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Role of the immune system in autism spectrum disorders (ASD)

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ABSTRACT

BACKGROUND: The evidence base supports that multifactorial and complex immune interactions play a role in autism spectrum disorders (ASD), but contradictory findings are also reported.

OBJECTIVE: The aim of this selective review was to identify trends in the research literature on this topic, focusing on immunology and other aberrations with respect to the different ASD subtypes.

METHODS: This selective review is based on original and review articles written in English and identified in literature searches of PubMed.

RESULTS: Several studies have found that the risk of ASD is greater among children whose mothers suffered from autoimmune diseases while pregnant. Moreover, individuals with ASD show increased levels of antibodies that are specific for several specific proteins. Studies also show that mothers of children with ASD have antibodies against fetal brain proteins. There are also reports on associations between increased levels of proinflammatory cytokines and ASD. Finally, infections in mothers during pregnancy are linked to an increased risk of ASD.

CONCLUSION: We propose that the large inconsistencies in findings among studies in the field are due to differences in subdiagnoses among the included children with ASD. Well-phenotyped ASD samples are needed to understand the biological and immunological mechanisms underpinning ASD and its subdiagnoses. Future research should apply new strategies to scrutinize the link between ASD and changes in immune responsiveness. Important new research avenues are to investigate the associations (a) between different ASD phenotypes and aberrations in (auto)immune pathways and (b) between reduced natural regulatory autoimmune responses during pregnancy, which are in turn associated with increased oxidative and nitrosative stress in maternal blood and putative detrimental effects in the offspring.

Introduction

The psychiatrist Leo Kanner described a new condition in 1943 based on a 5-year-old patient that he had met in 1938. Following this initial description of autism in the area around Baltimore, the condition has flooded the Western world, and recent epidemiological surveys have found prevalence rates of 0.5% to 1.5% (1, 2). Patients with ASD have a marked phenotypic variability, and 30–35% of them suffer from intellectual disability (3), almost 15% have epilepsy (4), and at least 50% exhibit language delay (5).

Autism spectrum disorders (ASD) are a group of complex, pervasive, and multifactorial neurodevelopmental conditions. The conditions constituting the spectrum are diagnosed based on impairments in social communication and interaction, and restricted and repetitive patterns of behavior, interests, or activities (6). One-fifth of ASD cases are of so-called regressive autism. These children initially develop normally but then start to lose their speech and social skills, typically between the ages of 15 and 30 months, and are subsequently diagnosed with autism (7).

An important point is that autism is not a unitary disease, with autistic patterns of behavior being found in many different medical conditions. This results in a considerable heterogeneity of phenotypes, with comorbid psychiatric and medical morbidities reported frequently (8). Autism, social anxiety disorder, oppositional defiant disorder, attention-deficit/hyperactivity disorder (ADHD), and intellectual disability are common psychiatric comorbid conditions (9). Common medical conditions that are reported frequently with ASD include congenital syndromes, gastrointestinal disorders, mitochondrial disorders, sleep disorders, and epilepsy (10).

In recent years there has been an increased focus on research relating to the role of the immune system in the development of ASD. Several studies have indicated that ASD can be associated with changes in immune responses (11–14), but the significance of abnormal

immune responses for the pathophysiology of ASD remains unknown. Moreover, contradictory research results have been reported. We also find it surprising that only a few of the reviewed studies differentiated ASD into its various subdiagnoses and that this lack of subtyping was not discussed as a major flaw. It would have been reasonable to differentiate the participants by applying criteria for any ASD diagnosis in the Autism Diagnostic Interview–Revised, the Autism Diagnostic Observation Schedule, or the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems.

Subdiagnoses such as childhood autism, atypical autism, Asperger’s syndrome, Rett syndrome, and other ASD diagnoses are likely to have different underlying biological mechanisms. Further, it may also be important to differentiate children with ASD into subgroups according to other clinical findings, such as intellectual disability, EEG irregularities, pathological findings, genetic abnormalities, a clinical diagnosis of epilepsy, as well as neurological abnormalities such as motor disturbances, nystagmus, cerebellar pathology, and sensory dysfunction. It is therefore possible that inconsistent findings for immune responses in ASD are due to its heterogeneity and different subdiagnoses, which may have different underlying biological and immunological mechanisms.

The evidence base for the impact of immunology on ASD is multifactorial and complex. However, some of the main areas involved reflect the following research fields: family history and autoimmunity, antibodies specific for brain proteins in children with ASD, antibodies specific for brain proteins in children with ASD, antifetal brain antibodies in the mother, changes in the cytokine profile, and prenatal infections. These research fields were chosen as the topics for inclusion in the present selective review, and the included references were selected as described below.

Methods: description of the knowledge base

This selective review is based on original and review papers written in English and identified in literature searches of PubMed. Several rounds of literature searches were carried out between May and September 2017. The searches were performed in different research fields, with “human studies” used as a filter for all searches. The searches were carried out by applying the following search strategies within the different research fields:

- **Family history and autoimmunity.** The search (“parental” OR “maternal”) AND (“autoimmune diseases” OR “autoimmunity”) AND (“associated with” OR “risk of”)

(“autism spectrum disorders” OR “autism”) produced 15 matches, of which 12 were included. Only studies that focused on investigating the putative link between autoimmune diseases in parents and ASD in their children were included.

- **Antibodies specific for brain proteins in children with ASD.** The search (“antibrain antibodies” OR “brain-specific autoantibodies”) AND (“children with autism spectrum disorder” OR “children with autism”) NOT “maternal” produced 20 matches, of which 15 were included. Only studies that focused on investigating whether children with ADHD have brain-specific autoantibodies were included.
- **Antifetal brain antibodies in the mother.** The search (“maternal autoantibodies” OR “maternal antibodies”) AND “fetal” AND “brain” AND (“autism spectrum disorder” OR “autism”) produced 21 matches, of which 9 were included. Only studies that focused on investigating whether mothers of children with ASD have antifetal brain antibodies were included.
- **Changes in the immune system, with a focus on changes in the cytokine profile.** We included a recent, high-quality overview article related to vaccinations, and also papers from our own archives, totaling three articles.
- **Prenatal infections.** The search “prenatal infection*” AND “risk” AND (“autism spectrum disorder” OR “autism”) produced seven matches, of which four were included. Only studies the focused on investigating the putative link between prenatal infections and ASD in the children were included.

Subsequent to an initial validation, the full texts of 43 articles were thoroughly read and included as references. We also included nine articles from our own archives.

Results

Family history and autoimmunity

Despite heredity and changes in the immune system being known influencing factors in ASD, whether maternal autoimmune diseases are an independent risk factor for ASD in the offspring remains controversial. Recent research has focused on a possible link between autoimmunity in parents - in particular the mother - and the development of ASD in children. Some studies have found an increased risk of ASD in children whose mothers had an autoimmune disease such as rheumatoid arthritis (15, 16), psoriasis (17), ulcerative colitis (18), or systemic lupus erythematosus (19). However, these studies are impaired by sample

smallness and the use of self-reporting (12). Some studies have also investigated the link between ASD in children and chronic inflammatory bowel disease in their parents, but the results are inconsistent, with two studies indicating a link (18, 20) and the two largest studies showing no link (16, 21). A study from Thailand also found no significant link between autoimmunity in parents and the development of ASD in their children (22); however, that report did not specify which diseases were included. The more-recent meta-analysis by Chen and colleagues included 9 large case–control studies and 1 cohort study covering 9,775 cases of ASD and 952,211 controls (23), and found a positive link between autoimmune diseases in the mother and the risk of ASD in the child. That meta-analysis indicated that the risk of ASD was 30% higher in children whose mothers have autoimmune diseases when pregnant (total odds ratio = 1.34). Those authors surmised that maternal autoimmune disease is probably an independent risk factor for ASD in children, but they also considered that more-extensive, prospective population-based cohort studies were needed to verify their findings. We are surprised that only one (21) of the above-mentioned studies differentiated ASD into its subdiagnoses, and that this lack of differentiation was not discussed. It is therefore plausible that the differences in findings among studies may be due to differences in subdiagnoses among the included children with ASD.

Antibodies specific for brain proteins in children with ASD

Increased levels of antibodies specific for several different proteins have been found in individuals with ASD (24–35). A link has been found between antibodies against brain proteins in children with ASD and impaired adaptive and cognitive functions, along with behaviors associated with autism (36). However, the researchers concluded that it remains unclear whether these antibodies have a direct pathological significance, or if they are merely a response to former damage, and hence that more research is required. A more-recent study found antibodies against brain proteins to be associated with the severity of autism (37). Prenatal and/or postnatal exposure to such autoantibodies might increase the severity by impairing cognitive processes and adaptive function, increasing motor stereotypes, inhibiting or curtailing neuronal development, and changing sleep cycles (37). This background indicates the possibility of antibrain antibodies being valuable biomarkers for ASD and so potentially useful in novel preventive and therapeutic strategies. However, again we question the absence of a focus on the subtypes of ASD diagnoses in studies in this field.

Antifetal brain antibodies in the mother

Another aspect that supports the importance of maternal immunity for ASD is the presence of maternal autoantibodies that target fetal brain proteins. Studies have shown that serum and plasma from mothers with children with ASD contain specific antibodies against fetal brain proteins (38–46). Maternal IgG antibodies are normally able to cross the placenta via the Fc receptor and transfer protective antibodies from mother to fetus. However, this route could also transfer hazardous autoantibodies. IgG antibodies against specific fetal brain proteins could therefore disturb neuronal development by blocking the function of their target molecule, deactivating a receptor or inducing inflammation of the brain (39). However, it is not clear whether the mother's antibodies have a pathological effect or are merely biomarkers for cell damage.

A recent study indicated that ASD could result from in utero exposure to maternal brain-reactive antibodies with a single specificity (47). Monoclonal brain-reactive antibodies isolated from the blood of women with brain-reactive serology and children with ASD were characterized as binding to contactin-associated protein-like 2 (Caspr2). Mice exposed in utero to this monoclonal antibody displayed several signs of abnormal cortical development, as well as impairments in sociability and flexible learning, and also repetitive behaviors. A human study found that the level of Caspr2 autoantibodies was elevated during pregnancy in the mothers of children with mental retardation and disorders of psychological development, but not in the mothers of children with autism (48). More research is therefore required in this field. Possible therapeutic strategies have already been proposed for blocking access to the fetus brain by brain-specific antibodies in the mother that negatively affect proteins that are critical for neuronal development in the fetus, with the aim of preventing irreversible damage (49).

Changes in the immune system, with a focus on changes in the cytokine profile

Cytokines are low-molecular-weight proteins that are secreted by different immune cells and other cell types into response to several types of stimuli. They play several different central roles in both the congenital and adaptive immune systems (50). Several cell types in the adult central nervous system express cytokines and cytokine receptors, including both glial cells and neurons. The cytokines interact with the nervous system and are involved in neuronal development and maintenance (51). Many cytokines and cytokine receptors are also

constitutively expressed during brain development in fetal life (52), and there is evidence that these cytokine pathways play an important role in the normal development of the brain. It is therefore assumed that abnormal levels of these molecules during critical periods during the early development of the brain can affect neurological processes and result in a higher susceptibility to complex brain disorders such as schizophrenia and autism (53).

Recent reviews (54, 55) found that several studies have identified abnormal levels of various cytokines in ASD patients in peripheral blood mononuclear cells, serum and plasma, brain tissues, and cerebrospinal fluid. In addition, processes related to immune activation - as characterized by increased M1 macrophagic cytokines [interleukin (IL)-1 and IL-6] and T-helper-1 cytokines such as interferon (IFN)- γ and IL-2 - are abnormal in ASD, including redox regulation and activation of the tryptophan catabolite (TRYCAT) pathway (56).

We conclude that despite differences in study designs and some inconsistencies and controversies across studies, there are significant associations between ASD and immune activation, mild chronic inflammatory responses, and related processes, including activation of the TRYCAT pathways and damage due to oxidative stress. A recent meta-analysis that included 17 studies involving 743 participants with ASD and 592 healthy controls and investigated 19 cytokines found peripheral alterations in cytokine levels in ASD [53]. That meta-analysis revealed elevations in the proinflammatory cytokines IFN- γ , IL-1 β , and IL-6 in ASD, while the concentration of the anti-inflammatory cytokine TGF- β 1 was reduced. IFN- γ and TGF- β 1 showed the largest effect sizes in ASD, with the concentration of IFN- γ being significantly elevated and that of TGF- β 1 being significantly reduced. Those authors concluded that their results provide evidence of an inflammatory state in ASD.

Prenatal infections/immunological effects

A study reported on in 2015 examined 4,184 children with ASD and compared them with healthy controls to detect whether children with ASD are exposed to infections in utero (57). Mothers who visited outpatient clinics two or three times for genital infections or bacterial infections in the third trimester showed an increased risk of ASD in their children. Only a few other studies have investigated the possible link between infections in the mother during pregnancy and ASD. Three of these are mentioned in an overview article from 2012 (58). A study based on the Danish births registry found that the risk of ASD was almost threefold

higher in mothers admitted to hospital for a viral infection in the first trimester, and significantly higher for the presence of a bacterial infection in the second trimester (59). A different study found that the levels of IL-4, IL-5, and IFN- γ in the middle of a pregnancy were significantly higher in mothers who gave birth to children who developed ASD than in mothers whose children did not develop ASD (60). A third study found that increased levels of tumor necrosis factor (TNF)- α and TNF- β in the amniotic fluid were associated with an increased risk of ASD in children (61). A very recent study found a potential association between symptomatic influenza virus infection and ASD, but without strong statistical support (62).

In summary, there is evidence that infections in mothers and disturbances in related cytokines are associated with an increased risk of ASD in their offspring. However, more research is required in this area (58), especially given the small amount of attention paid to ASD subtypes.

Discussion

An altered cytokine profile has been proposed to play a role in ASD, but further research is necessary to elucidate the precise role of cytokines, including studies analyzing immunological aspects of ASD with appropriate controls in a more-integrated fashion (12). There is a need for well-designed studies involving adequately powered patient samples, adequate control groups, and relevant clinical variables, including ASD phenotypes. We propose that the differences in findings among cytokine studies are due to different subdiagnoses among the included children with ASD. We have recently found that the cytokine profile in children diagnosed with ASD - regardless of the specific subdiagnosis - does not differ from that in healthy controls (63). However, differentiation into subgroups revealed significant differences in the IL-8 and IL-10 levels, which supports the presence of an inflammatory state in some phenotypes, such as childhood autism. Assuming that the TRYCAT pathway could interact with serotonin metabolism, excitotoxicity, inflammation, and oxidative stress, as described above (56), we explored the possible involvement of the TRYCAT pathway in children with ASD, especially across ASD subgroups (64).

Even if a definitive link is found between changes in the immune system and ASD, it will still remain unclear whether a change in the immune system is concomitant with ASD or whether immune dysregulation plays a causal role in the onset of ASD, such as via the impact of neurological processes. It has long been thought that the brain is “isolated” from the immune system via the blood–brain barrier, and that only microglial cells were significant to brain immunology (11). However, there is now evidence that the peripheral immune system can affect and modulate neuronal function in the brain. Cytokines play important roles in neuronal development (65), exerting both proinflammatory and negative immunoregulatory effects (66).

Studies have indicated that individuals with ASD also exhibit other changes in the immune system, such as in IgG and IgM antibodies and altered natural-killer-cell activity (11, 14, 67). A related research field is immunogenetics, especially HLA associations, but this falls outside the remit of the present article.

The causes of immune-inflammatory responses - including changes in the cytokine and immunoglobulin profiles - in subjects with ASD is unclear. A link between ASD and vaccinations, particularly the MMR vaccine, or effects in utero has been speculated, but a meta-analysis (68) concluded that there is currently no evidence of a link between vaccinations and ASD. Although exposure to organic mercury has the capacity to generate immune activation and oxidative processes in children with ASD, further investigations of the associations between environmental mercury and ASD subtypes are needed (69).

A particularly interesting finding is the association of pregnancy with reduced natural IgM-mediated autoimmune responses, which normally exert negative immunoregulatory and anti-inflammatory effects (70). This may increase the autoimmune and immune responses and oxidative stress pathways in maternal blood. By inference, it is possible that increased autoimmune responses in pregnant women are a consequence of these changes in natural autoimmune responses (70). These pregnancy-related changes in natural autoimmunity could also be accompanied by increased inflammatory responses to viral or bacterial infections. Therefore, future research should not only focus on IgG-mediated autoimmune or immune responses in the mother but also on changes in natural IgM-mediated autoimmune responses. A particularly important observation is that pregnant women with reduced IgM-mediated autoimmune responses show increased signs of inflammation and oxidative and nitrosative

stress, including severe protein oxidation, and more-depressive and physiosomatic symptoms (fatigue, dyspepsia, muscle cramps, pain, and gastrointestinal symptoms) (70). Activated oxidative pathways in pregnant women may be associated with behavioral problems in their children (71). This suggests that ASD can occur subsequent to not only infections, but also reduced protective autoimmune responses combined with increased damage due to oxidative stress in some pregnant women.

Conclusion

This review has produced evidence for associations between ASD in children and immune activation, autoimmune responses, and infections in their mothers. We were surprised to discover that previous research has generally not considered the effects of different ASD subdiagnoses. The large inconsistencies among studies in this field may be due to heterogeneity of the study samples, given that almost all studies have lumped the various ASD subtypes together. It is plausible that different immune pathways underpin the different ASD subdiagnoses, rather than ASD being a unitary disease. Well-phenotyped ASD samples are therefore needed to understand the biological and immunological mechanisms underpinning ASD and its subdiagnoses, including subtyping those with and without intellectual disabilities. As an example, children with regressive autism lose their earlier learned developmental skills when they are 15–30 months old, and this clinical profile may partly reflect the effects of subclinical infections.

It is clear that more research is required into the role of the immune system in the development of ASD and its subtypes. Well-designed and prospective studies are needed to consolidate the theory of a causal link between maternal (auto)immune responses or infections and ASD in children, especially prospective studies from the mother's pregnancy to the onset of ASD subtypes. These studies should focus on the following aspects:

1. Natural IgM-mediated autoimmune responses, and immune and autoimmune responses in the mother related to infections and pregnancy, or delivery-specific stressors.
2. Associations between immune pathways and oxidative and nitrosative stress in the mother and the onset of the various subtypes of ASD.
3. Delineation of the neuroimmune and oxidative pathways that are present in the different ASD phenotypes and which may differentiate them from each other.

4. The causes of activation of immune-inflammatory pathways in ASD phenotypes, including the effects of increased gastrointestinal permeability, gene X environmental interactions, autoimmunity, infections, and epigenetic changes.
5. The putative detrimental consequences of neuroimmune, neuro-oxidative, and neuronitrosative pathways on neuronal functioning in the different ASD subtypes.

It is likely that an interdisciplinary approach involving collaborations between immunologists, epidemiologists, neurologists, geneticists, biochemists, and molecular biologists will be beneficial in future studies.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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