

INVITED REVIEW

ADAPTIVE MATERNAL IMMUNE DEVIATIONS AS A GROUND FOR AUTISM SPECTRUM DISORDERS DEVELOPMENT IN CHILDREN

Alexander B. Poletaev<sup>1\*</sup>, Alina A. Poletaeva<sup>1</sup>, Alexander I. Pukhalenko<sup>1</sup>, Roza S. Zamaleeva<sup>2</sup>, Natalia A. Cherepanova<sup>3</sup>, Dmitry V. Frizin<sup>3</sup>

<sup>1</sup>PK Anokhin Institute of Normal Physiology, Russian Academy of Medical Sciences, The Medical Research Center "Immunculus", Moscow, Russia, <sup>2</sup>Kazan' Medical State Academy, Kazan, Tatarstan, Russia, <sup>3</sup>Volgsk' Central Hospital, Volgsk, Mary-El, Russia

АДАПТИВНЫЕ ИММУННЫЕ РЕАКЦИИ МАТЕРИ КАК ФАКТОР, ВЕДУЩИЙ К ФОРМИРОВАНИЮ РАССТРОЙСТВ АУТИСТИЧЕСКОГО СПЕКТРА У ЕЕ РЕБЕНКА

Александр Б. Полетаев<sup>1\*</sup>, Алина А. Полетаева<sup>1</sup>, Александр И. Пухаленко<sup>1</sup>, Роза С. Замалеева<sup>2</sup>, Наталия А. Черепанова<sup>3</sup>, Дмитрий В. Фризин<sup>3</sup>

<sup>1</sup>НИИ нормальной физиологии им. П.К.Анохина РАМН, Медицинский исследовательский центр "Иммункулус", Москва; <sup>2</sup>Казанская государственная медицинская академия, Казань, Татарстан, <sup>3</sup>Волжская центральная городская больница, Волжск, Мари-Эл, Россия

ABSTRACT

Autism is a vexed problem today. Overall, there is a high frequency of birth children (1:80 – 1:150) with late diagnosed autism spectrum disorders (ASD) and this trend is getting progressively stronger. The causes for the currently increased frequency of ASD and the pathogenesis of ASD are not fully understood yet. One of the most likely mechanisms inducing ASD may be a maternal immune imprinting. This phenomenon is based on transplacental translocation of maternal antibodies of IgG class and, as a consequence, on the epigenetic "tuning" of immune system of the fetus and child. This mechanism provides development of child's anti-infection resistance before meeting with microorganisms, but it can be also a cause of inborn pathology including the ASD appearance. The quantitative changes in maternal blood serum autoantibodies depend on a specific microbial population, or are induced by environmental chemical pollutants in association with some individual features of the maternal metabolism. These immune changes are adaptive in most cases for the maternal organism, but can be pathogenic for the fetus in some cases. We discuss in the present paper the possibilities to predict the risk from abnormal development of nervous system in fetus and early diagnosis of ASD in high-risk group of children.

**Keywords:** autism, diagnosis, ASD, CNS pathology, immune imprinting, autoantibodies, cytokines

Folia Medica 2014; 56(2): 73-80  
Copyright © 2014 Medical University, Plovdiv

РЕЗЮМЕ

Частота случаев рождения детей, страдающих расстройствами аутистического спектра (РАС) с каждым годом растет и сегодня составляет 1:80 – 1:150 в глобальном масштабе. Причины этого, как и "собственно" патогенез РАС, остаются не вполне понятными. Одним из наиболее вероятных механизмов, запускающих формирование РАС, во многих случаях, является феномен материнского иммунного импринтинга, основанный на трансплацентарном поступлении антител матери класса IgG к плоду и эпигенетической «настройке» иммунной системы будущего ребенка. Иммунный импринтинг обеспечивает формирование противoinфекционной резистентности у ребенка еще во внутриутробном периоде (до встречи с инфектами), но, в некоторых случаях, он может быть причиной ряда нарушений и, в частности, формирования РАС. Особенности репертуаров аутоантител (а-АТ) матери могут зависеть от превалирования у нее тех или иных бактериально-вирусных ассоциатов, а также от индивидуальных особенностей организма женщины. Соответствующие иммунные изменения как правило являются адаптивными для матери, однако, для будущего ребенка могут являться патогенными. Обсуждаются возможности прогнозирования риска развития плода и новорожденного с патологией нервной системы у женщин с аномалиями репертуаров а-АТ, а также ранней диагностики РАС у детей группы риска, начиная с первых месяцев жизни.

**Ключевые слова:** аутизм, диагностика, РАС, патология ЦНС, иммунный импринтинг, аутоантитела, цитокины

Folia Medica 2014; 56(2): 73-80

© 2014 Все права защищены. Медицинский университет, Пловдив

Article's history: Received: 7 March 2014; Received in a revised form: 2 April 2014; Accepted: 3 April 2014

\*Correspondence and reprint request to: A. Poletaev, PK Anokhin Institute of Normal Physiology, Russian Academy of Medical Sciences, The Medical Research Center "Immunculus" 30-A Okružhnoy Projezd, 151187, Moscow, Russia; E-mail: a-b-poletaev@yandex.ru

## AUTISM - GENERAL PROVISIONS

Forming a clear view on pathogenesis is necessary for the most effective prevention, diagnostics, and treatment of any disease. This statement is quite valid for autism cases or autism spectrum disorders (ASD). Nowadays, we do not have objective laboratory methods to diagnose ASD and usually autism diagnosis is based on behavioural deviations (impairments in communication and social interactions, stereotypic behaviour, deviations of sensory perception and emotional state, etc.).

Analysing in detail relevant publications that appeared in some highly rated medical journals (1971-2010), Rossignol and Frye<sup>1</sup> concluded that:

1. ASD are directly related to gene defects in only 6–15% of cases.
2. Different epigenetic factors are the reasons for 85-95% of ASD.
3. Immunity deviations, inflammation, toxic influences, oxidative stress or mitochondrial dysfunction probably play the most important role in the ASD development.
4. The most significant research defines immune abnormality and inflammation related deviations as the basis for ASD development.

The term autism spectrum disorders (ASD) is used to designate a heterogeneous group of disorders with common features but different pathogenesis and expressed behavioural disorders. A relatively small part of these disorders is evidently caused by aberrations of particular genes, but autism is predominantly a multifactor disease. These disorders may appear only if some epigenetic (environmental) factors influence them. It does not mean that most forms of ASD are totally independent from genetic peculiarities of the suffering individual. Genetic features may contribute to the risk of ASD and dozens or hundreds of genes associated with this disease will be evidently present<sup>2</sup>, however, this dependence will be comparable to genetically conditioned resistance/sensitivity to influenza. Different combinations of multiple genes may be a ground for multiple minor metabolic changes declining or elevating the general stability of the organism to the different environmental factors. According to genome-wide association studies (GWAS), some factors associated with an increased risk of ASD can be revealed<sup>3</sup> (as well as factors leading to an increased risk of catching a cold or suffering myocardial infarction), however such data would be of little predictive value for medical practice.

Most of ASD cases are associated with the ef-

fect of multiple environmental (epigenetic) factors, for example, heavy metal chronic action, pesticides (mercury, lead, polychlorinated biphenyls, toluene, etc.), immune deviations, inflammatory processes, acute infection diseases during pregnancy, chronic oxidative stresses, etc. A simple enumeration of different factors that induce ASD allows us to make some inferences.

Firstly, very different epigenetically conditioned ASD forms can be probably considered as a kind of equifinal pathophysiological phenomena. In other words, many different influences that touch different organs and tissues and affect different metabolic cycles can result in the same clinical consequences if the organism of a pregnant woman or the newborn is affected.

Secondly, ASD should be probably considered not as a neurological disorder, but as a form of pathology that affects a wide range of organs and systems: the digestive system (stomach, intestine, colon, pancreas), the endocrine system (thyroid, adrenals), and probably some other organs and systems that consistently reflect multisystemic disorders for ASD.

Thirdly, immune and inflammatory deviations, toxic environmental influences, chronic oxidative stresses, mitochondrial dysfunctions can be related not only to ASD but also to the development of many nervous system disorders, including schizophrenia, Alzheimer disease, bipolar disease, and several other disorders.<sup>1,4,5</sup> That is, none of noted factors can be defined as specific ASD-inducing factor. The question is: why the same influence leads to ASD development in some cases and to schizophrenia development - in other ones? Unlike other mental diseases, ASD can be diagnosed among small children only (emerges during intra-uterine development, but not in puberty period or in adults). It can be suggested that the vector of pathological development depends to a great extent on the ontogenetic period in which the inducing factors have been active. With respect to ASD such a period is the stage of primordial systems (nervous and other) differentiation and maturation.

## THE IMMUNE SYSTEM: AN INTERFACE BETWEEN AN ORGANISM AND ENVIRONMENT

The major function of the nervous system (as well as the immune system) is providing safety in the contacts between an organism and its environment.<sup>6</sup> Both system components are presented in organs and tissues, and evolutionary intended for

reception, integration, storing and retrieving of the incoming information and for forming an individual (non-inheritable) living experience providing the most adequate reaction to the repeating situation.<sup>6</sup> The nervous system is specialized in reception and reaction to physical stimuli (vision, hearing, tactile stimuli, and thermal stimuli). The specialization of the immune system is reception and reaction to chemical stimuli. Some authors suggest that the immune system appeared during evolution to receive and integrate chemical information unregistered by the nervous system.<sup>7,8</sup>

A multitude of external and internal environment chemical stimuli and pathogenic microbes can induce an immune system adaptive reaction that manifests by the changes in the levels of cytokines, chemokines, antibodies and autoantibodies. These immune changes manifest (at the organismal level) by inflammation, clearance enhancement, activation of regeneration, etc. Respective immunophysiologic changes in essence are adaptive and sanogenic. However, it can be transformed into pathogenic ones in some conditions.

Speaking about functionality, the immune system can be considered as an interface between the chemistry of the organism and the chemistry of the environment. Therefore, any chemically active substances entering into the system will inevitably induce some changes in the state of individual immune system, including production and secretion by lymphocytes, macrophages, and dendritic cells of many biologically active molecules. The latter in their turn will affect the state of the pregnant woman and fetus. Regarding ASD, the next question can be: are the effects of different toxins and infection agents related to pathogenesis of the disorder, primarily realized by immune deviations in a pregnant woman? Or induced immune deviations should be considered as an important but relatively small part of whole organism changes which leads to ASD development. The question is crucial, because if immune changes are the basic condition for development of autism, the preventive and corrective measures can be mostly directed to the state of the immune system. Otherwise, it will be principally impossible to manage prevention and correction of ASD without widely complex measures in addition to the immune correction ones. We suppose that available information does not permit to solve this question. We will consider some of immunopathological aspects of ASD below, because, in any case, immune deviations play an important role in the disorder development.

## CYTOKINES AS FACTORS RELATED TO ABNORMALITY OF FETOGENESIS

Cytokines, pro-inflammatory as well as contra-inflammatory (interleukins, interferons, chemokines, growth factors, etc.), are the most biologically active products expressed and secreted by cells of the immune system. It should be noted, that most of the immune-derived cytokines also possess a neurotropic activity and are involved in the regulation of the growth, maturation and functional differentiation of neurons and glial cells.<sup>6</sup> It was noted that  $\alpha$ -interferon can be an inducer of catatonia and depression in animal models, and C3 - a component of the complement, has an anorexogenic activity.<sup>9</sup> It was demonstrated that interleukin-6 had an anti-amnesic activity, which prevents binding of neuronal antagonistic ligands with m-cholinoreceptors.<sup>10</sup> A lot of data (fragmentary to some extent) is related to neurotropic, behavioural and psychotropic activity of different cytokines has been accumulated during the last 30 years. These phenomena became a base for the hypothesis about cytokines as "main conductors of the neuro-immune orchestra".<sup>9</sup> We accept an idea of cytokines participation in neuro-immune functional co-tuning, but suppose more complicate situation with the mechanisms of co-tuning, and have some doubts about the leading role exactly of cytokines in mutual coordination of the nervous and immune systems activity in each case.

## MATERNAL ANTIBODIES AND THE PHENOMENON OF EPIGENETIC IMMUNE IMPRINTING

The notable biological ability is an important characteristic of the cytokines (blood half-life of the most is just a few dozen minutes<sup>11</sup>). These molecules can be effectively used for regulation of different short-term physiological processes but hardly for regulating long-term ones. For example, such event as prolonged, high-ordered and high-protected transformation of the fetal nervous tube into anatomically and functionally matured nervous system of the newborn can be affected rather some long-acting (i.e. stable) and omnipresent regulatory molecules. From this point of view natural (physiological) maternal autoantibodies (auto-Abs) of IgG class could be most suitable candidates.

Many different auto-Abs (able to interact with any self-antigens) are synthesized in each person during his individual life-span.<sup>12,13</sup> Serum content auto-Abs of the each antigen specificity is nearly the same in all healthy adults, and changes in the auto-Abs production and content have been con-

sidered as a marker signs of pathology in defined organs and tissues, or may be induced by different chemicals and infection agents.<sup>12</sup> An averaged IgG molecules have a blood half-life of nearly 3 weeks and actively transferred to the fetus by means of a specialized mechanisms of active cross-placental transport (in contrast to auto-Abs of IgM, IgA, IgE, IgD classes that are not transported through placental barrier).<sup>14</sup> IgG molecules are the main instrument for realization maternal epigenetic immune imprinting.<sup>12</sup> The latter is probably related with cross binding the specific membrane antigen receptors of the fetal B-lymphocytes by maternal anti-idiotypic auto-Abs of the respective specificity. Such binding usually leads to the long-lasting specific inhibition or stimulation B-cells clones of the defined specificity and accordingly steady changes in the rate of production of the respective antibodies in a child.<sup>15,16</sup>

Maternal immune imprinting is impressing by the child's immune system of a peculiar features maternal immune state (takes place during pregnancy), but non paternal immune state. As a result, the child's immune state has acquired (for years sometimes) the main features of maternal immunity.<sup>12,16,17</sup> The biological meaning of the phenomenon is evident and is clearly illustrated by the next example. Yellow fever virus is endemic in tropical countries of Africa and America. Among native inhabitants, children were infected shortly after birth and this infection, in the presence of maternal antibodies, generally developed without symptoms, but induced lifelong immunity. As a consequence, the disease was almost exclusively observed when foreigners newly arrived in those countries. An especially striking example is the epidemics during the building of the Panama Canal when about 100000 foreign workers, but not natives, died of yellow fever.<sup>16</sup> This example indicates an imprinting meaning for *a priori* (before meeting with microbes) acquiring by the child of specific resistance against infection agents.

However, maternal imprinting may influence the child's health state not only positively. Negative influence may be also seen in cases when mothers have steady changes in their autoantibodies level during pregnancy.

#### PHYSIOLOGIC (SANOGENIC) MATERNAL AUTOIMMUNITY AND PATHOLOGY OF THE FETUS

In the past, molecules of auto-Abs and autoimmunity in general have been associated exclusively with the state of pathology (autoimmune diseases).

However, nowadays it is widely accepted, that auto-Abs are permanently and obligatorily produced in all healthy individuals. No longer is the presence of auto-Abs automatically associated with pathological processes; we now know that stable anomalies in their production and serum concentration occur not in relation to failures in immunoregulatory mechanisms. Multitudes of natural auto-Abs of IgG and IgM classes have been permanently synthesized, secreted and presented in the blood serum of all healthy persons. These data were clearly and repeatedly demonstrated in several laboratories.<sup>12,18</sup>

On the one hand, serum concentrations of auto-Abs with the same specificity in healthy individuals (having no tissue or organ damage to express corresponding antigens) is roughly equal; on the other hand, several diseases are accompanied by notable deviations in serum content of particular auto-Abs (against specific antigens of certain cells). This secondary rise in ("danger signal"-induced) production and secretion of auto-Abs against antigens of damaged cells should not be considered as a side effect but rather a reflection of one of the major roles of the ADS, namely its ability to execute the function of autoclearance.<sup>12,13,18</sup> Every day, in various compartments of an organism, clearance of hundreds of billions of apoptotically dying cells (efferocytosis) is required for normal tissue homeostasis and prevention of inflammation.<sup>13</sup> Obviously, the homeostatic importance of local activation of autoclearance mechanisms increases dramatically in case of tissue damage (of any etiology). This primary tissue damage then induces an evolutionarily fixed phenomenon of a secondary increase in the production of auto-Abs against tissue-specific antigens (and can be reflected by "mirror" of auto-Abs).

The idea of auto-Abs participation in the clearance was hypothesized by Pierre Grabar<sup>19</sup> and was developed by Kovalioff IE in his conception of immunochemical homeostasis.<sup>20</sup> In accordance with the basic statements of the immunochemical homeostasis concept, rates of natural auto-Ab production are regulated by quantity/availability of respective antigens via a feedback principle. The rates of production, secretion and/or release of any cytoplasmic, membranous, or nuclear antigen into the intercellular space are nearly equivalent in all healthy individuals (or differ insufficiently to effect real differences); therefore, serum levels of respective auto-Abs should also demonstrate only slight individual variability. This picture changes dramatically in nearly all cases of pathology. Many

disorders, especially those of a chronic nature, are directly associated with either cell necrosis or apoptosis in the involved organ or deviations in the production and/or excretion of certain antigens. It is typical for some isoforms of insulin receptors to be elevated in skeletal muscle fibers at the pre-disease and early stages of diabetes mellitus (probably as compensation for deteriorating receptor functionality). Accordingly, many patients with pre-clinical diabetes mellitus demonstrate abnormally increased serum levels of auto-Abs against insulin receptors. In most cases, this increase did not relate directly to the pathogenesis of diabetes but instead reflects abnormally increased expression of receptors in accordance with Kovalioff's rule: elevated quantity of antigen leading to rise of production of corresponding auto-Ab. Malignancy-associated increases in auto-Abs against the phosphoprotein p53, a regulator of apoptosis, may be attributable to the same principle. It is known that p53 alterations (missense mutations) appear to be present in 40 to 45% of patients with different forms of malignant diseases. Frequently, these alterations are accompanied by compensatory elevations in p53 expression and, secondarily, by a rise in corresponding auto-Abs. Lubin and co-authors especially noted that extensive accumulation of p53 is the cause of "self-immunization", i.e. appearance of excess anti-p53 Abs in the patient's serum.<sup>13</sup>

In accordance with the general logic of living systems, quantitative changes in physiologic parameters are usually aimed at correcting or compensating for an abnormal situation in the body. For example, a tremendous physical effort is accompanied by elevation of blood pressure, tachycardia, rise of blood glucose level, and other abnormalities that are all untypical of the resting state. Such reactions provide additional resources for "fight or flight" reaction and are physiologically and evolutionarily justified. Principally, the same physiological (sanogenic) autoimmune reactions may be observed, for example, in patients suffering from ischemic stroke. It was shown that prominent temporary elevation of "neurotropic" IgG auto-Abs in the serum, if observed soon after stroke and for a few weeks thereafter, is a favorable prognostic sign. Conversely, the lack of a notable stroke-induced secondary autoimmune reaction — that is, preservation of normal or low levels of "neurotropic" auto-Abs during the few days following a stroke — is a bad prognostic sign that is typical of non-survivors and of survivors suffering prominent motor and/or cognitive deterioration.

As one may suppose, stroke-induced sharp and relatively prolonged (up to 1-2 months) elevation of auto-Abs against proteins of the injured brain cells (GFAP, S100, MBP, and others) is a deeply rational autoimmune sanogenic phenomenon aimed at increasing clearance of damaged neural structures and functional restoration.<sup>21</sup> Besides auto-Abs may revealed trophic activity and stimulate the processes of regeneration.<sup>22</sup>

From a practical point of view, it is crucial to distinguish primary (pathogenic) and secondary (physiological) autoimmune processes. Primary autoimmune reactions (for example, virus-induced, or heavy metals induced, etc.) may be observed relatively rare and are usually pathogenic in essence; these events may even cause systemic or organ-specific autoimmune diseases. In contrast, secondary and transitory (physiological) activation of natural autoimmunity, following the primary (injury-associated) events in organs, often seems to be positive in essence by aiming for increased clearance of antigens in the involved organ and recovery of the disturbed physiological functions.

Maternal auto-Abs with any specificity, sanogenic in relation to own organism, may become a pathogenic for fetus if transferred through placenta in excess: a) because direct cytotoxic effects on a target cells<sup>23</sup>, b) because abnormal tuning of the immune system of future child by the mechanism of maternal immune imprinting. As examples there can be considered the cases of a thyroid dysfunction in newborns and children from mothers with thyroid gland<sup>24</sup>; newborn' lupus may be transferred from mother with SLE to her child, and the typical symptoms may arise in child at 4-6 months only, that is after complete elimination of maternal auto-Abs.<sup>25</sup> Elevated synthesis of anti-insulin auto-Abs (prognostic sign of diabetes type I) is typical for some children from diabetic mothers.<sup>26</sup> Maternal immune imprinting may be ground for not infrequent cases of pathology related to same organs in the mother and child (kidney, heart, endocrine organs).<sup>27</sup> In any case far from optimal intrauterine development, conditioned by the changes from different maternal auto-Abs production, will lead not obligatorily to miscarriages and stillbirth, but nearly always results in some negative changes in child health state.<sup>28</sup>

#### **EXCESS OF THE MATERNAL "NEUROTROPIC" AUTO-ABS AS REASON FOR PATHOLOGY OF THE NERVOUS SYSTEM IN THE FETUS AND CHILD**

Many infective agents may induce abnormal activa-

tion of T- and B-lymphocytes, that is elevating of the production of different cytokines and auto-Abs. Both, in their turn, can influence negatively fetal development. In accordance with Patterson, viral infection of pregnant woman does affect a fetal nervous tube development indirectly, by means of deviated cytokines production.<sup>29</sup> We support an idea of immune-mediated effects of viral agents upon fetal development, but we suppose, besides cytokines, auto-Abs deviations as a factors influenced on neural tube development, should be also taken in mind. Many representatives of herpesviridae (Herpes simplex, Cytomegalovirus, Epstein-Bar virus etc.) play a role of costimulators-inductors and activate different clones of the CD4+ T lymphocytes. The latter, in their turn, do induce the polyclonal activation of B-cells and rise of production of the different auto-Abs.<sup>30,31</sup>

Furthermore, for diminishing of antimicrobial immune activity, many infection agents use a "camouflage" tactic (molecular mimicry<sup>12</sup>). For these purposes an antigenic structures, similar to some antigens of the host-organism, are expressed on the surface. Nonetheless, the immune system reacts to microbe antigens, though not so actively. For example, different forms of human papilloma viruses (HPV) express viral proteins partly similar to the human S100 proteins. It is a reason for excessive production of auto-Abs against S100 by most persons with HPV infection.<sup>12</sup> But excess of auto-Abs against S100 may lead to deviations of the general morphogenesis and tissue differentiation in embryo. Moreover, S100 proteins participate in morphology and functional differentiation of neuroblasts of the fetal neural tube. Thus, excess of auto-Abs against S100 may cause deviation of the nervous system formation. Therefore the HPV infection in pregnant women may lead to frequent miscarriages, stillbirths or malformation of the fetus' nervous system. In any case, newborns and children from mothers with HPV-induced excess of auto-Abs against S100 characterized sharply elevated (by 10-12 times) frequency of different anomalies in the nervous system and mental/neurology problems.<sup>12</sup>

Specificity of changes in the repertoires of maternal serum auto-Abs may depend on prevailing bacterial and virus associates, as well as on the maternal genetic background and expression of defined MHC alleles. The character of the fetal reaction/changes inducing by maternal auto-Abs excessively entering to fetus will become formed depending on the antigenic specificity of auto-Abs transferred, and the

peculiar stage of fetogenesis influenced by auto-Abs.

#### MATERNAL AUTO-ABS AND ASD

If some ideas proposed here will be additionally confirmed in experiments and clinical observations this may give a serious impetus for elaboration of medical and organizational measures aimed at prominent decreasing frequency of ASD and other developmental (intrauterine formed) pathology. Because high prevalence of ASD (one case per 80 to 150 newborns<sup>32,33</sup>) wide screening of women prepared to pregnancy seems to be justified, especially if it includes women in the risk group. Besides screening the newborns of mothers with complicated disease history, mothers with signs of HPV infection, or mothers suffering of infectious disease during pregnancy, or those that have had any kind of toxic exposure, etc., will be quite justified also. Testing for the marker auto-Abs in the mother's blood serum samples as well as in the child's could be probably quite informative, simple, available and inexpensive.

A very preliminary data about some auto-Abs that probably can be useful for prognosis are presented below. The presented data were obtained by using ELI-Test methods<sup>34</sup> between 2012 and 2013 and based on analysis of profiles of the specific serum' immune reactivity. It should be specially noted, in accordance with our experience as well as conclusion of professor PL Merony and colleagues<sup>34,35</sup> that profiles of immune reactivity, reflecting on changes in partial content of different auto-Abs are a more sensitive and informative characteristic in comparison with the quantitative evaluation of any single auto-Abs.

Serum samples from children with diagnosed ASD (n = 152; age ranging from 1.5 to 4.5 years) were investigated. These results were compared with serum samples of clinically healthy children (n = 124; age 2-5 years)

The most typical features revealed in 40% of ASD cases or more and unrevealed or rarely revealed (no more than 2-3%) in healthy children were:

1. Anomalous peaks of the serum immune reactivity conditioned by auto-Abs of IgG class and directed to next antigens of the nervous tissue:
  - Glial fibrillar acidic protein; specific for astrocytes)
  - S100-b (Ca<sup>2+</sup>-binding protein of the nervous tissue; similar antigens are expressed by different viruses of papilloma)
  - Myelin basic protein
  - Dopamine receptors type D2

- Dopamine receptors type D3
  - Serotonine receptors type H-2A
  - N-Acetylcholinoreceptors
  - PPR1B (or DARPP-32; Dopamine- and cAMP-regulated neuronal phosphoprotein).
2. Anomalous peaks of the serum immune reactivity conditioned by auto-Abs of IgG class, and directed to next antigens of digestive system organs:
- Stomach wall antigen Gas
  - Stomach wall antigen Gam
  - Intestine wall antigen Itm-07
  - Colon wall antigen SCM-01
  - Insulin
3. Anomalous peaks of the serum immune reactivity conditioned by auto-Abs of IgG class, and directed to antigens of other organs:
- Spermal-prostatic antigen SPR-06 (elevated immune reactivity to SPR-06 may be induced by some intracellular bacteria by mechanisms of molecular mimicry)

The presented data should be considered as preliminary. The detailed and widening data will be presented in a following publication.

## CONCLUSIONS

The term “autism” (ASD) is used for the designation of similar neurologic symptoms and affected organs heterogenic group of disorders of gastro-intestinal tract and some others in addition to the nervous system.

A small part of ASD is based on genetic aberrations, and may be probably attended to monogenic disorders.

The greater part of ASD cases characterized the weak genetic association only, and can be attended to the peculiar form of intrauterine malformation, induced by different infectious agents and chemical influences.

Immune changes in the pregnant woman, including deviated production of many autoantibodies and proinflammatory cytokines, mediates pathogenic effects of the substantial part of infectious and chemical factors on the development of fetus.

Some serum IgG class auto-Abs can be generally used as perspective bio-markers for ASD prediction.

Mass-scale women screening before their planned pregnancy, especially ones belonging to the risk group, and their correction in necessity before pregnancy, may become an effective measure for significant decreasing of the frequency of ASD cases.

Revealing serum profiles characteristic of the immune reactivity, typical for children in ASD risk group during first months of their life and early

conducting of corrective measures could be most effective for diminishing of the disease manifestation.

## ACKNOWLEDGEMENT

This work was supported by the non-profit Foundation “VYKHOD”, Moscow, Russia.

Authors express their sincere gratitude to Dr. Elena Chachanidze (Non-profit Foundation “VYKHOD”, St-Petersburg Branch) for the invaluable help in the manuscript preparation.

## REFERENCES

1. Rossignol DA, Frye RE. A review of research trends in physiological abnormalities in autism spectrum disorders: immune dysregulation, inflammation, oxidative stress, mitochondrial dysfunction and environmental toxicant exposures. *Mol Psychiatry* 2012;17:389-401.
2. Popov NT, Madjirova NP, Minkov IN, Vachev TI. Micro RNA HSA-486-3P gene expression profiling in the whole blood of patients with autism. *Biotechnology & Biotechnological Equipment* 2012;26(6):3385-8.
3. Anney R, Klei L, Pinto D, et al. Individual common variants exert weak effects on the risk for autism spectrum disorders. *Hum Mol Genet* 2012;21:4781-92.
4. Khoroshko VK. The living organism reaction to administration of the nervous tissue [dissertation]. Moscow: Moscow Univ. Publishing; 1912.
5. Semenov SV, Popova NN. Nervous and mental diseases from point of view of the brain's immunopathology. Moscow: Meditsina Publishers; 1969.
6. Poletaev AB, Morozov SG, Kovaliov IE. Regulatory metasystem (the neuro-immuno-endocrine system for regulation of homeostasis). Moscow: Medicina; 2002.
7. Camara EG, Danao TC. The brain and the immune system: A psychosomatic network. *Psychosomatics* 1989;30:140-6.
8. Ferenchik M, Stvrtinov V. Is the immune system our sixth sense? Relation between the immune and neuroendocrine systems. *Bratisl Lek Listy* 1997;98:187-98.
9. Morley JE, Kay NE, Solomon GF, Plotnikoff NP. Neuropeptides: conductors of the immune orchestra. *Life Sci* 1987;41:527-44.
10. Bianchi M, Ferrario P, Clavenna A, Panerai AE. Interleukin-6 affects scopolamine-induced amnesia, but not brain amino acid levels in mice. *Neuro Report* 1997;8:1775-8.
11. Poletaev AB. Immunophysiology and immunopathology. Moscow: MIA; 2008.
12. Poletaev AB. Physiological Immunology. Moscow: MIKLOSH Publishers; 2010.

13. Poletaev A. The main principles of adaptive immune system function: self-recognition, self-interaction, and self-maintenance. In: Poletaev AB, editor. *Physiologic Autoimmunity and Preventive Medicine*. Sharjah, Oak Park, Bussum: Bentham Science Publishers; 2013:3-20.
14. Landor M. Maternal-fetal transfer of immunoglobulins. *Ann Allergy Asthma Immunol* 1995;74:279-83.
15. Basten A. Basis and mechanism of self-tolerance. In: Rose NR, Mackay IR, editors. *The autoimmune diseases*. San Diego, London: Acad Press, 1998:9-27.
16. Lemke H, Radu IT, Ahmad T, Lange H. Benefits and burden of the maternally-mediated immunological imprinting In: Poletaev AB, Dabilov AN, editors. *Immunophysiology: natural autoimmunity in physiology and pathology*. Proceedings of 2nd Moscow International Conference, Moscow; 2008:58-64.
17. Lemke H, Lange H. Is there a maternally induced immunological imprinting a la Konrad Lorenz? *Scand J Immunol* 1999;50:348-54.
18. Lacroix-Desmazes S, Kaveri S, Mouthon L, Ayoub A, Malanchere E, Coutinho A, Kazatchkine MD. Self-reactive antibodies (natural autoantibodies) in healthy individuals. *J Immunol Meth* 1998; 216:117-37.
19. Grabar P. About Autoantibodies. In: Ado AD, editor. *Problems of reactivity in pathology*. Moscow: Meditsina; 1968:35-52.
20. Kovaliov IE, Plevaya OY. *Biochemical grounds of immunity against low-molecular chemical compounds*. Moscow: Nauka Publishers; 1985.
21. Poletaev AB, Abrosimova AA, Sokolov MA, et al. Dialectics and implications of natural neurotropic autoantibodies in neurological disease and rehabilitation. *Clin And Developmental Immunol* 2004;11:151-6.
22. Bieber AJ, Warrington A, Pease LR, Rodriguez M. Humoral autoimmunity as a mediator of CNS repair. *Trends Neurosci* 2001;24(11 Suppl):S39-44.
23. Shoenfeld Y, Carp HJ, Molina V, et al. Autoantibodies and prediction of reproductive failure. *Am J Reprod Immunol* 2006;56:337-44.
24. McKenzie JM, Zakarija M. Fetal and neonatal hypothyroidism and hypothyroidism due to maternal TSH-receptor antibodies. *Thyroid* 1992;2:155-9.
25. Lim M-S, Liu Z, Drolet BA, Diaz LA. Cutaneous autoimmune diseases. In: Rose NR, Mackay IR, editors. *The autoimmune diseases*. San Diego, London: Acad Press, 1998:623-36.
26. Budykina TS. Autoantibodies against insulin, insulin receptors and NGF in pathogenesis of diabetic fetopathy [dissertation]. Moscow: University of defence, 1998.
27. Khlystova ZS. *Ontogenetic formation of the immune system in humans*. Moscow: Medicina Publishers; 1987.
28. Kluchnikov SO, Poletaev AB, Budykina TS, Generalova GA. New immunobiotechnology approaches in perinatology and pediatrics. In: Demin VF, Kluchnikov SO, eds. *Lectures in pediatrics*. Moscow: RGMU Publishers;2001:243-67.
29. Patterson PH. Maternal infection: window on neuroimmune interactions in fetal brain development and mental illness. *Current Opinion in Neurobiol* 2002;15:115-18.
30. Pistola V. Production of cytokines by human B-cells in health and disease. *Immunol Today* 1997; 18:343-9.
31. Wu Y, Liu Y. Viral induction of co-stimulatory activity on antigen-presenting cells bypasses the need for CD4+ T-cell responses. *Current Biol* 1994;4:499-505.
32. Ghosh A, Michalon A, Lindemann L, et al. Drug discovery for autism spectrum disorder: challenges and opportunities. *Nat Rev Drug Discov* 2013;12:777-90.
33. Weintraub K. The prevalence puzzle: autism counts. *Nature* 2011;479:22-4.
34. Meroni PL, De Angelis V, Tedesco F. Future trends. In: Shoenfeld Y, Gershwin ME, Meroni PL, editors. *Autoantibodies*. Elsevier, B.V. 2007:823-6.
35. Poletaev A. Autoantibodies: serum content or profiles? In: Poletaev AB, editor. *Physiologic autoimmunity and preventive medicine*. Sharjah, Oak Park, Bussum: Bentham Science Publishers; 2013:199-207.