down's disease (84).
Vascular lesions	Atherosclerosis and related complications (85).	Atherosclerosis and related complications (86).
Infertility	Multiple episodes of spontaneous abortions (87).	Multiple episodes of spontaneous abortions (88).
Hemocoagulation disorders	Tendency to thrombosis (89).	Tendency to thrombosis (88).

(intramonocytic) infectious agents (45). Now it can be argued that the author described the pattern of infection of children from GDFC. The data accumulated so far indicate the selective sensitivity of children with ASD to opportunistic and conditionally pathogenic microorganisms. According to the results of a controlled clinical study, it is associated with a heterogeneous lesion of the components of the immune system during the formation of GDFC-induced immunodeficiency (48). It has been found that children with ASD are more likely to suffer from herpesvirus infections (45,91,92), TTV infection (52), mycoplasmosis and chlamydia (91), yersiniosis (45), borreliosis (93), candidiasis (94), streptococcal infection (32), and toxoplasmosis (95) than mentally healthy peers. These microbes constitute a specific microbial spectrum associated with GDFC-induced immunodeficiency in children with ASD (52). Concepts regarding the specific microbial spectrum in ASD will require further study and significant clarification.

In fact, the immune status of a child with ASD largely determines the nature of the infection of the child, since we are talking mainly about opportunistic and conditionally pathogenic ubiquitous pathogens. As the results of a controlled clinical study show, reactivation of HHV-6-, HHV-7-, TTV infections in children with ASD are noted mainly with deficiencies of NK-, NKT - and CD8+ cytotoxic T cells. Streptococcal infection is associated with hypo- and disimunoglobulinemia, as well as myeloperoxidase deficiency. Candidiasis is associated only with myeloperoxidase deficiency. Toxoplasmosis is noted with a deficiency of CD3+CD4+ T-helper cells and combined immune disorders. The consequences of congenital CMV neuroinfection occur only in combined immune disorders (52).

In fact, the infectious factor can form an independent mechanism of damage to the central nervous system in children with ASD in some cases, which is confirmed by clinical reports of the development of the ASD phenotype after postnatal viral encephalitis (encephalitic mechanism) (96), an abnormally high incidence of congenital cytomegalovirus neuroinfection in this category of patients (teratogenic mechanism) (97) and development of signs of temporal median

sclerosis in some children (neurodegenerative mechanism) (98). According to the systematic review and meta-analysis of controlled clinical trials of Wipfler et al. in 2018 it became associated with HHV-6 (99), penetrating the mesolimbic system of the brain by transolfactory way (100).

Microbes in children with ASD can be both triggers of abnormal cerebral hyperinflammation (101) (inflammatory indirect mechanism) and autoimmunity to neurons (102-104) and myelin (105) of the central nervous system (autoimmune indirect mechanism). The phenomenon of selective influence of microorganisms of various taxonomic groups in relation to brain autoantigens and extracerebral autoantigens is noted. According to the results of a recent controlled clinical study, serological signs of autoimmunization to autoantigens of subcortical ganglia of the cerebral hemispheres are associated with *Streptococcus pyogenes* and *Borrelia spp.*, to neurons of the mesolimbic system-EBV, HHV-6, HHV-7, *Toxoplasma spp.* and Torque Teno Virus (TTV), to CNS myelin – EBV, HHV-6, HHV-7, *Borrelia spp.* and TTV, to the nuclei of connective tissue cells and lumbosacral muscles-EBV, HHV-6, HHV-7, *Borrelia spp.* and TTV (52). In addition, microbes can determine the intensity, nature and localization of immuno-inflammatory reactions. Thus, Hughes & Ashwood showed that seropositivity to candidiasis in children with ASD is associated with the clinical severity of immuno-inflammatory gastrointestinal lesions (94).

Therefore, children with ASD have an individual spectrum of microbes involved in pathogenesis, which dynamically changes during ontogenesis as a result of the interaction of the child's body with environmental factors, and neuropsychiatric syndromes themselves are characterized by a set of specific pathogenetically significant microbes that form individual pathological microbial systems, since microorganisms interact with each other in various ways within one macroorganism. Thus, there is a well-known synergy between EBV and *Streptococcus pyogenes*, whereas *Streptococcus pyogenes* and *Candida albicans* exhibit antagonistic interaction.

It is necessary to develop a special diagnostic panel to identify a specific microbial spectrum in children with ASD and other neuropsychiatric syndromes for clinical practice and to group such patients with preferred microorganisms with the determination of individual microbiological endophenotypes, as recommended by Kong et al. (106), since it affects the formation of mechanisms of damage to the central nervous system, the clinical picture, the outcomes of the disease and the need for certain therapeutic interventions. As the research results show, it is necessary to use various laboratory methods for microorganisms of different taxonomic groups. Thus, to identify HSV-1/2, VZV – specific IgM and IgA in the blood should be determined (52), EBV, HHV-6, HHV-7, TTV PCR of blood leukocytes (52,91), borreliosis and yersiniosis – immunoblots with simultaneous determination of IgM and IgG to many pathogen antigens (45,93), mycoplasmosis and chlamydia – specific IgM in blood serum (3,95), streptococcal infection – bacteriological examination on a selective medium and blood antitoxic immunity (ASLO, antistreptodornase, antistreptogialuronidase) (32), candidiasis – mycological studies and specific IgM in blood (94), toxoplasmosis – specific IgM in the blood and the method of paired sera (95). In addition, microorganisms of different types occur in children with ASD with varying frequency. Four groups of infectious agents were identified 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 spp.* - 59-34%; Group III – mycoplasmas, chlamydia, yersinia – 27-23%; Group IV – toxoplasma, congenital cytomegalovirus infection, HSV-1/2 with CNS lesion – 19-5% of cases) should be taken into account in the algorithm of step-by-step microbiological diagnostic search with planning the sequence of actions in assessing microbial load and determining the antimicrobial drugs usage (52).

Substantiation of the infectious factor role in the pathogenesis of the disease in GDFS creates prerequisites for testing antimicrobial treatment strategies prescribed on the basis of a personalized assessment of the patient's microbial profile. According to this, Snider et al. performed a double-blind placebo-controlled randomized clinical trial of long-term preventive therapy with penicillin VK at a dose of 250 mg twice a day and azithromycin at a dose of 250 mg twice a day 1 time a week for 1 year with PANDAS. A 96% decrease in the

frequency of exacerbations of streptococcal infections and a 61% decrease in the number of relapses of PANDAS in patients taking both penicillin and azithromycin compared with placebo was demonstrated (107). It is quite obvious that children with neuropsychiatric manifestations, in addition to antibiotic therapy, need antiviral, antifungal and antiprotozoal treatment in case of identification of the relevant infectious agents, which should be studied in controlled clinical trials.

Additional research is needed to clarify the microbial spectrum in children with ASD, as well as the participation of microorganisms in the pathogenesis of damage to the CNS and other organs in ASD.

Autoimmune reactions

Pathological immune reaction against brain autoantigens in children with ASD can be alloimmune (in the so-called feto-maternal immune conflict) (108) and autoimmune (43). If alloimunization is an antenatal phenomenon that is associated with immune dysregulation in the body of a pregnant mother, has a transient course and a tendency to self-injury a few months after birth due to catabolism of alloimunnial maternal antibodies in the child's body, then the autoimmune mechanism is chronic, has a dynamic course and develops postnatally during the first years of extrauterine ontogenesis, being associated with immune dysregulation in the body of the child.

Microbial and non-microbial factors (for instance, heavy metals as haptens) (106) under conditions of GDFC-induced immune dysregulation in children with ASD and other neuropsychiatric syndromes induce both anti-cerebral (44) and extracerebral (109) autoimmune reactions, which are the second immune-dependent pathway of CNS damage. In regard to the anticerebral autoimmunity, the described production of autoantibodies is related both to neuronal autoantigens (34,110) and myelin (105). It has been established that in children with ASD, not all nerve cells of the central nervous system become the target of autoimmune aggression, but neurons of individual anatomical zones, i.e., it has not a total, but a selective, or mosaic lesion of the gray matter of the brain. Kern et al having analyzed all available scientific reports on the identification of autoantibodies to CNS neurons in children with ASD in the period from 1985 to 2020, found that so far it is known about autoimunization to the precursor cells of neurons, neurons of subcortical ganglia, hippocampus, thalamus and hypothalamus, serotonin receptors of neurons, folic acid receptors of the blood-brain barrier, brain endothelium and neuron-axon filament protein. An autoimmune attack in children with ASD can also be directed at glial brain cells, in particular, glial fibrillary acidic protein (106). Thereafter, Whiteley et al. in a specially prepared scientific review defend the opinion on 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 (111). In regard to extracerebral autoimmunity in children with ASD, then autoimmunization to the nuclei of cells, lumbosacral muscles, collagen and endocrine organs has been described (58,109).

Typical associations between certain microorganisms and certain autoantibodies are shown, which indicates selectivity in the implementation of microbe-mediated trigger effects when inducing disruption of immune tolerance to brain and extrabrain 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 lumbosacral muscles, whereas *Streptococcus pyogenes* is associated with neurons of subcortical ganglia. *Borrelia spp.* is associated with autoimmunity to myelin, subcortical ganglia neurons, connective tissue cell nuclei and lumbosacral muscles, and *Toxoplasma spp.* – to hippocampal neurons (58). Thus, having determined the individual microbial spectrum of the patient, it is possible to reasonably predict the most likely pathways of microbe-induced autoimmune reactions, as well as by assessing the immune status, it is possible to conclude about the most likely pathogenetically significant microbes that can infect a particular patient.

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 individual autoimmune patterns in each case. This will make it possible to

justify the appointment and adequately evaluate the effectiveness of such immunomodulatory therapeutic agents as methylprednisolone, normal human IV immunoglobulin and rituximab, which benefits in children with ASD have been demonstrated in controlled clinical trials (33,112).

Immune inflammatory syndrome

Immunoinflammatory syndrome can be another manifestation of immune dysregulation in children with neuropsychiatric syndromes. It forms the third mechanism of immune-dependent brain damage. It has to be distinguished primary and secondary immune inflammatory syndromes. The primary is a consequence of an endogenous violation of the regulation of inflammation in conditions of immune dysregulation, and the secondary is a component of infectious and autoimmune syndromes that are characteristic of immunocompromised children with GDFC.

Evidence for the development of persistent systemic inflammatory response in children with ASD is based on the results of 2 systematic reviews and meta-analyses of RCTs. In particular, the data of the first systematic review and meta-analysis show an increase in serum concentrations 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 anti-inflammatory cytokine transformative growth factor beta 1 (p<0.001) in children with ASD (n=743) compared with healthy patients (n=592) (113). The results of a meta-analysis by Saghazadeh et al in 2019, which covers 38 trials involving 2,487 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.[114] Accordingly, Jyonouchi et al. in a specially planned clinical study show that an increase in serum concentrations of proinflammatory 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 by both the well-known neurotoxic effect of serum proinflammatory molecules in conditions of pathological increased permeability of the blood-brain barrier, and the associated induction of secondary low-productive intracerebral inflammation with subsequent dysfunction of CNS neuronal networks (32). Thom et al. (115) proposed to single out the immunoinflammatory mechanism as a separate link in the pathogenesis of cerebral lesions in ASD and to single out a separate subgroup of children from ASD in whom the multisystem immunosapal pathway of CNS damage prevails.

As the results of a recent controlled clinical trial show, tumor M2 pyruvate kinase, TNF-alpha and IL-6 in children with ASD demonstrate variability in sensitivity, lability and specificity, which suggests the need for a comprehensive data analysis. Tumor M2 pyruvate kinase is the most sensitive, but the least specific indicator of inflammation, whereas 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 (116). The studied indicators are associated with an increase in the blood serum indices of neuronal damage of neuron-specific enolase and S-100 protein (117), which confirms the idea of the role of systemic inflammation in the induction of central nervous system damage in children with ASD associated with GDFC, and opens the way to the testing of new therapeutic strategies with anti-inflammatory therapy to reduce severity of neuropsychiatric manifestations (118).

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 individual cytokine status of the patient, or the immunoinflammatory endophenotype, which characterizes the state of the immunoinflammatory reaction at a specific time in a specific compartment of the body as a separate mechanism of cerebral damage. The data obtained may be the 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 developing targeted anti-inflammatory strategies in children with neuropsychiatric syndromes that can modify the course of the disease (119).

Allergic syndrome

The results of a large population-based clinical study involving 199,520 children conducted by Xu et al. (2019) showed that food allergies, respiratory allergies and skin allergies occurred in children with ASD in 11.25%, 18.73% and 16.81% of cases, respectively, while in mentally healthy children such disorders were significantly less frequently reported (4.25%, 12.08% and 9.84%). The odds ratio in children with ASD relative to various types of allergies was 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 (120).

Allergic syndrome in children with neuropsychiatric syndromes is a consequence of immune dysregulation formed in conditions of GDFC-induced immunodeficiency, as well as the fourth immune-dependent mechanism of damage to the central nervous system.

It is possible to distinguish the Central and perferic mechanisms of the formation of allergic syndrome in children with ASD. The central mechanism of the allergic trap is characterized by the scientific concept of Theoharides T.C.S. et al, which provides for the production of neurotensin in the hypothalamus of the brain in children with ASD under the influence of stress factors, which activates mastocytes of the perivascular spaces of the thalamus and hypothalamus with subsequent induction of allergic inflammation in the parenchyma of the brain with neurotoxic influence (121). 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 (122). The peripheral mechanism of the development of allergic inflammation as a pathway to the central nervous system in children with ASD is associated with allergies to certain foods, including gluten and casein, with the onset of allergic inflammation in the intestinal wall and the further spread of such an inflammatory reaction in the blood and brain through the damaged blood-brain barrier. The validity of the peripheral concept is confirmed by the results of an experimental study by Cao et al. The development of inflammatory lesions of the central nervous system and related autistic-like behavior disorders in experimental mice was demonstrated during the induction of allergy to cow's milk casein in the intestine under conditions of immune dysregulation similar to observed in children with ASD (123).

The results of a meta-analysis and a systematic review of clinical studies by Yu et al. in 2022, which analyzed the results of 7 RCTs involving 338 children, showed that the elimination gluten-free and casein-free diet can significantly alleviate the main clinical symptoms of ASD and contributes to improving the social behavior of children with neuropsychiatric syndromes, which is a practical confirmation of allergic concepts of disease pathogenesis (124).

The concept of the functional axis of the microbiota–intestine–brain

The dynamics of the pathological process with a wave-like course, which implies periods of improvement and deterioration of the mental status of the child, is explained by the scientific concept of the functional axis of the microbiota–intestine–brain. Microbial antigens (115), food allergens (123) and environmental toxins, including heavy metals (125), during exposure to the damaged GDFC immune system associated with mucosa-associated lymphoid tissue (MALT), which is contained in the intestinal wall, induce a state of local intra-terminal inflammation among other things. Consequently, 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 (38, 126). It can be said that children with neuropsychiatric syndromes are characterized by a state of impaired intestinal-immune system interface. In this case, normally harmless stimuli from microorganisms, food products and substances lead to an abnormal hyperinflammatory response in the intestinal wall. The state of chronic inflammation is accompanied by a pathological increase in the permeability of the intestinal walls, which allows the local inflammatory reaction to easily generalize, leading to a state of systemic inflammation with the characteristic phenomenon of persistent hypercytokinemia. The concept

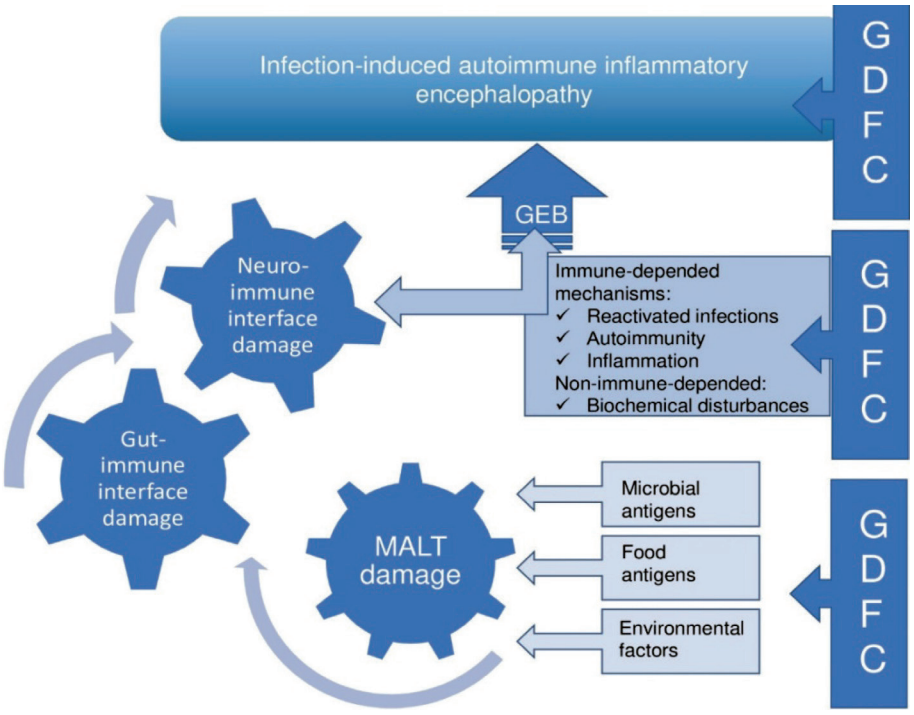

Figure 4. Mechanism of abnormal spread of inflammation from the intestinal wall through the blood to the brain in children with neuropsychiatric syndromes through the functional axis microbiota–gut–brain within the folate-centric concept.

of impaired barrier function of the intestinal epithelium in children with ASD is currently substantiated by Fiorentino et al. in the corresponding systematic review (127). In the future, systemic inflammation due to GDFC-induced violation of the neuroimmune interface and the associated pathologically increased permeability of the blood-brain barrier migrates to the central nervous system, where intracerebral inflammation develops, associated with a deterioration in the mental status of the child (Figure 4).

In this review, Fiorentino et al. put forward and substantiate the scientific concept of violation of the function of the blood-brain barrier in children with ASD (127). Disorders in the functioning of the functional system microbiota–gut–brain facilitate the implementation of both biochemical and immune-dependent mechanisms of central nervous system damage in children with ASD. A systematic review of the results of controlled clinical studies accumulated so far on the functioning of the microbiota–gut–brain mechanism in children with ASD has been prepared by Azhari et al. (128).

The concept of GDFC-induced encephalopathy

Setting exclusively psychiatric diagnoses for children with GDFC addresses an outdated descriptive approach to understanding the problem, however, it 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 recovery of the patient. In fact, brain damage is formed in children with ASD, i.e., encephalopathy occurs with a predominant lesion of the cerebral cortex, a violation of the phenomenon of neuronal connectivity and the implementation of synaptic plasticity processes. Bouboulis et al proposed to call such encephalopathy the term microbe-induced autoimmune encephalopathy (53). Since a separate immune inflammatory pathway of CNS damage has now been demonstrated that is not directly related to an autoimmune reaction or infection, in our opinion, the term infection-induced inflammatory autoimmune

encephalopathy should be more accurate. It is also possible to suggest simpler and at the same time more capacious terms: immune-dependent encephalopathy or GDFC-induced encephalopathy. We propose these terms for scientific discussion in order to assess the possibility of use in cases where the phenotype of ASD is formed in the case of the implementation of certain immune-dependent mechanisms of the development of damage to the nervous system, in which microbial agents play a pathogenetic role.

This encephalopathy is caused by the realization of polygenic biochemical, immune-dependent, gene regulatory and epigenetic disorders, which were mentioned above. Clinically, such encephalopathy is manifested by a complex of psychiatric and neurological syndromes that develop simultaneously or sequentially in the patient during ontogenesis when interacting with environmental factors. It is a case of ASD, attention deficit hyperactivity disorder, obsessive-compulsive syndrome, hyperkinetic syndrome, sleep disorders, eating disorders, cognitive decline, epileptic syndrome and motor disorders (3,34,129). If there are all these 9 syndromes, it can be said on the full clinical picture of GDFC-induced encephalopathy, if only some syndromes – on the partial phenotype of such encephalopathy (Figure 5).

Currently, ASD is considered morbid, and other syndromes are considered comorbid, thereby emphasizing the primacy of ASD in relation to 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 studies. Within the framework of the concept of GDFC-induced encephalopathy, the division into morbid and comorbid clinical syndromes should be discarded 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 the defeat of various parts of the central nervous system and various mechanisms of cerebral damage, and in general are equivalent and interpenetrating phenomena, and in a particular child, the severity of the condition and the prognosis of the disease can be prioritized by any of these syndromes, which is more significant. Some children with GDFC-induced encephalopathy do not develop a picture of ASD at all during ontogenesis, thus, this syndrome cannot be considered exclusively a key one in the clinical phenotype of the disease. The child's death because of an accident may occur not clearly by ASD, but due to attention and hyperactivity deficit disorder or an epileptic seizure (3).

According to the results of pathomorphological (86) and neuroimaging (131) studies, encephalopathy in children with ASD is characterized by signs of cortical damage, impaired neuron connectivity and

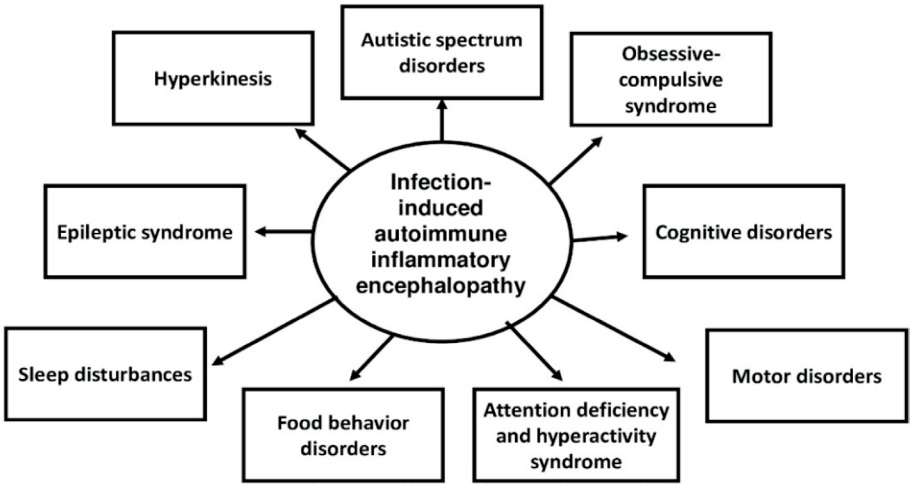

Figure 5. Structure of clinical manifestations of infection-induced autoimmune inflammatory encephalopathy in children with neuropsychiatric syndromes.

disorders of synaptic plasticity. For the time being, 5 main neuroradiological syndromes have been described in children with GDFC-induced encephalopathy, namely, leukoencephalopathy (132), hypertrophy of subcortical ganglia (34), temporal median sclerosis (98), signs of congenital CMV infection (97) and postnatally transferred neuroinfections (96) as well as small anomalies in the development of the brain and spinal cord brain (133). Concepts regarding the relevance of these radiological signs in ASD will require further study and significant clarification.

At the same time, the connections between neuroimaging phenomena and data on the assessment of the immune status, microbial spectrum, autoimmune profile and clinical syndromes with the formation of so-called immune-infectious-rheumatology-neuroimaging-clinical complexes have been demonstrated (134) (virus-induced temporal median sclerosis (98,99), autoimmune subcortical encephalitis (34), autoimmune limbic encephalitis (134), autoimmune leukoencephalopathy (105), congenital CMV neuroinfection (97,136)). 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 central nervous system damage at a specific time in children with neuropsychiatric syndromes. An instance of such a cluster may be a deficiency of IgG subclasses associated with deletions in the genes of the lower regions of immunoglobulins; oropharyngeal infection caused by beta-hemolytic streptococcus group A; autoantibodies to dopamine receptors type 1 and tubulin; hypertrophy of caudate subcortical ganglia on MR images; obsessive-compulsive syndrome and tics in the clinical picture of the disease (34).

The promotion of the concept of GDFC-induced encephalopathy radically changes the understanding of appropriate treatment approaches. The era of the dominance of psychotropic treatment, designed to temporarily reduce individual mental symptoms of the disease, which seemed to be the only obvious therapeutic interventions 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-induced mechanisms of cerebral damage. The success of the use of methylcobalamin, folinic acid and other means of biochemical correction not only confirms the relevance of the biochemical pathway of central nervous system damage in neuropsychiatric syndromes, but also provides practical medicine with effective means of neuroprotection by at least partially blocking the biochemical pathway of central nervous system damage (29,30). The validity of the proposed independent concept of encephalopathy formation in children with ASD associated with GDFC is confirmed by the clinical effectiveness of immunotherapeutic interventions, including therapeutic approaches aimed at achieving neuroprotection by blocking infectious, autoimmune and immuno-inflammatory pathways of central nervous system damage (Figure 6).

In particular, we are talking about the use of azithromycin or penicillin for the prevention and mitigation of PANDAS exacerbations (107), infliximab (anti-TNF-alpha therapy) to suppress TNF-alpha-induced systemic inflammation and associated cerebral damage (64), rituximab (anti-CD20 therapy) to suppress anti-cerebral autoimmune and the resulting autoaggression damage to the neurons of the central nervous system (112) and normal intravenous human immunoglobulin in a high dose, which has an integral therapeutic effect, inhibiting all known immune mechanisms of encephalopathy formation, through anti-inflammatory, anti-infective and immunomodulatory effects (33,137). The results of clinical studies in the field of immunoglobulin therapy of ASD are now summarized in the data of a systematic review and meta-analysis of clinical studies by Rossignol and Frye in 2021 27 relevant trials were analyzed, including 4 prospective controlled trials (one double-blind placebo controlled), 6 prospective uncontrolled trials, 2 retrospective controlled trials and 15 retrospective uncontrolled trials. The overall clinical result of the testing of normal human immunoglobulin preparations according to this meta-analysis is an improvement in communication, hyperexcitability, hyperactivity, cognition, attention, social interaction, eye contact, echolalia, speech, reaction to commands, drowsiness, decreased activity, and in some cases – complete elimination symptoms of ASD (33). The results of a recent retrospective analysis, covering data from the

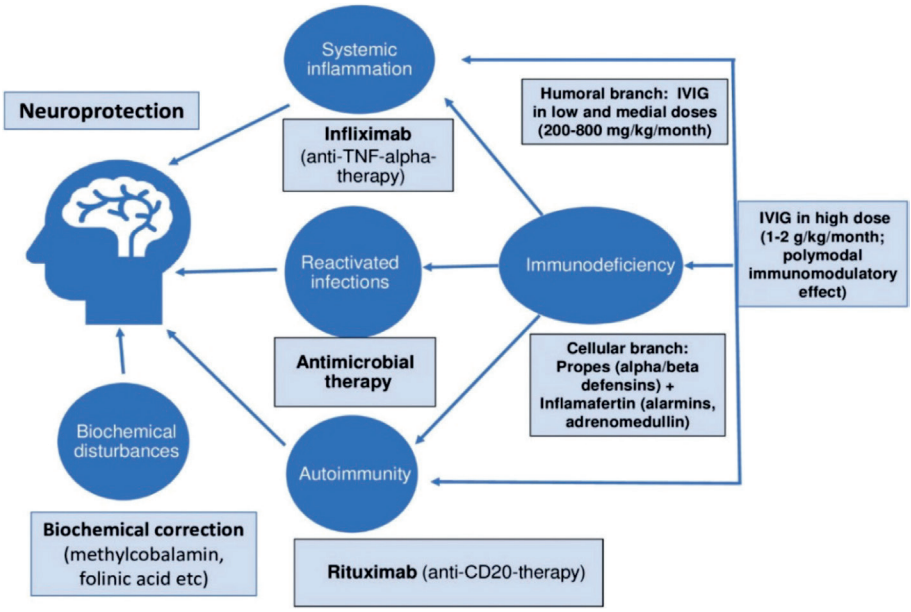

Figure 6. Available means of neuroprotection in the implementation of immune-dependent mechanisms of cerebral damage in the development of infection-induced autoimmune inflammatory encephalopathy in children with neuropsychiatric syndromes in the context of folate-centric concept.

experience of using a 6-month course of normal human IV immunoglobulin at a dose of 2 g/kg/month in 225 children with ASD, supplement the evidence base of the effectiveness and safety of IV immunoglobulin therapy in children with neuropsychiatric syndromes (137). Accordingly, data from a double-blind placebo-controlled randomized clinical trial by Perlmutter et al showed equivalent clinical efficacy of high-dose intravenous immunoglobulin therapy and plasmapheresis in children with PANDAS (138). Of course, the use of immunoglobulin must be justified in each specific case. Further studies are needed, the results of which clarified the effectiveness and indications for the use of IVIG in children with ASD.

Successful testing has been provided with combined immunotherapy with Propes and Inflamafertin to compensate for key disorders of cellular immunity (90) and normal human immunoglobulin in low and medium doses – to replace the deficiency of the humoral link of immunity (33) in GDFC-induced immunodeficiency provide practical medicine with effective means of preventing infections and immunodeficiency-related manifestations of immune dysregulation responsible for development of immune-dependent pathways of encephalopathy formation in children with neuropsychiatric syndromes.

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 the lack of attention in lesions of other organs and systems other than the nervous system. Indeed, the biochemical and immune-dependent mechanisms of lesion developing in GDFC concern not only the central nervous system, but also other organs (120). Such children have cerebral and extracerebral clinical manifestations of the disease. Extracerebral symptoms, although they mainly concern damage to the immune system and intestines can actually attract all organs and systems in a variable manner (1,38,130), there is a special form of damage to the whole organism, which can be called polygenic GDFC-induced multisystem disease (Figure 7).

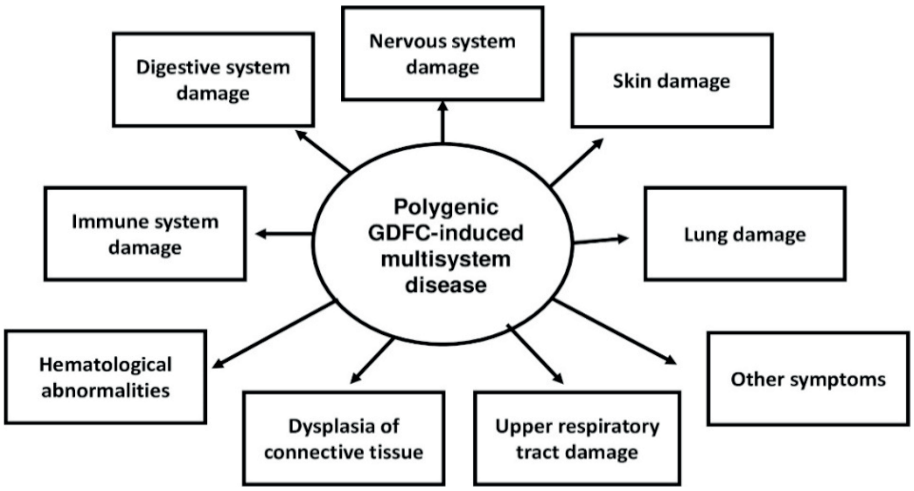

Figure 7. The structure of the clinical picture of polygenic GDFS-induced multisystem disease as a form of damage to the whole body of the child.

Minshew and Williams define autism as a polygenic neurobiological developmental disorder of a child with a multi-organ lesion, but with the leading involvement of the nervous system (130). However, there is a systematic error in this definition. Indeed, the disease in such children has polygenic inheritance is accompanied by a multi-organ lesion and a violation of the neurobiological development of the child, but autism as such is not the cause or essence of such a polysystem disease, but only one of its clinical manifestations. It cannot be said that it is the psychiatric symptoms of the disease that are always leading, and the defeat of other organs and systems is secondary, since the ratio of the severity of syndromes in different children differs significantly. There are patients with GDFC whose intestines are severely affected, but there are almost no psychiatric and neurological manifestations of the disease (38,81). 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 instance, the child death in patients 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 immune inflammatory intestinal lesion (3).

The integrated scheme of the pathogenesis of neuropsychiatric diseases in children in connection with the folate-centric concept, which demonstrates the links between genetic, biochemical, immunological and clinical manifestations is shown in Figure 8.

Scientific concepts of a personalized multidisciplinary approach to patient management

Since the pathogenesis of the disease involves interconnected lesions of the genome, metabolism, immune system, nervous system and many organs and systems in children with neuropsychiatric syndromes, a multidisciplinary approach to patient management is necessary with the help of a medical geneticist, clinical immunologist, pediatric neurologist, psychiatrist and other specialists. Since each patient is characterized by a unique pathological gene system and associated biochemical and immunological disorders, strict standardization of approaches to diagnosis and treatment is not possible, which justifies a personalized approach based on the results of controlled clinical trials. 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 of Bradstreet et al. of 2010 is based on the analysis of a large group of laboratory biomarkers, which relevance has been demonstrated in clinical studies, and further targeted correction of disorders that these biomarkers

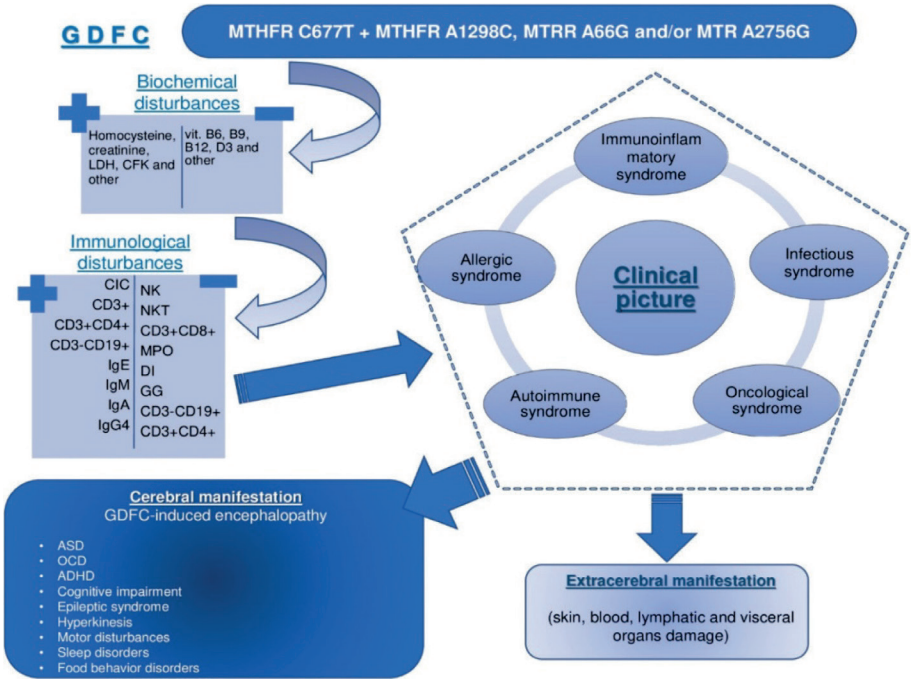

Figure 8. Integrated circuit of the pathogenesis of neuropsychiatric diseases in children in connection with the folate-centric concept, which demonstrates the links between genetic, biochemical, immunological and clinical manifestations.

describe (the so-called biomarker-guided interventions) (139). Although this approach is not holistic and systematized, but fragmented, mechanistic and empirical, biomarker-based diagnostics and therapy for the first time showed in practice certain successes in the treatment of children with previously non-curable neuropsychiatric diseases.

Liu et al in 2016 (140) demonstrated a wide range of possibilities for the practical application of biomarker-guided strategy in children with ASD on the instance of the use of sulfarophane. Subsequently Frye has developed a more progressive multidisciplinary personalized approach called Bas-VISTOR (collect Baseline data, search for Symptoms, measure Biomarkers, Select Treatment, Observe for Response), which is characterized by scientific validity, consistency, complexity, consistency and step-by-step stratification of approaches to assessing the patient's condition and prescribing corrective medications (6,141). This protocol concerns all forms of ASD in children in all their diversity, outlining only the general principles of disease diagnosis and clinical management of the patient.

In order to improve the 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, called GBINS (Genetic-Biochemical-Immunological-Neurological-Symptomatic). This approach shows the sequence of assessing the patient's condition and further prescribing corrective therapy according to the scientific evidence accumulated so far. In accordance with this approach, the individual pathological gene system is first studied, on which basis the individual volume of biochemical tests characterizing specific metabolic disorders induced by mutations/polymorphisms in the genome (biochemical status) is determined. The identification of an individual profile of biochemical disorders justifies 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 central nervous system damage (immunological status). The

obtained genetic, biochemical, immunological, microbiological and rheumatological results facilitate the assessment of clinical and neuroimaging data in the diagnosis of infection-induced autoimmune inflammatory encephalopathy (neurological status). The last stage is to go beyond the nervous system and a comprehensive assessment of the damage to the whole organism with an analysis of all the existing symptoms of the disease associated with a multisystem lesion of the child's body (symptomatic status).

Conclusion

No doubt, ASD is a complex multifactorial neurodevelopmental disorder in which many different genetic susceptibility factors possibly interact with epigenetic factors and early-environmental (in utero) factors to lead to a non-typical neurodevelopmental trajectory. This article focuses on the association of ASD with GDFC and other functionally related pathology, and analyzed data on the ways in which different disorders caused by the specified genetic factors affect the health of children with ASD. The results of genetic, biochemical, immunological, microbiological, immunobiochemical and neuroimmunological clinical studies allow revising the established scientific views on the nature of neuropsychiatric syndromes in children and indicate new potentially useful diagnostic biomarkers and points of application of 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 currently non-curable neuropsychiatric disorder, but will also contribute to stopping the large-scale threatening epidemic of neuropsychiatric syndromes in the modern pediatric population.

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Authors Contribution: Dmytro Maltsev is the research's author and creator.

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