AUTOIMMUNE CONCEPT OF SCHIZOPHRENIA: HISTORICAL ROOTS AND CURRENT FACETS

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Abstract: The review analyzes a possible role of autoimmune processes in the pathogenesis of schizophrenia and evolution of concepts on this issue from its origin to present. Risks of autoimmune processes causing schizophrenia are associated with several factors: an impaired functioning of dopaminergic and glutamatergic systems in the brain, kynurenine pathway disorder with overproduction of quinolinic, anthranilic and kynurenic acids (possibly altering both neurons and T-regulators), increased intestinal permeability, as well as food antigens’ effects, stress and infections with various pathogens at different stages of ontogenesis. An increase in the levels of proinflammatory cytokines and chemokines as well as a decrease in the levels of anti-inflammatory ones also may contribute to schizophrenia risks. Schizophrenia often occurs in those patients having various autoimmune diseases and their first-degree relatives. Cases of schizophrenia resulted from autoimmune pathogenesis (including autoimmune encephalitis caused by autoantibodies against various neuronal antigens) are characterized by quite severe cognitive and psychotic symptoms and less favorable prognosis. This severe course may result from the chronic immune damage of the neuronal receptors such as NMDA, GABA and others and depend on hyperprolactinemia, induced by antipsychotics, but aggravating autoimmune processes [with 2 tables, 4 figures, bibliography: 99 references].

Keywords: antineuronal autoantibodies, autoimmune diseases, autoimmune encephalitis, food antigens, kynurenine pathway, microbiota, prolactin, cytokines, schizophrenia, stress.

1. Introduction

The immune and nervous systems are strongly interrelated and perform both sensory and analytical functions. Moreover, the immune sensory function provides a particular stereochemical sense of antigenicity. The immune system takes part in unconscious analytical activities to maintain metabolic individuality [1, 2]. The phenomena of memory, synaptic formation and plasticity exist in both aforementioned systems and are based on the interactions of similar or identical molecules [3, 4].

In the early 1980s psychotic-like behavioral changes were demonstrated in experimental rats receiving intracysternal injections of autoantibodies to the cerebral antigens, particularly protein S100B [5]. Later, J. Knight and H. H. Fudenberg, working independently, have put forward an autoimmune hypothesis of schizophrenia. The hypothesis presumes that autoantibodies may penetrate the brain or be formed intrathecally in the intracerebral immune system compartment. The autoantibodies may disrupt neuronal networks functioning and alter synaptic transmission in the limbic system or in the septal region of the brain, leading to psychiatric disorders [6 - 8]. Hyperactivity of the dopaminergic system in various regions of the brain is involved in the pathogenesis of schizophrenia. However, there is no mere increase of the dopamine level despite the hyperactive dopaminergic system. J. Knight presumed the existence of stimulating (agonistic) autoantibodies towards dopamine receptor (by analogy to pathogenesis of Graves’ disease, with its
stimulating anti-TSH receptor immunoglobulins, earlier discovered by Knight’s teacher D. D. Adams). Such anti-receptor psychopathogenic autoantibodies could be triggered by the cross-reactivity or via anti-idiotypic mechanisms during the immune system response to viruses or other pathogens capable of binding neuronal receptor structures [9]. This hypothesis correlated with the epidemiological data on the relationship between the increase in the incidence of psychoses after the outbreaks of neurotropic viral infections observed at the beginning of the 20th century [10].

At the same time, H. Fudenberg came up with a similar assumption based on the general neuroimmunological considerations indicating the presence of opiate μ-receptors, dopamine receptors, and receptors for other neurotransmitters on the lymphocytes. Later, he suggested that there should be a neuro-analogue of the suppressor lymphocytes within the central nervous system (CNS), whose function, if failed, may lead to schizophrenia [11].

At present, the question of the immunosuppressing therapy efficacy in schizophrenia is of great importance (mainly regarding use of synthetic glucocorticoids in combination with azathioprine or 6-mercaptopurine, etc.), but the findings in this field are controversial [11, 12].

2. Schizophrenia’s mosaic: infections, immunity and genes

“Everything is autoimmune until proven otherwise” [13]. Hence, autoimmune aggression against the schizophrenic brain may depend on autoreactive T-lymphocytes and the products of their interaction with the cells of macrophagial lineage. Interleukin-2 and other cytokines were regarded in this aspect [14]. However, H. Fudenberg’s hypothesis was not accepted by the US psychiatric community, and practical attempts of this internist to cure autism with immunosuppressants cost him his medical license. As for another adept of autoimmune origin for schizophrenia, J. Knight – being an ecobiologist, he never tried to promote his idea into clinics [15]. The research of autoimmune links of schizophrenia pathogenesis has continued down to the present, although apart from the psychiatric clinical practice [16, 17]. The Fudenberg’s prediction that metabolic mechanisms of T-regulators’ function have something in common with neurotransmitter metabolism in the brain has been confirmed. In particular, T-regulatory cells for providing their suppressor function operate with enzyme indoleamine-2, 3-dioxygenase, and shift the metabolism of tryptophan and kynurenic acid to the lower production of the latter substance. But, the hyperproduction of kynurenic and anthranilic acids may be involved in pathogenesis of schizophrenia and other “classic” autoimmune diseases (such as rheumatoid arthritis and the type I diabetes mellitus) [18]. In addition, viral and bacterial infections may play an important role as triggers of the autoimmune process, although, their effect is vicious only in individuals having genetic predisposition [19]. So, “Everything is infectious until proven otherwise”[20]. Remarkably, schizophrenia is also associated with the exposure to infections in the prenatal period (rubella, influenza, Herpesviridae, poliovirus) as well as in later life (Coxsackie viruses, Toxoplasma gondii, Borrelia burgdorferi, retroviruses) [19, 20].

In addition to the direct pathogenic effect of an infectious agent on the fetal brain organogenesis, the pathological immune response of maternal organism may also increase the risk of endogenous cerebral diseases (for example, via an increase in the concentration of IL-8 in the mother’s blood during the second trimester of pregnancy). Furthermore, CNS infections in early childhood may lead to a five-fold risk of psychosis manifestation in adult life [21, 22]. Quite often the cases of pathologic anti-brain autoimmunity are related to chronic infection. The correlation was described between the level of IgG to Toxoplasma gondii and IgG to the food antigens in patients with schizophrenia infected with this parasite. T. gondii possibly increases intestinal permeability, but beyond that it plays the role of a risk factor for the development of schizophrenia [23]. Moreover, there was observed correlation between toxoplasmosis, intestinal inflammation, allergy towards food antigens, and, remarkably, an elevated serum concentration of anti-NMDA autoantibodies. Also, toxoplasmosis was accompanied by an increase in the concentration of the complement system factors, and increased titers of autoantibodies against gluten and casein [24]. Kannan et al. developing schizophrenia mice model have found that T. gondii infection in combination with intestinal and blood-brain barriers disturbances may cause an increase in autoantibodies against...
NMDA receptors, which results in cognitive impairment, especially as regards to memory. Besides, the severity of cognitive impairment in mice correlated with the serum concentration of anti-NMDA antibodies [25].

The genes, encoding the proteins responsible for the functioning of the adaptive immunity (CD19 and CD20 of B-lymphocytes) and genes linked to histocompatibility complex (located on chromosome 6) are also involved in pathogenesis of psychoses. Recent genetic studies have described 108 loci associated with the development of schizophrenia, including genes expressed both in cerebral and immune cells. Some of the genes associated with schizophrenia may also take an essential part in the life cycle of the above mentioned pathogens within the body [19]. Besides, autoantibodies against NMDA and GABA receptors can also contribute into pathogenesis of schizophrenia, including the cases of autoimmune limbic encephalitis [17, 18].

Patients with schizophrenia display the signs of the immune system activation. The neurotransmitters, such as dopamine, serotonin, acetylcholine, as well as ligands of NMDA receptors - all are involved in pathogenesis of schizophrenia. But the aforementioned ligands also have receptors on lymphoid cells and may alter many of their activities. Such bioregulators as neuregulin-1 (NRG1), dopamine, glutamate, gamma-aminobutyric acid, serotonin, and synapsin – all are the targets of some influences caused by infectious agents [26]. Moreover, in an experimental model, it was shown that the offspring of mice subjected to infection-caused immune activation had a phenotype associated with schizophrenic process [22].

A plenty of pathogens, like: Hepatitis C virus, Cytomegalovirus, Epstein-Barr virus, Adenovirus, Toxoplasma gondii, Borrelia burgdorferi – may affect the risk of schizophrenia [27]. A remarkable fact is that rubella and influenza viruses hit the complex involved in the myelination process as well as interfere into oligodendrocytes’ life cycle. Embedding viral DNA into the human genome was previously considered to be the prerogative of retroviruses only. However, the DNA insertion into mammalian genome is characteristic of a large spectrum of RNA and DNA-containing viruses. For example, the Herpes group virus type 6 (roseolavirus), known for its association with several autoimmune diseases, can be transmitted from parent to child through chromosomal integration. Thus, autoimmunity involves some antigens in the pathogenesis of schizophrenia and may result from homology of pathogen’s and host’s proteins, with cross-specificity of their peptides [16, 26].

### 3. Schizophrenia and other immune-mediated diseases

It was observed, that patients with schizophrenia and their close relatives are susceptible to "classic" autoimmune diseases, especially those characterized by the impaired metabolism of indole derivatives, like type 1 diabetes mellitus and celiac disease [28].

However, in rheumatoid arthritis, schizophrenia is less common than in general population [29]. A strong interrelation between the schizophrenic process and the development of bullous pemphigoid has been revealed [30]. There is an evidence that anaphylactic diseases (commonly considered to have mechanisms alternative to autoimmunity), such as bronchial asthma or atopic dermatitis (if diagnosed in childhood) also increase the risk of developing psychosis in adolescence and probability of schizophrenia in adulthood [16]. Susceptibility to autoimmune diseases is increased both in patients with schizophrenia and their healthy close relatives. There is common linkage of schizophrenia and autoimmunopathies with HLA DRB1*03 allele [31]. Schizophrenia is also associated with the presence of antibodies against a number of food proteins, such as gliadin, gluten and casein in blood sera [26] (Fig. 1). Antibodies towards gliadin peptides in first-episode schizophrenia patients are more common than in healthy donors [32]. Hashimoto’s thyroiditis also has comorbidity with schizophrenia. In a recent study about 7% of patients with schizophrenia were seropositive for antibodies against thyroid peroxidase (TPO-Abs) and thyroglobulin (Tg-Abs) [33].
4. Cytokines in schizophrenia

There are few evidences that schizophrenia is associated with microglial activation in some areas of the cerebral white matter. Microglia, when activated, may release pro-inflammatory cytokines, such as IL-6, IL-1β, IFN-γ, or chemokines, such as CCL-11 (eotaxin -1). In turn, pro-inflammatory cytokines, such as IL-1β, can affect the astrocytes activation. Astrocytes are able to produce more proinflammatory cytokines, such as IL-1β, CCL5 and TNF-α, and also affect the expression of glial fibrillary acid protein (GFAP) [34].

An ultrastructural analysis of brain tissue in patients with schizophrenia showed the presence of activated microglia in the proximity to the alteration zones (those with demyelinated and dismyelinated axons) as well as swelling and ballooning degeneration of astrocytes. In addition, patients with schizophrenia had an increase in the neuronal density of the white matter of the orbito-frontal region associated with an elevation of serum level of pro-inflammatory cytokines. Also, in cingulate gyrus and corpus callosum of schizophrenic patients an increase in astroglial density can be detected. Thus, neuroinflammation in schizophrenia, including its first episode may be one of the pathogenetic drivers [35]. Bloomfield et al., using brain positron emission tomography, confirmed the signs of neuroinflammation in patients with schizophrenia [36]. The cytokines produced by microglia act in paracrine and juxtacrine mode, hence via their neuronal receptors they may affect the balance of neurotransmitter production and synaptic plasticity, thus causing affective, cognitive and behavioral impairments [16]. Proinflammatory cytokines in hypothalamus enhance free-radical cell damage by increasing the concentration of nitric oxide and activating the hypothalamic-pituitary axis, which results in increase of blood cortisol level. It is also noteworthy that non-treated patients with schizophrenia may have an increased expression of D3-dopamine receptor and IFN-γ by their lymphocytes [16, 27].

Exacerbation of psychotic symptoms in schizophrenia is characterized by an increase in concentrations of few pro-inflammatory cytokines: IFN-γ, IL-1RA, IL-1β, IL-6, IL-8, IL-12, sIL-2R, TGF-β and TNF-α, as well as a significant decrease in the production of anti-inflammatory ones, like...
IL-4 and IL-10. The level of these bioregulators tends to normalize due to antipsychotic pharmacotherapy [37] (Fig. 2). Eftekharian et al. found significant increase in serum IL-4 level in schizophrenic patients during remission induced by dopamine antagonists [38].

There is also an assumption that serum IL-6 level increase in early childhood doubles the risk of developing the first episode of schizophrenia by the age of 18 [16, 27]. In a recent longitudinal study, adolescents with an increase of IL-6 and C-reactive protein levels had a higher risk of psychotic symptoms and schizophrenia development [39]. Furthermore, the patients resistant to antipsychotic therapy still had an increased content of proinflammatory markers for 3 months after treatment [40] (Fig. 2).

Patients with chronic schizophrenia (out of exacerbation) had increased levels of IL-6, IL-8, TNF-α, sIL-2R, IL-1β and decreased concentrations of IFN-γ and IL-2 compared to healthy controls [38, 41]. An increase in the mRNA of IL-6 (by 379%) and IFNβ level (by 29%) as well as an increase in mRNA of NFkB (by 86%) was registered in schizophrenia. Furthermore, a significant increase in the content of interferon-induced transmembrane protein (IFITM) mRNA in the prefrontal cortex (+304%) was found in mice model of schizophrenia [42]. An increased level of IL-6 mRNA, TNF-α, IL-1R1, TNFR1, and TNFR2 was reported in lymphocytes of patients with schizophrenia compared to healthy controls [43].

In schizophrenia, a decrease of BDNF levels in parallels with increase in the content of pro-inflammatary cytokines was reported. Patients with schizophrenia also had a significant decrease of TNF-α, and an increase in the content of IL-2, IL-6, and IL-8. In addition, the level of BDNF correlated with IL-2 and IL-8 concentrations. A decrease in the BDNF and TNF-α levels interrelated with the severity of cognitive impairment (according to the PANSS scale). It has also been suggested that TNF-α can interact with BDNF, thereby causing cognitive impairment [44]. In the meta-analysis, a severe cognitive impairment in schizophrenia was associated with an increased level of C-reactive protein, as well as with a decrease of the TNF-α level [45].

Of course, it is necessary to emphasize, that the cytokines are predominantly the bioregulators of zonal and local paracrine action, therefore all data about the shifts of their systemic blood concentrations in schizophrenia should be interpreted with a portion of healthy skepticism. Most probably, the range of their concentrations required for hormone-like systemic effects is not achieved in many of such studies.
It is not surprising, that the whole massive of data concerning the dynamics of cytokine blood levels in schizophrenia is very contradictory and far from any consistency. For example, Lee et al. found significant increase in levels of few pro-inflammatory cytokines in schizophrenia, but Simsek et al. denied any differences in serum concentrations of IL-2, IL-4, IL-6, IL-10, IL-17A, TNF-α, and IFNγ between samples of the sick and healthy persons [46, 47]. Local topical dynamics of the brain cytokine expression probably could be more informative, although such data in humans are still very scarce.

5. Chemokines in schizophrenia

Chemokines play an important part in targeting of cell migration, as they control leukocytes movement through the CNS, regulate cell proliferation and differentiation, and also take part in the neuronal-microglial communication [45]. Recent studies showed that chemokines contribute to neuromodulatory effects, rendering both direct and indirect influences on neurogenesis and possessing neurotransmitter-like action [48] (Fig. 2).

In schizophrenia, the CCL11 (eotaxin -1) and CCL3 levels are often increased. These changes can be combined with a decrease in the content of some chemokines, such as CXCL10 (IP-10). The eotaxin -1 level was directly related, while the IL-2 level - inversely related to the severity of negative symptoms in schizophrenia. The authors also suggested that therapeutic resistance may be associated with an increase in the level of both TNF receptors (sTNF-R1 and sTNF-R2) and chemokine CCL2 [49] (Fig. 2).

The levels of the chemoattractant protein-1 (MCP-1 / CCL2), macrophage inflammatory protein-1β (MIP-1β / CCL4), eotaxin-1 (CCL11), thymus activation-regulated chemokine (TARC / CCL17), and macrophage-derived chemokine (MDC / CCL22) in patients with schizophrenia were increased compared to controls. An increase in eotaxin-1 and MDC levels correlated with the severity of negative symptoms and duration of the disease [49].

6. Lymphocyte subsets in schizophrenia

A meta-analysis registered absolute lymphocytosis, increased CD3 + T-lymphocytes, T-helpers (CD4 +), and an increase in the ratio between T-helpers and cytotoxic cells (CD4 / CD8) in peripheral blood of drug-naive patients with schizophrenia. In exacerbated patients, an increase in the content of CD4 + and CD 56+ cells (T-helpers and natural killer cells) has been found. After treatment, a decrease in the CD4 / CD8 ratio was observed, while the content of CD-56 cells tended to increase [50].

Of course, subsets of lymphocytes in peripheral circulation differ from those acting intracerebrally. In recent post-mortem studies of the patients with schizophrenia, brain infiltration with CD3+ and CD20 + lymphocytes was described involving the areas responsible for the development of psychotic symptoms. [17].

However, in a recent study patients with schizophrenia had a significant decrease of CD 3+, CD 4+, and CD8+ T-lymphocytes and an increase of CD 20+ B- cells [51].

7. Schizophrenia and complement system

The complement system is one of the effector and regulatory instruments of immunity and (together with kinins, blood coagulation and fibrinolysis) - a constituent of the blood plasma contact polysystem based on stepwise proteolysis. It is involved in brain synaptogenesis, as well as in the processes of neuronal pruning and neurodegeneration. It takes part in clearance of immune complexes and apoptotic products, being associated with activated microglia. The complement system activation was proven in patients with schizophrenia [52]. Moreover, the activation of microglia in the gray matter and hippocampus of the human brain is related to neuroinflammation and complement activation which may lead to a decrease in the volume of gray matter and cognitive impairments in patients with schizophrenia [52, 53].

A complement C4-fragment is a pivotal agent of some complement-depending effects. An increased expression of C4 component in the brain of patients with schizophrenia was reported. In
addition, an excessive activity of the complement system can lead to changes in the neuronal development as a result of excessive synaptic pruning [53].

Plasma concentrations of IL-17, IL-23 and TGF-β1 in patients with schizophrenia were significantly higher compared with the control group, while the C3 level was significantly lower [52]. The concentrations of IL-17, IL-23 and TGF-β1 correlated with the level of aggressiveness (MOAS scale) and with severity of productive and negative symptoms in schizophrenia (PANSS scale). Thus, presumably, the levels of Th-17-associated cytokines directly correlated with the severity of psychotic symptoms and aggressive behavior, while the C3 level is inversely related to the severity of disease [54].

8. Kynurenine pathway in immune regulation and in schizophrenia

Actually speaking, dopaminergic system plays an important role in the pathogenesis of schizophrenia with dopaminergic hyperfunction in the limbic system and hypofunction in the frontal cortex. In addition, it is likely that the glutamatergic system may disturb the balance of dopamine production in psychiatric patients. Glutamatergic regulators may be linked to the kynurenine pathway of tryptophan metabolism both within the nervous and immune systems, and such a similarity seems to be essential for the pathogenesis of schizophrenia (Fig. 3) [55].

![Kynurenine pathway of tryptophan metabolism](image)

*Figure 3. Kynurenine pathway of tryptophan metabolism [55, 56].*

In schizophrenia, an impaired immune response may be associated with an imbalance in the kynurenine pathway of tryptophan metabolism (as a result of hyperactivity of indoleamine dioxygenase (IDO)), which can lead to an excessive kynurenic and quinolinic acid production. But, such cytokines as IFN-γ, IL-2 and IL-6 are responsible for the activation of indoleamine-2,3-dioxygenase (Fig. 3, 4). Quinolinic acid is an N-methyl-D-aspartate receptor (NMDAR) agonist, which can cause excitotoxic neurodegeneration. Kynurenic acid is a NMDAR antagonist, so it has to play a role of a protector against apoptotic and neurotoxic agents. Nevertheless, the increased level
of kynurenic acid in the brain may lead to a NMDAR blockade (as a known trigger of psychotic symptoms and cognitive impairment) [55, 56] (Fig 4).

In addition, an imbalance in the immune system may cause activation of astrocytes with an accelerated oxidation of tryptophan in them with overproduction of a number of cytokines (IL-4, IL-10 and IL-13) leading to a further accumulation of kynurenic acid [55] (Fig. 4). In a recent study patients with schizophrenia had significantly lower levels of plasma tryptophan, kynurenic acid and high kynurenine/tryptophan ratio. The degree of this ratio positively correlated with levels of CRP. Patients with high levels of kynurenine/tryptophan ratio and CRP, IL-1β and IL6 have shown worse attention parameters comparing to the group of patients without high levels of proinflammatory cytokines[56].

Using the mass spectrometry method in patients with schizophrenia, some authors have described a twofold increase of the anthranilic acid level and a threefold decrease in the concentration of 3-OH-kynurenine compared to controls [19].

Antipsychotic therapy positively affects kynurenine pathway metabolism reducing the kynurenic acid production. Because tryptophan metabolites are also essential for immunosuppressive function of T-regulators, such disorders of their metabolism may cause the immunological imbalance, which in turn activates an inflammatory process with an increased production of prostaglandin E2 (PGE2) and cyclooxygenase 2 (COX2). It is noteworthy to mention that (COX-1) leads to an increase in the kynurenine concentration, and inhibition of COX-2 causes its decrease. There is evidence that celecoxib (a COX-2 inhibitor) has a positive effect on the severity of
psychotic symptoms in the early stages of schizophrenia, but slight effect in the late stages of the disease [16].

Thus, the NMDA receptor antagonism and glutamatergic hypofunction may affect the development of psychotic symptoms and cognitive impairment in schizophrenia.

9. Schizophrenia and abzyme autoantibodies

Elimination of the autoantibodies from patients’ sera by means of plasmapheresis reduced psychotic symptoms in patients with the first psychotic episode. Also, there is evidence of the activating interaction between antineuronal antibodies and microglia. These antibodies are present in 5% of patients with the first psychotic episode [57].

In patients with schizophrenia, the titer of the autoantibodies against myelin basic protein (MBP) was 1.8 fold higher compared to the controls, but 5-fold lower compared to multiple sclerosis patients. The authors emphasized the direct catalytic role of these autoantibodies as abzymes. It is known that abzymes are antibodies with catalytic activity able to play the role of the earliest markers in several autoimmune diseases, for example, in multiple sclerosis. The patients with schizophrenia also produce abzymes active against the myelin basic protein (anti-MBP) damaging MBP within the myelin proteolipid axon sheath. The activity of MBP hydrolysis is a typical IgG characteristic in schizophrenia. The IgG abzymatic activity in patients with severe negative symptoms was 2.5 fold higher than in schizophrenic patients with predominant productive symptoms increasing with the duration of the disease [58].

There is also evidence, that some autoantibodies in patients with schizophrenia have RNase activity. An unexpected result was obtained in the following study: Site-specific hydrolysis of four known microRNAs typical for schizophrenia (miR-137, miR-9-5p, miR-219-2-3p, and miR-219a-5p) is involved in regulation of gene expression. The three main cleavage sites are located on the miRNA loops or duplex parts directly connected to the loops. Abzymes with RNAse activity can reduce the miRNAs effect on the expression of numerous genes and alter the availability of their transcription products. Therefore, abzymes with RNAse activity may be embedded in the pathogenesis of schizophrenia [59].

10. S100B, neuron specific enolase, c-reactive protein and schizophrenia

The occurrence of neuron-specific antigens in the peripheral blood may be a marker of destructive processes in nervous system, involving either astrocytic or oligodendrocytic glia (S-100, MBP, GalC-1), or myelin sheath of axons (MBP), or, finally, neuronal plasma membranes (MemAg). The release of brain tissue proteins in a bloodstream provides the development of autoimmune reactions.

In a recent study, blood serum levels of neuron specific enolase (NSE), C-RP and S100B protein were measured in 91 patients with schizophrenia. One-third of patients have shown C-RP levels between 3 and 10 mg/l, what indicates the presence of marked acute phase response signs. Cases torpid for therapy had higher levels of NSE (n = 34, 8.9 ± 3, 1 versus 5, 1 ± 3,0 ng/ml). Patients with family history of mental diseases have shown significantly higher levels of S100B (0,046 ± 0,026 versus 0,038 ± 0,015 mcg/l, p = 0,026). The positive correlation between the levels of NSE, S100B and a number of previous psychiatric hospitalizations was observed (r=0.281, p=0.012 and r=0.289, p=0.010 respectively) [51].

The higher levels of NSE and S100B characterized patients with more severe course of disease, who also have experienced more often exacerbation, but not the longer duration of the disease. A family history of mental disorders played a significant role in patients with increased levels of S100B protein. At the same time patients with later onset of the disease have shown higher levels of C-RP. [51].

11. Schizophrenia and microbiota: pathogenetic role of intestinal permeability

The interaction between the gastrointestinal tract (GT) and brain has recently become an object of a profound psychiatric interest, especially as regards to so-called microbiota-intestine-brain axis.
GT with its non-encapsulated lymphoid elements (GALT) is the largest immune organ associated with the life cycle of 70-80% of body immune cells [60].

The gut microbiota may activate the immune response through the local elements of immune system or mediators that are able to penetrate the blood-brain barrier (BBB). Microbiome takes part in regulation of neurotransmitter synthesis (including serotonin, dopamine, and GABA [61]. In addition, various microbial species can produce intestinal analogues of true and false neurotransmitters and affect ileal corticosterone metabolism that may change the activity of neuroendocrine apparatus [62]. Recently gut microbiota features have been associated with anxiety and memory, cognition, and locomotor activity disturbances [61].

Stressors can both directly and indirectly cause an increase in intestinal permeability, sensitization towards gut microbes, provoke immune cross-reactivity with self-antigens, and subsequent development of both autoimmune and psychopathological disorders [60, 61].

The effect of immune activation on the risk of schizophrenia was described, associated with the influence of the lipopolysaccharides of Gram-negative bacteria, as well as the influence of various exogenous food antigens (gluten, gliadin, casein etc). In addition to structural breaches of the intestinal barrier with an increase in the intestinal permeability, disturbances in the BBB also play a role in enhancing the effect of local antigens on the development of psychotic symptoms. In rodent stress model it was found that chronic psychological stress may increase intestinal permeability for E. coli by 30 times, and almost 4 times for sterile antigenic protein — horseradish peroxidase (HRP). Furthermore, after 10 days of continuous psychological stress, a threefold increase in both concentration of corticosterone in serum and the number of mucosal mast cells was detected [63].

Schizophrenia may be characterized by a decreased microbiome diversity index. In a recent study it was shown that patients with schizophrenia had significantly decreased shares of Bifidobacterium, E. coli and Lactobacillus and higher presence of oral Lactobacillus bacteriophage. However, in other study patients with schizophrenia displayed high level of fecal Lactobacillus [61, 64]. The memory function was impaired in women with schizophrenia who were seropositive for C. albicans [61].

Bacterial lipopolysaccharides also have a significant effect both on the immune system and brain functioning, namely mediated via activation of Toll-like receptors type 4 (TLR4) [65]. Of great interest for immunopathology of psychoses is their ability to induce the tryptophan-kynurenine pathway enzymes (in particular, activity of IDO), which in turn can produce neurotoxic effects by quinolinic acid overproduction and alter the function of T-regulators [66].

12. Autoimmune encephalitis versus schizophrenia (or instead of it?)

In view of healthy conservatism of medicine as an applied science, one of the most difficult tasks in it always was the revision of the established diagnostic labels, especially if new nosological entities were coined by medical specialties different from those installed initial ones. However, such cases are not uncommon, including those in Psychoneurology. Thus, the Kozhevnikov epilepsy and Rasmussen’s disease, which were considered different ailments for many years, at one moment turned out to be similar varieties of encephalitis with different mosaics of focal lesions, caused by viral provocation and autoimmune pathogenesis [67].

Hopefully, in future the deepening of knowledge about diseases and description of new particular cases will bring together or even identify some forms of schizophrenia with some kinds of autoimmune encephalitis.

Autoimmune encephalitis is a disease involving the brain focally or generally associated with autoantibodies against the extracellular epitopes of neurons, or against synaptic proteins [68]. Such encephalitides were previously interpreted as rare and exclusively paraneoplastic ones, but with the development of techniques for supravital imaging of cerebral structures and progress of clinical immunology, it turned out that autoimmune mechanisms are responsible for not less than 1% of all cases of encephalitis [69].

Anti-neuronal antibodies may render negative effects on behavior and cognitive functions, as well as on the development of related affective disorders, psychotic symptoms, convulsive syndrome or dyskinesias (Table 1) [69, 70].
**Table 1.** Autoantibodies, associated with pathogenesis of schizophrenia [69, 70].

<table>
<thead>
<tr>
<th>Type of autoantibody</th>
<th>Target</th>
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<tbody>
<tr>
<td>Autoantibodies against intracellular antigens</td>
<td>• Presynaptic vesicles: GAD (GAD65)</td>
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<td></td>
<td>• DNA (antinuclear autoantibodies)</td>
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<tr>
<td>Antineuronal autoantibodies to superficial antigens</td>
<td>• To ionotropic channels or receptors: AchR, NMDAR (NR1, NR2 subunits), AMPAR (GluR1, GluR2), Ca-channel, KIR4.</td>
</tr>
<tr>
<td></td>
<td>• Metabotropic channels and receptors: GABAR – GABABR1, GABA</td>
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<td></td>
<td>• Other membrane structures: CASPR2, MOG, MBP</td>
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<tr>
<td>Autoantibodies to extracellular antigens</td>
<td>• Synaptic proteins: LGl1</td>
</tr>
<tr>
<td>Autoantibodies to other antigens, probably cross-reacting with CNS</td>
<td>• Food antigens: gluten, casein, gliadin</td>
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Moreover, the level of these autoantibodies correlates with the severity of psychotic symptoms. The main pathogenetic markers of schizophrenia are leukocyte elastase (protein secreted by neutrophils), α1-proteinase inhibitor (α1PI, protein of the acute phase of inflammation), as well as autoantibodies to neuroantigens: myelin basic protein (MBP) and protein S100B [71].

Patients with schizophrenia had a significant increase in the titers of antinuclear antibodies (ANA), as well as increase in autoantibodies towards neuroendothelium of hypothalamic, hippocampal, and cerebellar regions compared to healthy controls. The authors assumed that in the acute phase of schizophrenia there is a nonspecific diffuse involvement of autoantibodies against cerebral vasculature within various areas of the brain. Due to the significant alteration of the hypothalamus, there is a possibility of autoimmune links in the pathogenesis of hypothalamopathies causing affective disorders [72].

In the last few years, many anti-neuronal and anti-glial antibodies have been identified (associated with paraneoplastic and non-paraneoplastic syndromes with various clinical manifestations, including those of schizophrenia-like and neurological nature). According to 1566 registered cases of autoimmune encephalitis by the end of 2018 – in 70.5% of cases, it was characterized by psychiatric clinical manifestations (Table 1, 2) [69].

Anti-NMDAR autoimmune encephalitis is the best studied one among all its types. It is often accompanied by mental disorders (Table 2). Although this autoimmune encephalitis has very severe symptoms, it can be more prone to treatment than other forms, and hence it has the most favorable prognosis [71, 73].

The NMDA receptors belong to subtype of ionotropic glutamate receptors, widely distributed in the CNS. They are involved in regulation of synaptic plasticity and transmission as well as in excitotoxicity. NMDA receptors are heterotetramers consisting of 7 different structural subunits (NR1, NR2A-D, NR3A and NR3B). Most NMDA receptors contain two NR1 and two NR2 subunits. NR2 subunits act as a link for glutamate, while the co-agonist glycine binds to a homologous site on the NR1 and NR3 subunits. NR2 subunits are expressed in various ratios in different areas of the brain, while NR1 subunits are ubiquitous [73, 74]. As a rule, autoantibodies against the NMDA receptor belong to IgG1 and IgG3 subtypes and bind to the epitope located on the NR1 subunit. Antibodies that bind to the NR1 subunit often do not alter other subunits. In case of NMDA-encephalitis, antibodies affect the extracellular part of NR1, as well as NR2, resulting in a raise of glutamate levels, dopaminergic dysregulation and development of excitotoxicity, which may cause clinical manifestations of mental disorders [73, 74].
Table 2. Types of autoimmune encephalitis, defined in mental disorders [69, 71, 73].

<table>
<thead>
<tr>
<th>Type of autoimmune encephalitis</th>
<th>The most characteristic symptoms</th>
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| Anti-NMDAR encephalitis          | • Behavioral, personality changes, psychotic symptoms;  
|                                  | • Cognitive impairment, dysmneistic manifestations;  
|                                  | • Dyskinesias, stereotypes, catatonic symptoms;  
|                                  | • Speech disorders;  
|                                  | • Convulsive syndrome / to epistatus;  
|                                  | • Disorders of sleep, consciousness, hypoventilation (up to 25% of the norm) |
| Anti-AMPAR encephalitis          | • Behavioral disturbances;  
|                                  | • Perplexity, confabulations, agitation, anxiety;  
|                                  | • Short term memory loss;  
|                                  | • Nystagmus;  
|                                  | • Spasmodic syndrome: focal motor convulsions, generalized tonic-clonic convulsions;  
|                                  | • Adiadochokinesis, gait ataxia;  
|                                  | • Sleep disorders  
|                                  | • Consciousness. |
| Anti-LGI1 encephalitis           | • Impairments in behavior, personality changes, psychotic symptoms;  
|                                  | • Cognitive impairment, dysmnesia;  
|                                  | • Cervico-facial myoclonias and muscles of the lower extremities, generalized tonic-clonic seizures;  
|                                  | • Hyponatremia. |
| Anti-GABAA-R 1 encephalitis      | • Behavioral disturbances;  
|                                  | • Paranoid syndrome, psychotic symptoms, taste or visual hallucinations;  
|                                  | • Confusion, disorientation, confabulation, agitation;  
|                                  | • Memory impairment;  
|                                  | • Pathological orolingual movements, aphasia;  
|                                  | • Convulsive syndrome: complex partial seizures, generalized tonic-clonic convulsions up to the development of epistatus;  
|                                  | • Sleep disturbances;  
|                                  | • Hypoventilation requiring mechanical ventilation, danger of coma. |
| Anti-GABAA-R encephalitis        | • Cognitive impairment  
|                                  | • Seizures  
|                                  | • Sleep disturbances  
|                                  | • Hallucinations  
|                                  | • Disorientation in time and place  
|                                  | • Combination with autoantibodies to TPO |

It is remarkable, that autoantibodies may be produced on both sides of the BBB. For example, anti-NMDA antibodies can be cloned from the CSF-derived cell that highlights their intrathecal production. Thus, the BBB damage is not a compulsory condition of anti-brain autoimmunity, although for an additional damaging effect of anti-neuronal autoantibodies and autoreactive lymphocytes, a violation in BBB integrity is relevant [73]. Chemokines are involved in control of the NMDAR autoantibodies production. For example, the level of the B-cell attracting chemokine
CXLC13 is associated with the intrathecal NMDAR autoantibodies production and also with poor response for treatment [75].

Autoantibodies to the NMDA receptor were identified in patients with schizophrenia, schizoaffective disorder, bipolar affective disorder and recurrent depression [73, 76]. Besides, the presence of anti-neuronal autoantibodies against the surface cell antigens is typical for patients with the first episode of schizophrenia in the absence of neurological symptoms (such as convulsions or dyskinesias). Their concentration significantly decreased after plasmapheresis or treatment with corticosteroids. A case of psychotic symptoms relief was described in a patient with the first episode of schizophrenia after sole immunotherapy without use of any antipsychotics [77].

For the first time, anti-NMDAR autoimmune encephalitis was described in 2005 in 4 young women suffering from acute psychotic symptoms, convulsive syndrome, impaired memory, and hypoventilation – in comorbidity with ovarian teratomas. Two years later, the same authors described the presence of autoantibodies directed against the NMDA receptor subunit NR1 in these patients [78]. Profound studies involving hundreds of patients with this disease showed that autoimmune anti-NMDAR encephalitis can be detected in men and children as well, although it is most common among young women [71, 73].

Presumably, in some patients with schizophrenia and bipolar affective disorder, autoantibodies to NMDA receptors can be detected both in the initial period and in the onset of the disease resulting in gradually developing chronic hypofunction of NMDA receptors, which causes the development of severe cognitive impairment and psychotic symptoms [69, 71, 73].

The anti-NMDAR type of autoimmune encephalitis in the onset of mental disorder is usually associated with cognitive impairments, mood, behavior and perception disorders. Initially, the manifestations are insignificant, but later (after several days or weeks), an acute worsening of symptoms up to a catatonic state may occur. The development of affective impairments may be manifested by manic syndrome / mixed affective state with a possible rapid development of delirium or stupor. In the clinical picture, emotional instability is observed with a wide range of emotional disturbances from hypothyria to euphoria, irritability, apathy or agitation interspersed with somnolence. Cognitive impairments are observed in the form of short-term memory and attention disorders with dyssomnia [73]. In most patients, impaired mental functions may persist for months after the acute period of the disease [71]. Moreover, in some cases aphasia, catatonic symptoms and delirious stupor may occur [69].

The development of clinical symptoms in this kind of autoimmune encephalitis proceeds in several phases. In 70% of patients, the disease begins with the development of the prodrome phase, which lasts from 5 to 14 days.

The prodromal syndrome is characterized by the cytokine-driven acute phase response symptoms, including subfebrility, fatigue, malaise, headache, nausea and diarrhea. These symptoms may be accompanied by leukocytosis in cerebro-spinal fluid (CSF), all above mentioned being probably associated with infectious reasons. By the time the disease clinical picture completion, the CSF parameters may return to normal ranges, but oligoclonal autoantibodies may appear in both serum and CSF. Their level in the blood is significantly higher than in CSF [69, 71].

After the initial phase, mental, emotional and behavioral disorders develop, such as apathy, anxiety, panic attacks, fear, depression, and cognitive impairment. In most cases, manic and mixed affective syndromes develop. Affective disorders are often associated with cognitive impairments of various severity and some psychotic manifestations, such as hallucinatory symptoms, Capgras syndrome, paranoid and paranoiac syndrome [71].

A psychotic phase can be replaced by the somatic exacerbation, including hypo- and hyperthermia, hypoventilation, cardiac arrhythmia, and short-term memory loss. Some patients may develop a convulsive syndrome, often as generalized seizures, but also in the form of partial seizures. Early initiation of anticonvulsant therapy may mask convulsive manifestations of the disease. Dyskinesias, extrapyramidal symptoms, stereotypical movements and motor automatisms can occur during this phase of autoimmune encephalitis [79].
In the early stages of autoimmune encephalitis, magnetic resonance imaging (MRI) of the brain determines transient foci on T2-weighted images and in the FLAIR mode, located in the regions of the cerebral cortex, basal ganglia, subcortical and medial surfaces of the temporal lobes. The foci of contrast medium accumulation are observed in 10-15% of cases. There is a lack of correlation between symptoms severity and MRI brain changes. Temporal atrophy may develop in survivors [80].

13. Crosstalk of pathogenesis between schizophrenia and autoimmune encephalitis

To understand entirely the clinical manifestations of antibody-mediated disorders of the synapse, it is necessary to consider the target antigens’ functions in the brain synaptic networks or circuitry. When this is done, it reveals points of convergence with other disorders, such as schizophrenia. One of the leading theories of schizophrenia is based on data showing the NMDAR hypofunction, which may actually underlie the hyper-dopaminergic state typical of this disorder [81].

Psychiatric symptoms, including hallucinations, delusions, agitation, and thought disorders, which are common in schizophrenia, in 68%–80% of cases have also been observed during the most common pattern of anti-NMDAR encephalitis initial presentation [82].

Additionally, the NMDAR antagonists use results in appearance of both positive (hallucinations, delusions and hyperactivity) and negative (decreased motivation, flat affect, deficits of memory and learning) symptoms resembling not only anti-NMDAR encephalitis, but also schizophrenia [80]. There are electrophysiological, neuroimaging, genetic, and postmortem pathomorphological evidences that patients with schizophrenia have the NMDAR system hypofunction, similarly to that shown in animal models of psychoses [83].

It was highlighted, that the NMDAR-related cognitive network includes 3 main zones: Hippocampus (involved in declarative memory), dorsolateral prefrontal cortex (executive function, working memory), and ventral tegmental region (facilitates episodic and working memory and motivation) [83]. In this network, a decrease in the NMDAR availability (of genetic, pharmacological, or autoimmune etiology) may lead to an increased pyramidal firing and downstream signaling, lessening normal inhibitory tonic influence over the dopaminergic neurons in the ventral tegmental region. As a result, there may be an increased dopamine production, typically observed in psychoses, accompanied by the impaired working memory related to the abnormal functioning of NMDAR-bearing parvalbumin-positive GABAergic interneurons of the prefrontal cortex [84]. Dopamine is produced also in immune (T-regulators) and endocrine (adrenal medullar) cells. The dopamine produced by T-regulatory lymphocytes decreases their immunosuppressant activity on T-helpers, thus facilitating the immune responses [84]. In addition, on the one hand, a decrease of NMDAR function does not imply any decrease of extracellular glutamate. On the contrary, an increase of extracellular glutamate may develop after a decrease of GABAergic inhibitory activity or signaling pathways modulating NMDAR, which was shown in clinical schizophrenia and in animal models (in the frontal cortex and hippocampus of rats after injection of human anti NMDAR antibodies) [81]. Moreover, it was recently observed that anti NMDAR antibodies may lower threshold of seizures and alter neuronal electric activity [85].

As much as 9.9% of patients with schizophrenia and 2.8% of depressed patients had an increased serum concentration of autoantibodies to NMDA receptors. In those patients with schizophrenia seropositive for anti-NMDAR, the IgG antibodies were detected not only against the NR1 subunit of the NMDA receptor, but also towards NR1a / NR2b subunits [86].

However, the data on the association between autoimmune encephalitis and schizophrenia are still a bit controversial. The anti NMDA autoantibodies were found in sera of 36 out of 213 patients with psychotic symptoms (but absent in the control group) [87]. In a later study, the level of six main antineuronal antibodies in the serum of patients with schizophrenia was checked. There was registered the presence of anti-NMDA antibodies in 7.6% of patients, CASPR2 antibodies (contactin-associated protein-like 2) – in 2.5%, GAD65 autoantibodies (glutamic acid decarboxylase) – in 1.9%, and anti-AMPAR antibody (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
receptor) – in 0.1% of cases. It was also shown that the antibodies to LGI1 but not to CASPR2 were present in 2 out of 144 (1.4 %) patients with schizophrenia [88].

But, in discrepancy with aforementioned data, in the study by Van Mierlo et al., none of the 104 patients with schizophrenia showed any anti-neuronal surface autoantibodies in sera (Table 1) [89]. Moreover, in a more recent study, the autoantibodies to neuronal superficial antigens were absent also in CSF of patients with schizophrenia [90].

In a later study, 2817 individuals, including 1325 healthy donors and 1492 patients with schizophrenia, Parkinson disease, or affective-disorders, were examined for the presence of serum antibodies against NMDAR. In this study, 10.5% of all subjects were anti NMDAR positive. The authors suggested that BBB impairment in NMDAR antibody positive patients with schizophrenia may correlate with the severity of psychotic symptoms [75].

Moreover, recently NMDAR antibodies were detected only in 2 out of 68 patients with schizophrenia [91].

An interesting case of anti-NMDAR antibodies positivity was described in a female patient with 7 year history of schizophrenia, for years successfully treated with conventional antipsychotics until the last exacerbation of the disease when she became resistant to psychopharmacotherapy and electroconvulsive therapy. However, this patient was successfully treated with immunotherapy [92].

Anti-GABAR antibodies may also exist in patients with schizophrenia. The GABAergic hypofunction is a possible cause of severe schizophrenic symptoms. The postmortem studies proved this hypothesis by showing dysfunctional GABAergic interneurons within various brain areas. In a study of 2017, the case of schizophrenia with severe psychotic symptoms and antiGABA B1 antibodies in serum was described [93]. Also 2 patients (of 57, 8.5%) with schizophrenia were seropositive for IgG antibodies against GABAARα1 [94].

14. Prognosis and treatment of autoimmune brain involvement

An early treatment of autoimmune encephalitis is a must. In the acute period, corticosteroids, polyclonal human IVIG followed by plasmapheresis are recommended.

It is worth mentioning, that the first successful attempts of efferent therapy in schizophrenia and in drug addicts based on the elimination of immune effectors by means of cerebrospinal liquor pheresis were made by N.G. Mikhailova and co-authors in the mid-1990s [95].

With ineffectiveness of the aforementioned anti-inflammatory drug and efferent therapy, the treatment with a long-term immunosuppressive therapy is necessary [69, 71]. In average, between 75% and 80% of autoimmune encephalitis cases have a good prognosis and a fine response to immunotherapy, despite the severity of the clinical symptoms.

In addition to immunotherapy, it is important to start the most adequate psychopharmacotherapy in proper time (antipsychotics, antiparkinsonian drugs, antidepressants, tranquilizers) [69]. The hyperprolactinemic effect of dopaminolytic antipsychotics may cause torpidity to treatment in autoimmune cases of schizophrenia, because prolactin as a paracrine and endocrine promotor of autoimmunity can aggravate pathogenic autoimmune process [96].

15. Conclusions

The autoimmune hypothesis of schizophrenia dates back to ideas of last century and even to the earliest attempts of Russian psychoneurologist V.K. Khoroshko to induce psychotic behavior in animals by injection of “neurocytotoxic antisera” (1911-12) [97] and reveal of anti-cerebral immunoreactive substance in CSF taken from schizophrenic patients by German physician H. Lehmann-Facius (1935) [98].

But it sounds contemporary and has become the most relevant in the last decade. There is a growing amount of witnesses that schizophrenia may develop as an autoimmune disease caused by the autoantibodies that affect neuronal receptors of the limbic system (anti-neuronal antibodies), as well as by autoantibodies against the brain vascular endothelium, or abzymes with RNase and protease activities. However, the findings in this field are controversial. It is significant that schizophrenia is often comorbid with other autoimmune diseases, such as diabetes mellitus type 1,
bullous pemphigoid, celiac disease, Graves’ disease and Hashimoto’s thyroiditis etc., and a susceptibility to various autoimmunopathies is also observed in the closest relatives of such patients. There is a possibility that deregulations of the glutamatergic system, including the ones brought in by the influence of immune effectors, may disrupt the balance of dopamine production and thus alter both neuro- and immunoregulatory functions. This factors interact with the kynurenine pathway of tryptophan metabolism both in immunocompetent cells and neurons, which may play part in pathogenesis of schizophrenia. Changes in the kynurenine pathway metabolism, like hyperproduction of potentially neurotoxic metabolites, such as 3-hydroxykynurenine and quinolinic acid, as well as disturbances in the ratio of anthranilic and kynurenic acids also increase the risk of endogenous psychotic process. At the same time, tryptophan metabolites and dopamine also control suppressor functions of T-regulators, which restrain autoimmunity. The viral, bacterial or parasitic infections at different stages of ontogenesis (Coxsackie, Hepatitis C viruses, Herpesviridae, influenza, SARS, Toxoplasma, Borrelia, etc.) can play the triggering role in pathological autoimmunity, including association with autoimmune encephalitis, especially in an increased permeability of the gut wall and BBB. Also, schizophrenia associated with autoimmune encephalitis is characterized by a greater severity of psychotic symptoms, deeper cognitive impairment, frequent development of convulsive syndrome and lower efficacy of psychopharmacotherapy, which may result from the prolactogenic action of antipsychotics and the stimulation of autoimmunity in hyperprolactinemia [96]. Another important element that plays a noteworthy role in the development of schizophrenia is a change in the state of the intestinal microflora (reduction of microbiotic multiplicity), which can also act as a predictor of the endogenous psychopathological process and affect the development of autoimmune disorders.

Nowadays Psychiatry, step by step converted into biomedical science, stands in front of the plenty of facts proving that human behavior is not constructed by brain solely and on the basis of genetic and social stereotypes only. The whole immunoneuroendocrine integrating and communicating apparatus of human body is responsible for individual behavior both in health and disease, and behavior is the integral result of metabolism [99]. Thus, autoimmune alterations in combination with other mechanisms may be important factors in the etiology and key links in the pathogenesis of schizophrenia. A further research question is to evaluate the effectiveness of immunotherapy and psychopharmacotherapy in the treatment of schizophrenia associated with autoimmune phenomena and to create experimental animal models of schizophrenia using autoantibodies obtained from the schizophrenic patients.

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