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Pregled
Review

IMMUNOGENETIC ASPECTS OF AUTISM SPECTRUM DISORDERS

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Background: Autism spectrum disorders (ASD) are highly heritable disorders from all neurodevelopmental conditions in pediatrics caused by genetic and environmental factors. ASD has polygenic model of inheritance. Multiple factors have been implicated in its pathogenesis such as: genetic predisposition and environmental agents.

Objective: To review immunogenetic factors that underlies the pathogenesis of autism spectrum disorders and their contribution to disorder outcome.

Method: A review of literature on immunogenetics of ASD was conducted. This is web based research. Data used in this paper are taken from the following data bases: PubMed and Google Scholar. Key words were autism, immune genes and immunogenetics.

*Results: Research has revealed associations between ASD and immune genes located in the human leukocyte antigen (HLA) which is located at 6p chromosome. Studies have shown an association for classical MHC class I, II and III alleles and ASD. The HLA genes/haplotypes can also be involved in immune dysfunction and autoimmune diseases. It is now becoming apparent that many of the non-antigen-presenting HLA genes make significant contributions to autoimmune diseases. It has been showed that children with autism often have associations with HLA genes/haplotypes, suggesting an underlying dysregulation of the immune system mediated by HLA genes. Immune disturbances in ASD may involve HLA and related genes in genetic and epigenetic mechanisms. Macedonian study demonstrated the association of HLAC*03 and HLA-DRB1*01 alleles in children with ASD.*

Conclusions: Immune disturbances in ASD may involve HLA and related genes in genetic and epigenetic mechanisms.

Descriptors: AUTISM SPECTRUM DISORDERS (ASD), NEURODEVELOPMENT, IMMUNOGENETICS, IMMUNE GENES, HLA

Abbreviations:
ASD - autism spectrum disorders; CNS - central nervous system; CSF - cerebrospinal fluid; DNA - deoxyribonucleic acid; HLA - human leukocyte antigen; MHC - major histocompatibility complex; MMR - measles-mumps-rubella; USA - United States of America

Introduction

Autism spectrum disorders (ASD) are severe neurodevelopmental and neuropsychiatric disorders characterized by impaired social interaction, verbal and non-verbal communication deficit, and restricted interests and repetitive behavior (1). Autism was first described in 11 case reports by Leo Kanner 73 years ago (2). In last twenty years, autism has become most common neurodevelopmental disability in childhood and one of the main pediatric problems. The disorder occurs four-five times more frequently in boys than in girls (3). The condition manifests in the first three years of life and it is a lifelong disability.

Autism has become a huge mental health problem of every society. Because of that pediatricians should have basic knowledge. After over seven decades of research, the etiology and pathogenesis of autism spectrum disorders still remains unknown. Multiple factors have been implicated in its pathogenesis such as: genetic predisposition and environmental agents.

There is strong evidence for multiple interacting genetic factors as the main cause of autism (4). Those genes play a key role in brain development or associated with brain structures and neurotransmitters defects. Some of them may code for immune proteins (5).

Literature data shows a large amount of evidence over the few past decades that some cases of autism spectrum disorders are associated with immune disturbances, pathogen-autoimmune processes and association with MHC system. Autism is considered as autoimmune neuropsychiatric disorders. Strong evidence suggests that the autoimmunity plays a key role in the pathogenesis of neurodevelopmental disorders, including autism (6, 7). The immune response could play a role in the impairment of the central nervous system (CNS) that characterizes autistic children (8). Another finding is

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that prenatal maternal-fetal immune interaction was confirmed to affect the fetal brain development (9).

The aim of this paper is to review immunogenetic factors that underlie the pathogenesis of autism spectrum disorders and their contribution to disorder outcome.

Method

A review of literature on immunogenetics of ASD was conducted. This was web based research. Data used in this paper was taken from the following data bases: PubMed and Google Scholar. Key words were "autism", "immune genes" and "immunogenetics", focusing on the most commonly implicated candidate immune genes in autism. In this paper, "significant" is used to describe study results that reach statistical significance, as based on a p value of <0.05.

Autoimmunity and autism

Some studies provide clinical evidence for a relationship between autism and autoimmune disorder. Money, Bobrow, and Clarke published a family case study of an autistic boy who along with two of his three brothers suffered from multiple autoimmune diseases (10). In 2000 authors reported a case of autism secondary to onset of autoimmune lymphoproliferative syndrome (11). Another case report described autism co-occurring with systemic-onset juvenile rheumatoid arthritis. A mutation in a Fas gene and an Epstein-Barr virus infection, respectively, were implicated in the onset of the disorders. Both disorders responded positively to steroid therapy (12). Comi et al. in 61 families of autistic children and 46 normal controls, found the mean number of autoimmune diseases to be increased in families with autistic children compared to families with healthy children. Autoimmune disease was especially increased in mothers of autistic children (13).

Group of authors investigated the association of maternal autoimmune disease, allergies, and asthma around the time of pregnancy with a subsequent diagnosis of autism in their child via a case-control study. Maternal autoimmune disorders present in women around the time of pregnancy were found unlikely to contribute significantly to autism risk. However, a greater than 2-fold risk of ASD was noted for maternal asthma and allergy diagnoses recorded during the second trimester (14).

Autoimmunity was demonstrated by the presence of brain autoantibodies, abnormal viral serology, brain and viral antibodies in cerebrospinal fluid (CSF), a positive correlation between brain autoantibodies and viral serology, elevated levels of proinflammatory cytokines and acute-phase reactants, and a positive response to immunotherapy. Many children with autism harbored brain myelin basic protein autoantibodies and elevated levels of antibodies to measles virus and measles-mumps-rubella (MMR) vaccine. Measles might be etiologically linked to autism because measles and MMR antibodies correlated positively to brain autoantibodies-salient features that characterize autoimmune pathology in autism. Children with ASD also showed elevated levels of acute-phase reactants-a marker of systemic inflammation (15).

The Human Leukocyte Antigen Genes

The MHC is a highly polymorphic cluster of genes with some of the greatest allelic diversity in the genome. MHC genes are both polygenic (containing multiple genes) and polymorphic (containing multiple variants of each gene). The HLA molecules bind peptide fragments derived from pathogens and display them to the cell surface of antigen presenting cells for recognition by the appropriate T cells. The consequences of this presentation lead to destruction of virus-infected cells, activation of macrophages to kill bacteria, and production of antibody by B cells. Two different characteristics of HLA molecules make it difficult for pathogens to evade immune response. First, several different HLA class I and class II encode proteins with different ranges of abilities to bind pathogenic peptides. Second, the HLA is highly polymorphic and HLA genes are the most polymorphic genes known in the human genome. These include genes for the class I molecules, called HLA-B, genes for two HLA class II molecules, called HLA-DR, and HLA-DQ, and genes for 3 of the complement components. The particular combination of HLA alleles found of various HLA genes on an individual chromosome is known as an HLA haplotype. The products of individual HLA genes may differ from the another by up to 20 amino acids, making each allele quite distinct. Most of these differences are confined to the site on the HLA molecule that binds peptides (peptide-binding groove). The amino acids lining the peptide-binding groove determine the peptide-binding properties of the different HLA molecules. T cells responding to a protein antigen presented by several different HLA molecules will usually have to recognize different peptides. In some cases, a protein will have no peptides capable of binding to any of the HLA molecules expressed on the antigen presenting cells of an individual. In this situation, the individual fails to respond to the antigen (16).

The HLA region is located on chromosome 6p21 (about 4×106 bp) and it is of major interest in basic research as well as medicine, as genes/proteins in this region are involved in many biological processes such as histocompatibility, inflammation, ligands for immune cell receptors, and the complement cascade. The HLA region has 20 typical HLA genes and 112 non-typical HLA genes that are inherited together as frozen blocks of DNA called ancestral or extended haplotypes (17).

Immune related genes and ASD

The strongest evidence for a link between autism and immune system comes from immunogenetic studies. HLA antigens are involved in the qualitative and quantitative aspects of immune system response. If autism is in some cases the result of immune system attack, then particular HLA antigens might be involved as a sufficient or predisposing factor (18).

HLA genes also play a role in reproduction, pregnancy maintenance, mate selection, and even kin recognition; and have been associated with over 100 diseases/disorders including autism. The proteins encoded by HLA genes are ligands, receptors, cytokines, signaling factors, heat shock proteins, transcription regulators, and so forth (19).

Stubbs and Magenis found that the HLA region might be important in autism 36 years ago (20). Warren et al. first reported that the HLA ancestral haplotype B44-SC30-DR4 was associated with autism with a relative risk of 7.9 (21). That result was replicated in a separate case/control population (22). Interestingly, the individual components of AH 44.1 (A2-B44-SC30-DR4) include a deleted C4B gene and DRβ1*0401, both of which have been shown independently to be significantly associated with ASD (23). Examination of different genetic markers other than those used by Warren suggested that certain HLA haplotypes are associated with autism in Sardinian and Italian families (24, 25).

Warren et al. found that the shared epitope binding pocket (DRβ1*0401, *0404, and *0101) in the third hypervariable region of DRβ1 has a strong association with autism. A relative risk of 19.8 for autism was reported for subjects with one of the two extended HLA haplotypes. Both of these haplotypes have many allelic similarities especially the DRβ1*0401 (26).

Familial studies reported the contribution of DR4 alleles to autism susceptibility, because it may disrupt the normal fetal brain development due to the triggered immune response (27). Its frequency was increased in their mothers, suggesting the contribution of maternal DR4 to autism (28). The reason behind that might be the interaction with other risk alleles factors for autism or environmental factors such as maternal infections and thus affect the brain development in children with autism (27). Another study confirmed the contribution of DR4 in the disease susceptibility and also suggested a protective role of DR13 (29). A study carried out by Lee et al. reported an interesting finding; the frequencies of DR4 alleles were significantly increased in autistic children and their mothers in a Tennessee, but not across the USA. This result is consistent with the hypothesis that specific MHCII genes may alter fetal brain development within a population residing in a geographically-defined region, and may contribute to the inconsistencies from study to study where location was not considered (30).

Significant increased frequency of HLA-DR4 was found in mothers of individuals with ASD as compared to mothers of typically developing children. This led to the idea that enrichment in HLA-DR4 of the mothers may be responsible for ASD in the child and is consistent with the hypothesis that prenatal maternal fetal immune interaction can alter fetal brain development (31). Subjects with ASD exhibit enhanced astroglial and microglial activation; increased HLA-DR expression by activated microglia is observed most prominently in the cerebellum, but also in cortical regions and white matter of postmortem autistic patients (32). The increased expression of HLA-DR during development and disease is considered to be a marker of astroglial and microglial activation and their capacity to present antigen to T-helper cells. It has been shown in Han Chinese that the HLA-DRβ1 allele frequencies including DR4 are different in subjects with autism versus control subjects (33).

Children with autism showed a significantly higher frequency of HLA-DRB1*11 allele, and a significantly lower frequency of HLA-DRB1*03 allele compared to the controls, suggesting a significant risk association of HLA-DRB1*11 with autism, especially in families with history of autoimmune disorders, as well as a protective association of HLA-DRB1*03 (34), unlike Torres et al who reported a protective association of DR13 in Caucasians (28).

Al-Hakbany et colleagues demonstrated for the first time the association of number of HLA alleles and haplotypes with the disorder, HLA-A*01, A*02, HLA-B*07, DRB1*1104, and the haplotype A*02-B*07 were positively associated with autism, whereas DQB1*0202, and DQB1*0302, and DQB1*0501 were negatively associated with the disorder (35).

Only a few genes encoded within the MHCIII region have been analyzed for association with ASD. Genes encoding complement gene C4 have been linked to ASD. It was demonstrated a significant increase in the C4B null allele in autistic children compared to controls (21, 23). C4B is involved in numerous immune functions, including lysing and marking pathogens for clearance by immune cells. Eleven (58%) of 19 autistic subjects and their mothers were found to have the null allele for the C4B gene versus 17 (27%) of 64 healthy controls, a significant difference. In a follow-up study, 54% of 50 autistic subjects had the null allele compared with 20.2% of 79 controls (26). Few years ago Mostafa and Shehab reported a significant increase in the deletion of the C4B gene in the Egyptian population. They also reported an increased risk when there was a family history of autoimmune diseases in the autism population (36).

There are no reports to date linking ASD and MHCIII genes encoding TNFα or β, but there are several reports of increased TNFα protein levels in the CSF, blood, and post-mortem brain tissue from individuals with ASD (32, 37).

Regarding the HLA non-classical genes, the tolerogenic molecule HLA-G is known to be responsible for preventing the destruction of the fetal tissues by the maternal immune system. However, HLA-G/KIR interaction is responsible for the immune tolerance during pregnancy. The activated HLA/KIR complexes were detected in autistic children and their mothers; it leads to the neurodevelopmental impairment presented in autism. A recent study showed that a 14-bp insertion polymorphism in the HLA-G gene was significantly associated with autism development due to the prenatal immune activation. The polymorphic gene was detected in autistic children and their mothers and not in their non-autistic siblings, supporting the fact that prenatal immune activation plays an important role in autism development (38).

Macedonian immunogenetic study

In previous study, we reported the first DNA analysis of HLA class I and class II alleles in Macedonian autistic subjects and matched local controls in order to investigate more precisely the genetic association. Thirty-five Macedonian patients (25 boys and 10 girls) with autism were studied. Our results showed significantly increased frequencies of HLA-C*03 and HLA-DRB1*01 alleles in autistic patients when compared to the controls. HLA-A, -C, -B, and -DRB1 allele frequencies were used for the Hardy-Weinberg equilibrium analysis. The detection of A*11-C*12-B*52-DRB1*15 (2.9 %), A*24-C*03-B*55-DRB1*16 (2.9 %), and A*24-C*03-B*55-DRB1*16, most common haplotypes in autistic persons are not shown as susceptible haplotypes. These haplotypes have not been detected in the healthy Macedonian population, but there is no statistically significant association, probably because of the small number of investigated persons with autism. By testing the linkage disequilibrium for all pairs of loci, we get the following results: persons with autism have a statistically significant linkage disequilibrium between locus HLA-DRB1 with the other 3 loci HLA-A, B and C, as well as between HLA-C and HLA-B locus.

Our results for the connection between type I and II alleles in persons with autism in the Macedonian population are different from those published in the literature. These differences could be due to a different genetic structure of the Macedonian population or to different association of the HLA alleles with the autism in the Macedonian population. Additional examinations of the HLA alleles in the families with autism are necessary to get more answers about the Macedonian population. This first immunogenetic study in persons with autism in Macedonia found the association with two susceptible loci HLA-C*03 and HLA-DRB1*01 which are possible predictors for ASD. We have not found predisposing or protective haplotypes for autism spectrum disorders in our population (39).

Discussion

The main implication of this review study is that a subset of children with autism could be mediated by immune system alterations that involve DRB1 alleles in group those children. Although the etiopathogenic mechanism of autism is not clear, genetic and environmental factors are believed to play a role in the onset of the autism (40). Both genetic and environmental interdependence studies came in support of a pivotal role for immune-related genes and immune responses to environmental stimuli (41).

Immunogenetics provides an opportunity to investigate on a genetic level the relationship between ASD and the immune system. In the area of immunogenetics, the research has mainly focused on HLA associations. Studies have shown an association for classical MHC class I, II and III alleles and ASD. The findings are inconsistent. There is still no consensus on the HLA link with autism susceptibility and protection and large inconsistent results exist between the findings of different studies. Studies associating autism with HLA class I and class II are scarce and have generated contradictory findings. This may be attributed to the complexity of the disease spectrum and a small number of cases studied (42).

HLA molecules are vital to recognition of foreign substances such as pathogens. T cells react to foreign antigens only when they are presented by self-HLA molecules on antigen presenting cells. There is an emerging concept suggesting that disruptions in MHC expression in the developing brain caused by mutations and/or immune deregulation may contribute to the altered brain connectivity and function characteristic of autism (29). Over a decade ago we reported that children with autism have increased plasma concentration of immunoglobulines. Increased immunoglobulines in children with autism could be a result of impaired development of the immune system, and/or immunogenetic factors connected with defense mechanism in these children (43).

There is growing evidence for both MHC mutations and immune dysregulation in brain development, which may indirectly alter CNS MHC molecule expression, and contribute to ASD. However, there is not yet a clear role for MHC proteins in ASD (29).

Immune disturbances in ASD may involve HLA and related genes in genetic and epigenetic mechanisms. Some studies have demonstrated that disrupting the epigenetic regulation of transcription plays crucial roles in the development of autoimmune diseases. Beyond studies investigating the potential immunogenetics component of ASD, there is new interest in evaluating potential epigenetic mechanisms associated with ASD (44).

Conclusions

Pediatricians have to increase their knowledge about pathophysiological mechanisms of ASD which will help them to better understand treatments and possible prevention of this very frequent disorder. Increasing incidence of autism will enable further studies which will provide better understanding of etiopathogenesis of autism. HLA genes/proteins should be more carefully examined due to increasing evidence of autoimmune type associations in autism.

There is need of continued researching and conduction of some meta analysis study. Attempts to identify linkages with autoimmunity, extensive pedigree analysis of children with autism and their relatives, and further exploration of immune abnormalities may offer a way of identifying families at increased risk for autism. Understanding the etiopathogenesis of ASD will help in the development of biomarkers for its diagnosis, early treatment, prognosis and possible prevention. Future work in clarifying changes in HLA genes and in other brain immune-related molecules in individuals with ASD, as well as clarifying affected molecular pathways in mouse models, is essential to test the hypothesis that alterations in expression of HLA molecules in the developing brain contribute to the pathogenesis of ASD.

Established treatments that modulate inflammatory signaling pathways in autoimmune conditions may usefully be investigated as possible treatments for such subsets of children with ASD.

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Sažetak

IMUNOGENETSKI ASPEKTI POREMEĆAJA IZ SPEKTRA AUTIZMA

V. Trajkovski

Uvod: Poremećaji iz spektra autizma nasljedni su poremećaji, više od svih drugih neurorazvojnih stanja u pedijatriji uzrokovanih genetskim i okolišnim faktorima. Poremećaji iz spektra autizma slijede poligenski model nasljeđivanja. Mnogostruki faktori sudjeluju u patogenezi, kao što su: genetska predispozicija i okolišni čimbenici.

Cilj: Pregled imunogenetskih faktora koji čine podlogu patogeneze poremećaja iz spektra autizma te njihovog doprinosa na sam ishod poremećaja.

Metode: Proveden je pregled literature o imunogenetici poremećaja iz spektra autizma. Radi se o istraživanju baziranom na internetskoj mreži. Podaci korišteni u ovom članku su uzeti iz slijedećih baza podataka: PubMed i Google Scholar. Ključne riječi koje su korištene su autizam, imunološki geni i imunogenetika.

*Rezultati: Istraživanje je ustanovilo povezanost između poremećaja iz spektra autizma sa imunološkim genima lociranima u ljudskom leukocitnom antigenu (HLA) koji je smješten na 6p kromosomu. Studije su pokazale povezanost alela MHC razreda I, II i III i poremećaja iz spektra autizma. HLA geni/haplotipovi mogu također biti uključeni u imunološku disfunkciju i autoimune bolesti. Postaje očito da mnogi od ne-antigen-prezentirajućih HLA gena čine značajan doprinos u razvoju autoimunih bolesti. Dokazana je česta povezanost HLA gena/haptlotipova u djeca sa autizmom, što sugerira podliježeću disregulaciju imunološkog sustava posredovanu HLA genima. Imunološki poremećaji u djece s poremećajima iz spektra autizma mogu uključivati HLA i povezane gene u genetskim i epigenetskim mehanizmima. Makedonska studija je pokazala povezanost HLAC*03 i HLA-DRB1*01 alela u djece s poremećajima iz spektra autizma.*

Zaključak: Imunološki poremećaji u djece s poremećajima iz spektra autizma mogu uključivati HLA i povezane gene u genetskim i epigenetskim mehanizmima.

Deskriptori: POREMEĆAJI IZ SPEKTRA AUTIZMA, NEUROLOŠKI RAZVOJ, IMUNOGENETIKA, IMUNOLOŠKI GENI, HLA

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