IMMUNOLOGICAL CHARACTERISTICS OF SCHIZOPHRENIA

Gordana Rubesa[1,2], Lea Gudelj[1] & Dolores Makovac[2]

[1]*Department of Psychiatry, University Hospital Centre Rijeka, Rijeka, Croatia*
[2]*School of Medicine, University of Rijeka, Rijeka, Croatia*

SUMMARY

There are many theories about the etiology of schizophrenia. This paper presents the assumptions and latest findings about many immunological characteristics of schizophrenia. According to the neuroimunological theory, this disorder is due to neuroimuno-logical disbalance, increased microglial activity and increased levels of proinflammatory cytokines. Studies have found that intrauterine infections in pregnant women have an effect on the fetal brain development, and that infections with rubella, measles, herpes virus, and toxoplasma are associeted with schizophrenia onset in adult life. In the first episode of schizophrenia and during exacerbation in the serum of the patient, an increased level of proinflammatory cytokines was found. Increased levels of IL-6, TNF-α and IL-1β, and decreased levels of anti-inflammatory cytokines, Il-10. Interleukin 6 levels increase in the psychotic phase of the disease and normalize after the antipsychotic drug treatment. Increased level of IL-6 is associated with severe cognitive impairment and it is more common with patients who had been without adequate treatment for a long time and patients with therapeutic-resistant schizophrenia. Treatment of schizophrenia could be improved by the introduction of anti-inflammatory drug in the therapy.

Key words: *schizophrenia – etiology – immunology – cytokines - intrauterine infections - autoimmune diseases – antipsychotics - anti-inflammatory drugs*

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INTRODUCTION

Although the clinical manifestation of schizophrenia has been recognised and described over 100 years ago, the pathophysiology and etiology of this disease remain unclear to this day (Elaine et al. 2004, Rubesa et al. 2011). Limited understanding of brain functions in schizophrenia prevents us from recognizing and defining molecular treatment targets, as well as preventive strategies. Multifactoriality of the disease has brought together scientists of different neuroscientific areas in the attempt to clarify the pathophysiology of schizophrenia. There are numerous research results that point out the biochemical basis of schizophrenia, but with no unified basic findings (Rubesa et al. 2011). The discovery of well defined etiological factors might enable the prevention of development of schizophrenia.

At the moment it is well established that schizophrenia has a genetic basis combined with environmental agents (Heston 1970). Massive gene deletions (>500 kb) were found in schizophrenic patients. In general population massive gene deletions are rare but penetrant, meaning they can significantly contribute to the development of the disease (Turnpenny & Emeryjeve 2011). However, the deletions are not exclusively linked to schizophrenia. More recent genetic studies have identified the association with HLA-region at the chromosome 6p21.3-6p21.1, introducing thus the immune system components as risk factors for the development of the disease (Turnpenny & Emeryjeve 2011). The interest for genetic aspect of schizophrenia is enormous, and has sparked in 2016 the largest whole genome association study with a total of 36989 patients and 113075 control subjects. The study revealed 108 independent schizophrenia-linked loci, 83 of them were previously unknown. Some of the newly discovered loci suggest that immune functions are indeed involved in the etiology of schizophrenia, and further research is granted (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014).

The most widespread theories on the etiology of schizophrenia are neurodevelopmental, neurodegenerative, viral, and neuroimmunological theory (Sadock & Sadock 2009).

This brief review is focused on neuroimmunological theory.

As early as at the beginning of the last century, scientists have observed that schizophrenia occurs more frequently in children born in the winter and early spring. They later made a connection of that fact with influenza epidemics that were also more frequent at that time of the year (Menninger 1926, Machón et al. 1983). Following those results, many more infective diseases that were considered detrimental for neurological development of a foetus were scrutinised (Suvisaari et al. 1999, Brown 2000, Brown et al. 2001, Buka et al. 2001, Mortensen et al. 2007, Ellman et al. 2009). Recent research has revealed a number of inflammatory proteins that are elevated in schizophrenia (Buka et al. 2001, Miller et al. 2011, Canetta et al. 2014, Upthegrove et al. 2014). PET scans of schizophrenic patient's brains show increased activity of microglia (Doorduin et al. 2009), while experimental treatment that combined antiinflammatory and antipsychotic agents produced better outcome than antipsychotic medication treatment alone (Yrjanheikki et al. 1998, Müller et al. 2004, Giuliani et al. 2005, Müller et al. 2010, Laan et al. 2010, Grazio 2015). However, more well designed studies are necessary in order to allow for accurate conclusions on the role of autoimmunity in a disease as complex as schizophrenia.

SCHIZOPHRENIA AS A CONSEQUENCE OF INTRAUTERINE OR EARLY CHILDHOOD INFECTIONS

Various intrauterine and early childhood infections that might contribute to the development of the disease were the first arguments proposed to represent immunological component in the etiology of schizophrenia. The earliest link between schizophrenia and infections was found in the environmental studies that had concluded that more children born in winter and early spring develop schizophrenia during their lifetime. That is also the time of a year when influenza epidemics are most frequent (Machón et al. 1983).

Early in 20th century scientists tried to establish the link between inflammatory processes and schizophrenia. In 1926, Menninger described 200 cases of psychosis in the survivors of the great influenza epidemics in Boston in 1918. As many as one third of the patients were diagnosed as 'dementia praecox' (Menninger 1926). Following the initial idea of influenza as a potential cause of schizophrenia, scientists started scrutinizing every possible perinatal infection that was likely to produce similar consequences. Other than influenza, some other intrauterine infectious diseases were proposed as culprits: rubella (Brown et al. 2001), juvenile paralysis (Suvisaari et al. 1999), upper respiratory tract inflammations (Brown et al. 2000), birth canal infections, herpes virus type 2 (Buka et al. 2001), and parasitic infection with Toxoplasma gondii (Mortensen et al. 2007). The infections were thought to be the agents that might have altered the foetal brain development, or were able to modify the genetic material already predisposed for schizophrenia which is going to be phenotypically expressed (Clarke et al. 2009, Brown & Derkits 2010).

Some scientists proposed that the increase of inflammatory proteins in pregnancy, without actual infection is enough to cause schizophrenia in a child. C-reactive protein (CRP) and tumor necrosis factor alpha (TNF-α) are the most frequently quoted causative agents (Buka et al. 2001, Canetta et al. 2014). Except during pregnancy, the infections may have a role in the etiology of schizophrenia in postnatal period as well. Meta-analysis of 2424 cases showed that a CNS viral infection in early childhood almost doubles the probability for the development of schizophrenia in comparison to healthy counterparts (Khandaker et al. 2012). It has been shown that childhood infection with Epstein-Barr virus increases the frequency of subclinical psychotic symptoms in adolescence (Khandaker et al. 2014). Paramyxovirus parotitis also appears to be a significant contributing factor in the etiology of schizophrenia. Following parotitis infection children may suffer from long lasting neurological disturbances and difficulties in memory functions (Julkunen et al. 1985).

It is interesting to point out that adult patients in the acute stage of schizophrenia are more susceptible to infections; for example, hospitalised patients are 30 times more likely to develop urinary infections than stable outpatients (Miller et al. 2013).

CORRELATION BETWEEN SCHIZOPHRENIA AND AUTOIMMUNE DISEASES

Patients with schizophrenia show various features of immunological diseases, such as previous infections (Khandaker et al. 2012), presence of autoantibodies (Pearlman et al. 2014), antiinflammatory cytokines (Miller et al. 2011) or other inflammatory proteins in the blood, or co-existence of other autoimmune disease (Benros et al. 2011).

The pivotal task of the immune system is differentiation between the self and alien. Once alien matter is detected, a series of responses are activated with the aim to eliminate the intruder. Immune system is capable to recognise microorganism's antigens as well as altered self and tumor antigens (Gamulin et al. 2005). Autoimmune diseases develop when the basic function, that is, differentiation between self and alien, fails, i.e. natural tolerance towards some of the self antigens is abolished (Andreis 2010).

Autoimmune diseases are frequently found in schizophrenic patients (3.6%), and as many as 3.1% of autoimmune disease patients have a relative with schizophrenia (Benros et al. 2014). Many comparisons between autoimmune diseases and schizophrenia were made. In the study which compared genome of schizophrenic patients with that of patients suffering from Crohn's disease, multiple sclerosis, psoriasis, rheumatoid arthritis and ulcerose colitis, 6 independent mutant loci were found in genomes of both schizophrenic and autoimmune diseases patients. 6 of 108 loci of the genome previously linked to schizophrenia, were found to encode proteins involved in immunological processes within brain (Pouget et al. 2016).

In cerebrospinal liquor of patients with schizophrenia anti-NMDA-receptor autoantibodies were found (Dekaris et al. 2014). These patients are three times as likely to have elevated titre of anti-NMDA-receptor autoantibodies, when compared to healthy controls. This is also the case in depression and bipolar affective disorder (Pearlman & Najjar 2014). Anti-NMDA-receptor cause autoimmune process in anti-NMDA receptor encephalitis, which is a progressive disease that is initially manifested with psychiatric symptoms. Elimination of autoantibodies and immune therapy provide clinical recovery of a patient (Lennox & Vincent 2012). Antagonism of NMDAR and glutamate hypofunction has long been proposed as causal mechanisms of psychotic symptoms and cognitive dysfunctions in schizophrenia. Injection of a NMDAR antagonist ketamine in healthy volunteers causes positive psychotic symptoms such as hallucinations and delusional ideas, as well as negative symptoms (Pomarol-Clotet et al. 2006).

CORRELATION BETWEEN SCHIZOPHRENIA AND ATOPIC DISEASES

Atopic diseases in children, particularly asthma, are found more often in patients who later developed schizo-

phrenia. Besides asthma, other atopic disease that are found more frequently in patients with schizophrenia, such as atopic dermatitis, urticaria and atopic rhinitis (Pedersen et al. 2012).

Recent study by Wang et al. (2017) that included 75069 subjects showed that asthmatic patients indeed do have greater risk to develop schizophrenia. 25023 asthmatic patients were included in the study; after 6 years follow up 100 of them developed schizophrenia. On the other hand, only 138 out of 50046 healthy control subjects developed schizophrenia. One must also consider that asthmatic patients often regularly take corticosteroids that are often considered potentially psychosis-inducing (Drozdowicz & Bostwick 2014).

MICROGLIA AND SCHIZOPHRENIA

Microglia are resident macrophages within central nervous system. By producing inflammatory cytokines, chemokines and proteases in the brain tissue they are essential for the communication between peripheral immune system and brain. Activated microglia express mitochondrial translocation protein 18kDa (TSPO) which is used as a quantitative indicator of neuro-inflammation (Cosenza-Nashat et al. 2009). PET brain images during acute schizophrenia show augmented expression of translocation protein (TSPO) and activation of microglia in cerebral grey matter and hippocampus (Doorduin et al. 2009). Brain has long been considered immunologically privileged, protected by brain-blood barrier. However, in response to systemic inflammation, microglia release cytokines which get linked to specific neuronal receptors and modify neurotransmitters, synaptic plasticity and cortisole concentration, resulting in alterations of mood, cognition and memory (Khandaker et al. 2015).

CYTOKINES IN SCHIZOPHRENIA

The most reliable studies that consider schizophrenia to be predominantly inflammatory disease are those based on quantification of citokyne level in peripheral blood. Namely, multiple meta-analyses showed that in the first schizophrenic episode, as well as during relapses, there is an increase in serum level of inflammatory cytokines. The levels of interleukin 6, TNF-α and interleukine 1β are increased, with simultaneus decrease of antiinflammatory cytokine interleukin 10. Following antipsychotic medication treatment and stabilization of the disease, the levels of cytokines return to their normal values (Miller et al. 2011, Upthegrove et al. 2014)

On the other hand, levels of citokynes show variations in many different circumstances, such as age, sex, inflammatory diseases and infections, trauma, metabolic syndrom, obesity, smoking; in females they are additionally influenced by hormonal status. They are also influenced by diet and caffeine intake. Insomnia is another influencing factor; often encountered in schizophrenia, it contributes to abnormal citokyne levels (Koola 2016).

Increased levels of proinflammatory citokynes in patients with schizophrenia

Large number of studies confirmed the increase of levels of IL-1β, IL-6 i TNF-α, with simultaneous decrease of antiinflammatory citokynes such as interleukin 10. Following antipsychotic medication treatment and stabilization of the disease levels of citokynes return to their normal values (Miller et al. 2011, Upthegrove et al. 2014). Experiments conducted with healthy volunteers showed that peripheral immune activation increased circulating citokynes, induced anxiety, bad mood and reduced cognitive functioning (Reichenberg et al. 2001).

Interleukin 6 is the most quoted factor in the immunological theory of the etiology of schizophrenia. IL-6 is a multifunctional proinflamatory citokyne. It's over-expression is found in many diseases: rheumatoid arthritis, juvenile idiopathic arthritis, systemic lupus erithematosus, ankyloze spondilitis, psoriasis and Crohn's disease (Simpson et al. 1997, Gabay 2006). Interleukin 6 is also often quoted as important factor in the pathophysiology of schizophrenia. Animal research showed that interleukin 6 stimulates the survival of cathecholaminergic neurons and stimulates the transmission of serotonin and dopamine in hippocampus and in prefrontal cortex (Zalcman et al. 1994). Increased level of IL-6 is related to more severe cognitive defects. Visual perception, speed of information processing, working memory and speech and articulation abilities are reduced in patients with schizophrenia with increased level of interleukin 6. Also, increased level of IL-6 are found in patients with long duration of the disease that caused significant deterioration, as well as in the patients that remained untreated for a long time during acute psychotic episode (Frydecka et al. 2015). Treatment-resistant schizophrenia is also associated with increased level of IL-6 (Lin et al. 1980). The level of IL-6 increases during first psychotic episode and also during relapses, and only go back to normal value following antipsychotic medication treatment (Miller et al. 2011).

ANTIINFLAMMATORY DRUG TREATMENT OPTIONS IN SCHIZOPHRENIA

In present times, the most frequently used drugs for treatment of schizophrenia are atypical antipsychotics that act on dopamine and serotonin receptors. Although dopamine abnormalities are frequent target for antipsychotic agents, they are not present in all patients with schizophrenia. The complexity of brain functioning is still far from being fully understood, as are the mechanisms of processes that cause schizophrenia. Therefore, the treatment is at least partly experiential. Currently used antipsychotic drugs are highly efficient and are certainly the method of first choice in the treatment of schizophrenic symptoms. On the other hand, in cases of treatment-resistant schizophrenia, when not even cloza-

pine helps, further investigation of pathophysiological mechanisms that produce particular set of symptoms is necessary in order to create adequate treatment (Lobos et al. 2014).

Celecocsib (Müller et al. 2004, Müller et al. 2010, Grazio 2015), aspirin (Laan et al. 2010) and minocyclin (Yrjanheikki et al. 1998, Giuliani et al. 2005), to name but a few antiinflammatory drugs that might, combined with antipsychotics, contribute to the treatment of schizophrenia. Groups of patients that were treated with combination of antipsychotic agents and minocyclin showed greater improvement in PANSS score than the group of patients treated with antipsychotic–placebo combination. Furthermore, the most pronounced improvement was found in negative and cognitive symptoms PANSS subscales, i.e. in the symptoms that are often more difficult to treat (Miyaoka et al. 2008, Levkovitz et al. 2010).

Other than known antiinflammatory drugs, antipsychotics, risperidone more than others, show similar activity. Risperidone is capable of significant stabilisation of citokyne levels in the first episode patients. In the early days of risperidone treatment, citokyne levels return to normal before the improvement of psychiatric symptoms, indicating direct action of risperidone on the concentration of some citokynes, independently of its antipsychotic effects (Noto et al. 2015). Risperidone inhibits the synthesis of IL-1β, IL-6 i TNF-α; it also produces antiinflammatory effects by reduction of nitric oxide synthesis and suppression of microglial activation that may be toxic to neurones and may inhibit neurogenesis and oligodendrogenesis (Kato et al. 2007). Research in rats showed that risperidone reduces the levels of proinflammatory proteins, such as TNF-α and IL-1β when the inflammation was intentionally induced with the known potent inflammatory endotoxine lipopolysaccharide (MacDowell et al. 2013).

DISCUSSION

More than a century of research of etiology and pathophisiology of schizophrenia yielded no definitive conclusions. Most authors quote the stress-diathesis as a cause of schizophrenia, meaning that some stress factors combined with preexisting biological diathesis may cause schizophrenia.

A lot of biological diatheses were investigated in schizophrenia. Genetics of schizophrenia is one of them, and has been extensively investigated (Heston 1970, Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). Results confirm the genetic base of schizophrenia. The exceptional interest for genetics of schizophrenia is probably best illustrated by enormous whole genome association study in 2016. It included a total of 36989 patients and 113075 controls. The study detected 108 independent loci linked to schizophrenia, as many as 83 were newly discovered, previously unknown. Several loci suggesting immunological component in the etiology of this disease were also

discovered indicating the course for further research (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014).

However, the importance of epigenetic (environmental) factors has become very pronounced. The theory of double hit is often quoted; it conceptualises the combination of genetic factors that are responsible for faulty brain development and synaptic links, and the wide range of environmental components that may cause additional damage to neurological functions. Biological environmental components may occur during pregnancy and delivery, e.g. intrauterine fetal hypoxia, infections and malnutrition. Non-biological components are psychosocial stressors, e.g. urban living, dysfunctional families (Tsuang 2000).

Wide spectrum of phenotypic manifestations in schizophrenia dictates the necessity for wide range of research of multiple etiological agents that might be pivotal in triggering schizophrenia, determining the gravity of clinical presentation and therapeutic response. Parallel to most prominent neurodevelopmental and neurodegenerative theories of schizophrenia, neuroimmunological theory, discussed in this paper, is also being widely investigated. A hunch that immunological mechanisms might play an important role in the pathophyisiology of schizophrenia took place when scientists realized that schizophrenia occurs more frequently in children born in the winter and early spring. This finding was linked to the influenza epidemics, also more frequent in those seasons. It further sparked the research of many other infective diseases with the potential to cause disturbances of neurological development in infants. The proofs were produced that maternal exposure to rubella (Brown et al. 2001), polio virus (Suvisaari et al. 1999), Toxoplasma gondii (Mortensen et al. 2007) or having upper respiratory tract inflammations during pregnancy (Brown et al. 2000), increases the risk in children for the development of schizophrenia later in life.

Infections may have important role in the etiology of schizophrenia postnatally as well. The meta-analysis of 2424 cases showed that viral CNS infection in childhood doubled the likelyhood of developing schizophrenia in comparison with the individuals that had no viral CNS infection (Khandaker et al. 2012). Parotitis can also cause neurological damage and memory defects (Julkunen et al. 1985); children who had Epstein-Barr virus infection are more likely to develop some form of psychosis during adolescence (Khandaker et al. 2014).

The cause of immunological mechanisms involved in schizophrenic process, such as increased levels of proinflammatory parameters, is unknown in majority of cases. Possible proinflammatory activity of antipsychotic drugs that also cause obesity and metabolic syndrome must certainly be considered. Furthermore, many patients with schizophrenia are smokers, stressed out by their disease, stigma, family problems, job loss and many other adversities (Rojo et al. 2015).

Findings suggest autoimmune disease elements in schizophrenia. Interestingly, autoimmune diseases are more frequent in patients with schizophrenia, while as many as 3.1% autoimmune diseased patients have a relative with schizophrenia (Benros et al. 2014). Many comparisons between autoimmune diseases and schizophrenia were conducted. In genome comparison study of patients with schizophrenia and Crohn's disease, multiple sclerosis, psoriasis, rheumatoid arthritis and ulceroze colitis, 6 independent loci carrying schizophrenia-specific mutations were also found in those autoimmune diseases. Among 108 loci of the genome previously linked to schizophrenia, 6 were identified to code for immunological proteins that act within brain. Those were the single-nucleotide polymorphism (SNP) mapped at chromosomes 2, 5, 8, 11 and 16, namely genes DPP4, HSPD1, EGR1, CLU, ESAM i NFATC3 (Pouget et al. 2016).

Besides autoimmune diseases, atopic diseases, especially asthma, are more frequent in patients with schizophrenia (Pedersen et al. 2012). However, one must consider that atopic patients are often given long term corticosteroid drugs, that are considered as possible cause of psychotic symptoms (Drozdowicz et al. 2014).

Scientists often underline that increased microglial activity plays pivotal role in the neuroimmunological theory of the etiology of schizophrenia. The proofs of increased microglial activation are based on PET brain images during acute stage of schizophrenia. Increased expression of translocational protein (TSPO) is visible. It is indicative of the activation of microglia in gray matter and hippocampus (Doorduin et al. 2009). Microglia in schizophrenia produces increased amounts of cytokines that have specific receptors on neuronal membranes and cause mood changes, cognition and memory disturbances (Khandaker et al. 2015). Citokynes are local inflammation mediators, they influence neuronal functions and synaptic plasticity, metabolism and re-uptake of neurotransmitters such as serotonin, noradrenaline and dopamine (Dantzer et al. 2008). Several meta-analyses showed an increased levels of proinflammatory citokynes in the first episode schizophrenia and during exacerbation in the serum of schizophrenic patients. The levels of proinflammatory citokynes interleukin 6, TNF-α and interleukin 1β are increased, while the level of antiinflammatory cito-kyne interleukin 10 is decreased. Following antipsychotic treatment and stabilization of the disease, levels of citokynes return to their normal values (Miller et al. 2011, Upthegrove et al. 2014). However, cytokines are susceptible to a number of factors, such as age, sex, inflammatory diseases and infections, trauma, metabolic syndrome, obesity, smoking, also hormonal status in females. Their levels also depend on nutrition and caffeine intake. Insomnia, frequently present in schizophrenia, causes citokyne levels abnormalities (Koola 2016).

Peripheral proimflammatory citokynes IL-6 or TNF-α that were released during an inflammation may communicate with the brain in several ways: neuronally, via humoral and cellular pathways. Once within the CNS they stimulate microglia activity. Microglia secretes proinflammatory citokynes, chemokynes and proteases within brain. Those substances metabolise tryptophane in crinurenine pathway, increase oxidative stress and activate hypothalamus-hypophysis-adrenal axis. Those changes are operational in the development of negative, cognitive and positive symptoms of schizophrenia, as well as mood alteration, cognition and perception (Khandaker et al. 2016). The same mechanism, activated microglia, causes the impairment of cognitive functions, due to reduced release of glutamate, as well as psychotic symptoms accompanied by cognitive deterioration mediated by NMDAR antagonism (Schwarcz et al. 2002). Additional proof is the onset of positive symptoms, such as paranoid and delusional ideas, as well as negative symptoms after an NMDAR antagonist ketamine injection to healthy volunteers (Pomarol-Clotet et al. 2006). The presence of NMDA-receptor autoantibodies in the cerebrospinal liquor of patients with schizophrenia is an important finding (Deakin et al. 2014). NMDA-receptor autoantibodies cause autoimmune anti-NMDA receptor encephalitis, a progressive disease which presents itself with psychiatric symptoms at the onset. Elimination of the autoantibodies and immunological therapy provides significant clinical improvement (Lennox & Vincent 2012). Intentional blocking of NMDA receptors with ketamine causes auditory and tactile hallucinations, visual sensations – distorsion of surrounding objects, and detachment from one's body (Pomarol-Clotet et al. 2006). Similar symptoms occur in acute schizophrenia.

Interleukin 6 is also often considered to be significant factor in the immunological theory of the etiology of schizophrenia. In autoimmune diseases IL-6 sustains the inflammation, as well as modifies immune reactions (Gabay 2006). Animal models showed that interleukin 6 aids the survival of catecholaminergic neurons and stimulates transmission of serotonin and dopamine in hippocampus and in prefrontal cortex (Zalcman et al. 1994). Increased level of IL-6 is correlated with heavier cognitive impairment. IL-6 level increases in the first psychotic episode as well as during exacerbations of the disease, and decline to normal values after antipsychotic drug treatment (Miller et al. 2011). Higher increase of IL-6 was found in patients with longer duration of untreated disease, who sustained severe damages or were not adequately treated during the first psychotic episode (Frydecka et al. 2015). Treatment – resistant schizophrenia also shows increased level of IL-6 (Lin et al. 1998).

The research of immunological aspects in schizophrenia offers some new therapeutic options. Much attention is directed to the studies of the role of antiinflammatory drugs that might be efficient in the treat-

ment, particularly for drug-resistant schizophrenia. Celecoxib, aspirin and minocyclin are some of the antiinflammatory drugs that are considered, in combination with antipsychotic medication, potentially beneficial in the treatment of schizophrenia. Most of them act by the inhibition of cyclooxygenaze enzyme, which reduces the production of proinflammatory prostaglandins (Müller et al. 2004, Grazi 2015). The poor therapeutic response for negative symptoms of schizophrenia is well established; alternative treatment approaches might provide some benefit in this area (Müller et al. 2010). Besides antiinflammatory drugs, a second generation tetracyclin antibiotic minocyclin showed promising results. It exerts antimicrobial properties, but is also antiinflammatory, it penetrates into brain tissue and is neuroprotective. Minocyclin inhibits the synthesis of nitric oxide and has some activity on dopaminergic system. Antiinflammatory effects are realised by reduced production of prostaglandins and citokynes, thus the microglial activation and proliferation cannot take place (Yrjanheikki et al. 1998). Minocyclin also reduces the level of TNF-α produced by T lymphocytes in an effort to attach themselves to the microglia (Giuliani et al. 2005).

Other than known antiinflammatory agents, such as previously mentioned celecoxib, aspirin and minocyclin, atipical antipsychotic risperidone exhibits similar action. However, the reduction of proinflammatory citokynes' level is not primarily correlated with clinical improvement, a one might expect. Following risperidone treatment, normalisation of citokyne level precedes symptom improvement, indicating the direct action of risperidone on the citokyne'd level, independently of its antipsychotic activity (Noto et al. 2015). Namely, research showed that risperidone significantly corrects the levels of IL-1β, IL-6 i TNF-α, in that way it reduces microglial activity which is neurotoxic and inhibits neurogenesis and oligodendrogenesis (Kato et al. 2007).

In spite of many proven facts about the involvement of immunological processes in the etiology of schizophrenia, none of them qualifies as a unique biological marker of schizophrenia. Furthermore, immunological theory of schizophrenia fails to explain all phenotypic properties of schizophrenia. Further research in this field is clearly necessary.

CONCLUSIONS

Contemporary findings define schizophrenia as a mutifactorial disease of different genotype and different phenotype. To this day the etiology of schizophrenia remains unclear. Although investigated for over a century, numerous theories stil co-exist, immunological theory being one of them. Prenatal and postnatal infections might have their role in the etiology of schizophrenia. Different studies confirmed correlation of proinflammatory citokynes and schizophrenia. Several meta-analyses

showed increased levels of proinflammatory citokynes in the first episode and during the exacerbation of schizophrenic process. The levels of interleukin 6, TNF-α and interleukin 1β are increased, while the level of antiinflammatory citokyne interleukina 10 decreases. Interleukin 6 is the most frequently mentioned citokyne in the immunological theory of the etiology of schizophrenia. Key element of the neuroimmunological theory of the etiology of schizophrenia is the activation of microglia in the brains of patients with schizophrenia. Study results clearly demonstrate some elements of autoimmune disease in schizophrenia. Many immunological properties of schizophrenia were described, and none of them stands out as a unique biological marker for this disease.

References

1. *Andreiset I: Immunology. Medicinska naklada, Zagreb, 2010*

2. *Benros ME, Nielsen PR, Nordentoft M, Eaton WW, Dalton SO & Mortensen PB: Autoimmune diseases and severe infections as risk factors for schizophrenia: a 30-year population-based register study. Am J Psychiatry 2011; 168:1303-10*

3. *Benros ME, Pedersen MG, Rasmussen H, Eaton WW, Nordentoft M & Mortensen PB: A nationwide study on the risk of autoimmune diseases in individuals with a personal or a family history of schizophrenia and related psychosis. Am J Psychiatry 2014; 171:218–26*

4. *Brown AS, Schaefer CA, Wyatt RJ, Goetz R, Begg MD, Gorman JM et al.: Maternal exposure to respiratory infections and adult schizophrenia spectrum disorders: a prospective birth cohort study. Schizophrenia Bulletin 2000; 26:287–95*

5. *Brown AS, Cohen P, Harkavy-Friedman J, Babulas V, Malaspina D, Gorman JM, et al.: Prenatal rubella, premorbid abnormalities, and adult schizophrenia. Biol Psychiatry 2001; 49:473-86*

6. *Brown AS & Derkits EJ: Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. Am J Psychiatry 2010; 167:261–80*

7. *Buka SL, Tsuang MT, Torrey EF, Klebanoff MA, Bernstein D & Yolken RH: Maternal infections and subsequent psychosis among offspring. Arch Gen Psychiatry 2001; 58:1032–7*

8. Buka SL, Tsuang MT, Torrey EF, Klebanoff MA, Wagner RL & Yolken RH: Maternal cytokine levels during pregnancy and adult psychosis. Brain Behav Immun 2001; 15: 411–20

9. Canetta S, Sourander A, Surcel HM, Hinkka-Yli-Salomaki S, Leiviska J, Kellendonk C et al.: Elevated maternal C-reactive protein and increased risk of schizophrenia in a national birth cohort. Am J Psychiatry 2014; 171:960–8

10. Clarke MC, Tanskanen A, Huttunen M, Whittaker JC & Cannon M: Evidence for an interaction between familial liability and prenatal exposure to infection in the causation of schizophrenia. Am J Psychiatry 2009; 166:1025–30

11. Cosenza-Nashat M, Zhao ML, Suh HS, Morgan J, Natividad R, Morgello S et al.: Expression of the translocator protein of 18kDa by microglia, macrophages and astrocytes based on immunohistochemical localization in abnormal human brain. Neuropathol Appl Neurobiol 2009; 35:306–28

12. Dantzer R, O'Connor JC, Freund GG, Johnson RW & Kelley KW: From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 2008; 9:46–56

13. Deakin J, Lennox BR & Zandi MS: Antibodies to the N-methyl-D-aspartate receptor and other synaptic proteins in psychosis. Biol Psychiatry 2014; 75:284–91

14. Doorduin J, de Vries EF, Willemsen AT, de Groot JC, Dierckx RA & Klein HC: Neuroinflammation in schizophrenia-related psychosis: a PET study. J Nucl Med 2009; 50:1801–07

15. Drozdowicz LB & Bostwick JM: Psychiatric adverse effects of pediatric corticosteroid use. MayoClinProc 2014; 89:817–34

16. Elaine W, Lisa K & Annie B: Schizophrenia: Etiology and Course, Annu. Rev Psychol 2004; 55:401-30

17. Ellman LM, Yolken RH, Buka SL, Torrey EF & Cannon TD: Cognitive functioning prior to the onset of psychosis: the role of fetal exposure to serologically determined influenza infection. Biol Psychiatry 2009; 65:1040-7

18. Frydecka D, Misiak B, Pawlak-Adamska E, Karabon L,Tomkiewicz A, Sedlaczek P et al.: Interleukin-6: the missing element of the neurocognitive deterioration in schizophrenia? The focus on genetic underpinnings, cognitive impairment and clinical manifestation. Eur Arch Psychiatry Clin Neurosci 2015; 265:449–59

19. Gabay C: Interleukin-6 and chronic inflammation. Arthritis Res Ther 2006; 8(Suppl 2):S3

20. Gamulin S, Marušić M & Kovač Z: Pathophysiology, 6th ed., Medicinska naklada, Zagreb, 2005

21. Giuliani F, Hader W & Yong VW: Minocycline attenuates T cell and microglia activity to impair cytokine production in T cell-microglia interaction. J Leukoc Biol 2005; 78:135–43

22. Khandaker GM & Danzer R: Is there a role for immune-to-brain communication in schizophrenia? Psychopharmacology (Berl) 2016; 233:1559–73

23. Grazio S: Celekoksib – prvi selektivni inhibitor COX-2 u kliničkoj praksi. Medicus 2015, 173-82

24. Heston LL: The genetics of schizophrenic and schizoid disease. Science 1970; 167:249-56

25. Julkunen I, Koskiniemi M, Lehtokoski-Lehtiniemi E, Sainio K & Vaheri A: Chronic mumps virus encephalitis. Mumps antibody levels in cerebrospinal fluid. J Neuroimmunol 1985; 8:167–75

26. Kato T, Monji A, Hashioka S & Kanba S: Risperidone significantly inhibits interferon-gamma-induced microglial activation in vitro. Schizophr Res 2007; 92:108–15

27. Khandaker GM, Zimbron J, Dalman C, Lewis G & Jones PB: Childhood infection and adult schizophrenia: a meta-analysis of population-based studies. Schizophr Res 2012; 139:161–8

28. Khandaker GM, Stochl J, Zammit S, Lewis G & Jones PB: Childhood Epstein-Barr virus infection and subsequent risk of psychotic experiences in adolescence: a population-based prospective serological study. Schizophr Res 2014; 158:19–24

29. Khandaker GM, Cousins L, Deakin J, Lennox BR, Yolken R & Jones P: Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. Lancet Psychiatry 2015; 2:258–70

30. Koola MM: Cytokines in Schizophrenia: Hope or Hype? Indian J Psychol Med 2016; 38:97–100

31. Laan W, Grobbee DE, Selten JP, Heijnen CJ & Burger H: Adjuvant aspirin therapy reduces symptoms of schizophrenia spectrum disorders: results from a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2010; 71:520-7

32. Lennox BR & Vincent A: Antibody-mediated encephalitis: a treatable cause of schizophrenia? Br J Psychiatry 2012; 200:92–4

33. Levkovitz Y, Mendlovich S, Riwkes S, Braw Y, Levkovitch-Verbin H, Gal G et al.: A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia. J Clin Psychiatry 2010; 71:138–49

34. Lin A, Kenis G, Bignotti S, Tura GJ, De Jong R, Bosmans E et al.: The inflammatory response system in treatment-resistant schizophrenia: increased serum interleukin-6. Schizophr Res 1998; 32:9–15

35. Lobos CA, Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S et al.: Clozapine versus other atypical antipsychotics for schizophrenia, Cochrane Database Syst Rev.Author manuscript; available in PMC 2014 Sep 19. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4169186/

36. MacDowell KS, Garcia-Bueno B, Madrigal JL, Parellada M, Arango C, Mico JA et al.: Risperidone normalizes increased inflammatory parameters and restores anti-inflammatory pathways in a model of neuroinflammation. Int J Neuropsychop 2013; 16:121–35

37. Machón RA, Mednick SA & Schulsinger F: The interaction of seasonality, place of birth, genetic risk and subsequent schizophrenia in a high risk sample. Br J Psychiatry 1983; 143:383–8

38. Menninger KA: Influenza and schizophrenia. An analysis of post-influenzal "dementia precox," as of 1918, and five years later further studies of the psychiatric aspects of influenza. Am J Psychiatry 1926; 4:469–529

39. Miller BJ, Buckley P, Seabolt W, Mellor A & Kirkpatrick B: Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry 2011; 70:663–71

40. Miller BJ, Graham KL, Bodenheimer CM, Culpepper NH, Waller JL & Buckley PF: A prevalence study of urinary tract infections in acute relapse of schizophrenia. J Clin Psychiatry 2013; 74:271–7

41. Miyaoka T, Yasukawa R, Yasuda H, Hayashida M, Inagaki T & Horiguchi J: Minocycline as adjunctive therapy for schizophrenia: an open-label study. Clin Neuropharmacol 2008; 31:287-92

42. Mortensen PB, Norgaard-Pedersen B, Waltoft BL, Sorensen TL, Hougaard D & Yolken RH: Early infections of Toxoplasma gondii and the later development of schizophrenia. Schizophrenia Bulletin 2007; 33:741-4

43. Müller N, Ulmschneider M, Scheppach C, Schwarz MJ, Ackenheil M, Möller HJ et al.: COX-2 inhibition as a treatment approach in schizophrenia: immunological considerations and clinical effects of celecoxib add-on therapy. Eur Arch Psychiatry Clin Neurosci 2004; 254:14-22

44. Müller N, Krause D, Dehning S, Musil R, Schennach-Wolff R, Obermeier M et al.: Celecoxib treatment in an early stage of schizophrenia: results of a randomized, double-blind, placebo-controlled trial of celecoxib augmentation of amisulpride treatment. 2010; 121:118-24

45. Noto C, Ota VK, Gouvea ES, Rizzo LB, Spindola LMN, Honda PHS et al.: Effects of Risperidone on Cytokine Profile in Drug-Naïve First-Episode Psychosis. Int J Neuropsychopharmacol 2014; 18: pii: pyu042

46. Pearlman DM & Najjar S: Meta-analysis of the association betweenN-methyl-d-aspartate receptor antibodies and schizophrenia, schizoaffective disorder, bipolar disorder, and major depressive disorder. Schizophr Res 2014; 157:249–58

47. Pedersen MS, Benros ME, Agerbo E, Borglum AD & Mortensen PB. Schizophrenia in patients with atopic disorders with particular emphasis on asthma: a Danish population-based study. Schizophr Res 2012; 138:58–62

48. Pomarol-Clotet E, Honey GD, Murray GK, Absalom AR, Lee M, McKenna PJ et al.: Psychological effects of ketamine in healthy volunteers. Phenomenological study. Br J Psychiatry 2006; 189:173–9

49. Pouget JG, Gonçalves VF, Schizophrenia Working Group of the Psychiatric Genomics Consortium, Spain SL, Finucane HK, Raychaudhuri S et al.: Genome-Wide Association Studies Suggest Limited Immune Gene Enrichment in Schizophrenia Compared to 5 Autoimmune Diseases. Schizophr Bull 2016; 42:1176–84

50. Reichenberg A, Yirmiya R, Schuld A, Kraus T, Haack M, Morag A et al.: Cytokine-associated emotional and cognitive disturbances in humans. Arch Gen Psychiatry 2001; 58:445–52

51. Rojo LE, Gaspar PA, Silva H, Risco L, Arena P, Cubillos-Robles K et al.: Metabolic syndrome and obesity among users of second generation antipsychotics: A global challenge for modern psychopharmacology. Pharmacol Res 2015; 101:74-85

52. Rubesa G, Gudelj L & Kubinska N: Etiology of schizophrenia and therapeutic options. Psychiatr Danub 2011; 23:308-15

53. Sadock BJ, Sadock VA: Kaplan PR & Sadock's comprehensive textbook of psychiatry – 9th ed., Lippincot Williams & Wilkins, Philadelphia, 2009

54. Schizophrenia Working Group of the Psychiatric Genomics Consortium: Biological insights from 108 schizophrenia-associated genetic loci. Natur 2014; 511:421–7

55. Schwarcz R & Pellicciari R: Manipulation of brain kynurenines: glial targets, neuronal effects, and clinical opportunities. J Pharmacol Exp Ther 2002; 303:1–10

56. Simpson RJ, Hammacher A, Smith DK, Matthews JM & Ward LD: Interleukin-6: structure-function relationships. Protein Sci1997; 6:929-55

57. Suvisaari J, Haukka J, Tanskanen A, Hovi T & Lonnqvist J: Association between prenatal exposure to poliovirus infection and adult schizophrenia. Am J Psychiatry 1999; 156:1100-2

58. Tsuang M: Schizophrenia: genes and environment. Biol Psychiatry 2000; 47:210–20

59. Turnpenny PD & Emeryjeve ES: Osnove medicinske genetike; 15. Poglavlje: Genetički čimbenici u čestim bolestima. Medicinska naklada, Zagreb, 2011; pp 242-3

60. Upthegrove R, Manzanares-Teson N & Barnes NM: Cytokine function in medication-naive first episode psychosis: a systematic review and meta-analysis. Schizophr Res 2014; 155:101–8

61. Wang WC, Lu ML, Chen VCH, Ng MH, Huang KY, Hsieh MH et al.: Asthma, corticosteroid use and schizophrenia: A nationwide population-based study in Taiwan, PLoS One 2017; 12:e0173063

62. Yrjanheikki J, Keinanen R, Pellikka M, Hokfelt T & Koistinako J: Tetracyclines inhibit microglial activation and are neuroprotective in global brain ischemia. Proc Natl Acad Sci USA1998; 95:15769–74

63. Zalcman S, Green-Johnson JM, Murray L, Nance DM, Dyck D, Anisman H et al.: Cytokine-specific central monoamine alterations induced by interleukin-1, -2 and -6. Brain Res 1994; 643:40–9

Correspondence:

Gordana Rubeša, MD, PhD
Department of Psychiatry, University Hospital Centre Rijeka
Krešimirova 42, 51 000 Rijeka, Croatia
E-mail: goradna.rubesa@medri.uniri.hr