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The Role of Infection, Inflammation and Genetic Alterations in ASD Etiopathogenesis: A Review

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Abstract

There is a large number of existing evidence showing the connection between ASD and inflammation and infection as etiologic factors. In this paper, we considered the major theories regarding ASD etiology and show how they either: lack evidence or can be explained by the infectious and inflammatory processes in ASD. As well we reviewed dozens of animal, human and epidemiological studies that have supported the basis that ASD is rooted in prenatal infection and inflammation. Based on the knowledge that has accumulated in scientific literature during the last 70 years, we offer a more sophisticated and complex explanation of ASD, which not only accounts for a better understanding of ASD symptoms, but also takes pathogenetic processes and etiologic factors into account. The understanding of the etiologic and pathogenetic nature of ASD may help in finding the methods of prevention, early diagnosis and treatment of ASD.

Keywords: *Autism Spectrum Disorder; Genetics; Immune System; Infection; Inflammation*

Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder with symptoms and signs that include: social interaction disruption, language impairment and repetitive patterns of behavior, interests or activities [1]. ASD has become a prominent issue in the United States and around the world, with the official rate of ASD prevalence increasing exponentially; although, it is often suggested that the increase in the rate is caused by the development of the diagnostic instruments and an increase of awareness about the disorder. Officially in the USA in 2018, the estimated prevalence was 1 case per 59 children [2], while 50 years ago it was almost 40 times rarer than today, with only 1 case in 2500 [3]. There is no current treatment that cures the disorder due to no established understanding and agreement of the etiology and pathogenesis of the disorder.

There are many existing theories that attempt to explain the etiology of the disorder. Based on a wide range of theories concerning the etiology and pathogenesis of ASD, there have been many treatment approaches proposed. In a study, 764 parents of ASD children were interviewed about the types of treatments that had been prescribed for their children [4]. The results revealed that 111 types of treatment had been used, the most common being: interventional corrective therapies including speech therapy, interventional therapy and ABA therapy and nutritional supplement administrations including vitamin B6, fatty acids and magnesium. Medications were used infrequently, but the most common medications were: sleep aids, antipsychotic, antihypertensive and antidepressant drugs. The effectiveness of common drugs and therapies was assessed by meta-analysis of the existing clinical studies, and despite a variety of approaches, there was no therapy that produced significant improvements in treatment cohorts [5]. It was therefore concluded that there is no effective treatment for ASD children.

Nevertheless, most of the research done on autism is not focused on the etiology. 20% of the grants in the USA and 15% in the UK are provided for research on the etiology of autism; while, most of the funding (35% in the USA and 55% in

the UK) is spent on the biology of autism that includes cognitive, comorbidity and developmental pathway studies [6]. In a study assessing the trends in autism research, the main topic of 129 out of the 820 sampled papers was the genetics of autism; and only 18 of those papers were dedicated to different etiological hypotheses of the disorder [7]. Etiological research, in turn, also includes genetic studies, a number of which significantly outweighs studies on environmental and epigenetic factors [8]. Moreover, the analysis of the grants for autism research on the official NIH website [9] showed that the area of interests include: epidemiology, screening, early identification and diagnosis, genetic studies, brain mechanisms, shared neurobiology of ASD with Fragile X syndrome or other related cognitive science, communication skills, pharmacological/biological interventions, pharmacogenomics studies, psychological/behavioral interventions and services research. As shown, etiology is not included in the areas of research interests by NIH.

This article aims to discuss the existing theories on the etiology of ASD and the evidence based on the following components of the definition: ASD is a congenital, genetic and inflammatory disease. We realize that ASD is a multifactorial, complex disease, which, apart from etiological factors, includes many co-factors and comorbidities such as: gastrointestinal issues, nutrient deficiencies, endocrine alterations, psychological problems, anti-phospholipid syndrome and mitochondrial abnormalities. However, it would not be reasonable to consider all of these factors here at once; this paper aims to focus on the main etiologic factors.

ASD is Epigenetic

ASD children have significant alterations in DNA, with many genes being either over-expressed or suppressed. Most research is focused on finding genes that might play a major role in ASD development, rather than on the underlying mechanisms leading to genetic changes. In ASD, alterations in gene expression take place to a greater extent than genetic mutations [10], so a trigger must exist to cause these alterations. Thus, genetic changes should be considered a component of pathogenesis, not as an etiological factor. It is widely accepted that genetic changes contribute to the factors in ASD etiopathogenesis, but there is no consensus regarding the etiology or the initial factor triggering the disorder.

Although there is no agreement regarding the environmental factors inducing ASD initiation, it is commonly agreed that genetic components play an equal role in the disorder [11-13]. The genetic factors were first confirmed in studies of twin children by [14]. Since then, a growing number of studies have confirmed the role of genes participating in the disorder and identified the mechanisms. It is difficult to say how many genes are involved. The number may vary from a single gene (life NF1) to 5,000 genes [15,16]. It is also difficult to estimate the contribution of hereditary genes and de novo mutations; the heritability varies from 20 to 50% [17,18]. Despite the lack of consensus, critical analysis of the literature allows for a proposition that ASD is a result of de novo alterations in a gene complex.

For instance, attempts to find inherited chromosomal regions resulted in the identification of only two loci that could be replicated [19,20]. The first one is chromosome 7q35 associated with the gene CNTNAP2 and the second in chromosome 20p13. Some of the autistic phenotype features were linked to CNTNAP2 on chromosome 7q35 [19]. Moreover, there is convincing evidence that de novo alterations are strongly associated with ASD, and autistic children possess many more de novo alterations that their age-matched healthy controls [10].

De novo mutations do not play the only role in ASD, because it is not possible to accumulate mutations in a large number of genes that were reported to be involved in the disorder. In the literature on de novo alterations in ASD, de novo LoF, SNV and CNV are reported more often than mutations. For example, it was proposed that there are only 61 genes that are involved in ASD [21]. Out of these, 46 were de novo loss of function (LoF). They mostly participate in synaptic transmission, transcriptional regulation and RNA processing functions and are usually expressed in the brain prenatally. De novo CNV (copy number variation) may include large deletions or duplications, such as duplication of 15q, deletion of 22q11.2, deletion of Xp22.3 and duplication or deletion of 16p11.2, which were already reported as genetic risk factors for ASD [22]. Some shared biologic pathways for genes with two or more de novo or rare, inherited variants in ASD were listed [22]. These genes, which indicated in the Table 1, are mostly biological process genes.

Apart from the genes indicated in the table, genes responsible for innate and adaptive immune system functioning are often dysregulated in children with ASD [23]. For instance, it was revealed that HLA A2 (MHC Class I) and HLA DR4 (MHC Class II) loci contained single-nucleotide polymorphism which was associated with ASD diagnosis. MCH – is a locus that is involved in innate, adaptive, and autoimmune systems (reviewed in [23]). This indicates that genetic changes not only affect the brain development but also immune system functioning.

The expression of several gene modules that are often affected in ASD children was analyzed in pre- and postnatal periods [24]. Module, in this context, refers to a set of genes that are enriched in de novo alterations such as SNV. There were five modules analyzed: M2, M3, M13, M16 and M17. M2 includes 24 genes, 10 of which possess LoF and 11 are missense.

These genes include CALM1, GRIN2A, GRIN2B, MAPK1, PRKCB, and RPS6KA3 [25]. M3 includes 150 genes, some of which are postsynaptic density genes. Mainly, these genes are responsible for cognitive ability, processing speed and delayed recall [26]. The hubs of M13 include the NMDA and GABA receptor subunits GRIN2A and GABRA1, which regulate synaptic activity [27]. M16 encoded proteins are responsible for cation transporter activity, homophilic cell adhesion and nervous system development [27]. Some of the proteins encoded by the M17 module are responsible for calcium-dependent regulation of synaptic activity [27].

Function	Genes
Histone modification	KMT2E, KMT2C, WAC, KMT5B, KDM5B, KDM6B, PHF2
Methylation	KMT2E, KMT2C, KMT5B
Demethylation	KDM5B, KDM6B, PHF2
Regulation of gene expression, epigenetic	ARID1B, TNRC6B, PHF2
Wnt signaling pathway	CUL3, TNRC6B, CHD8, TCF7L2
Negative regulation of intracellular signal transduction	CUL3, DYRK1A, SYNGAP1
Multicellular organismal signaling	SCN2A, ANK2, CACNA2D3
Regulation of ion transmembrane transport	SCN2A, ANK2, CACNA2D3
Single-organism behavior	ADNP, TBR1, SYNGAP1, GRIN2B
Cognition	ADNP, TBR1, SYNGAP1, GRIN2B
Rhythmic process	ADNP, KDM5B, DYRK1A
Regulation of cell morphogenesis	RIMS1, ADNP, BCL11A, TBR1, DSCAM, SYNGAP1
Regulation of cellular component size	NCKAP1, ADNP, DSCAM

Table 1: Genes with two or more de novo or rare inherited variants in ASD. Adopted from [22]

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In fetuses that develop the autistic phenotype, from week 10 to 17 in utero, M2 and M3 are overexpressed, while M13, M16 and M17 are suppressed [24]. After week 23, M13, M16 and M17 are overexpressed, while M2 and M3 are suppressed. This state of gene expression is maintained after birth. This study supports three claims proposed in our paper: ASD is initiated in the prenatal period, ASD is associated with alterations in gene complexes, and gene alterations, such as changes of the level of expression, are more common in ASD children than are mutations.

It was also found that cellular epigenomic modifications, including DNA methylation, were common in ASD [28] and methylation was found to be the result of DNA damage [29]. This can explain the unhealthy expression or inhibition of specific genes responsible for brain development. For instance, DNA damage was shown to contribute to the genetic basis of the Fragile X syndrome [30], common in ASD children [31], and responsible for the connection of neurons [32] and the development of cerebellar vermis lobules VI-VII [31]. These and other studies show that the nervous system is highly vulnerable to DNA damage because of the limited capacity for cell replacement in adulthood, which leads to the accumulation of damaged and irreplaceable terminally differentiated neurons [33].

Another role of the genetic component in the disorder is sex bias. It is estimated that the disorder affects males 4-times more often than females [34]. Pinares-Garcia., et al. discussed the possible explanation of this phenomenon [35]. According to the authors, the bias might be explained by the Y-chromosome, which only can be passed from father to

son. Advanced parental age (both maternal and paternal) at the time of conception is associated with an increased risk for both autism and de novo mutations [36], while the chromosomal instability in humans and other mammals is associated with aging [37]. Although the Y-chromosome participates in testis development and spermatogenesis, it also contributes to the brain development. Two of the Y-chromosome genes Dby and Eif2s3y are expressed in the mouse brain at 10.5 days post coitum [38]. Moreover, the Y-chromosome is more vulnerable to environmental effects, such as viral infection, while the X-chromosome is more stable [39]. The genetic elements of the Y-chromosome regulate inflammatory immune responses and the pathogenesis of infectious diseases as well as some autoimmune reactions like multiple sclerosis [39]. The role of inflammation, immunity and infection will be discussed further in the article.

As it was stated in the article by [40]: "So what if a hundred or more genes are linked to autism? What is the SOLUTION in Autism?" ASD is a result not of genetic alterations alone but a combination of genetic susceptibility and environmental factors; ASD is epigenetic disease [41,42]. The environmental factors contributing to the genetic alterations and ASD risk are discussed in the ensuing sections.

ASD is characterized by anatomo-physiological differences in the brain

According to several studies, autistic children have differences in some regions of the brain, which can result in behavioral and skill disturbances [43-45]. For example, the differences have been found in the cerebral cortex, temporal cortex and cerebellum, which are responsible for the impaired skills found in children with ASD [45,46]. Specifically, the cerebral cortex is responsible for language, movement, sensation, planning, social behavior and social/face processing functions. In magnetic resonance brain images, some regions of the cerebral cortex in autistic children were significantly asymmetric in comparison to healthy controls and increased numbers of altered connections between the neurons in this brain area were observed [45]. The temporal cortex enables face recognition, and when subjects with ASD were shown images of faces, they were found to show temporal cortex activation similar to the activation in brains of non-ASD subjects when they were shown nonface objects [47]. The cerebellum plays a role in mental imagery, reflexes, planning, attention, affective behavior, visual organization, and sensory acquisition [31]. Almost all the postmortem brains of autistic individuals studied to date, regardless of age, sex and cognitive ability, have shown differences in the cerebellum, including overgrowth of brain volume early in life, prominent monocyte and macrophage accumulation in the cerebellum, reduced cortical thickness with age, abnormalities of the deep cerebellar nuclei and a significant decrease in the number of Purkinje cells (PCs) [31].

Apart from anatomical changes, Rossignol also observes the shift in the immune markers in brains of children with ASD.In a review article and Frye [48], the publications showing evidence of inflammation in the brain of ASD children published in the years from 2005 to 2013 were reviewed. These studies revealed that ASD children have: activation of microglia and astroglia in the middle frontal gyrus, anterior cingulate gyrus and cerebellum, increased levels of anti-inflammatory cytokine tumor growth factor–1 and pro-inflammatory macrophage chemoattractant protein-1, increased levels of IFN-gamma, MCP-1, TGF-beta2 and IL-8 in cerebrospinal fluid (CSF), decreased quinolinic acid and neopterin, an increased level of biopterin in CSF, increased TNF-alpha level in CSF, elevated expression levels of some of the immune-related genes in the superior temporal gyrus, reactive gliosis in BA22, BA44 and BA39, increased proinflammatory cytokines in the frontal cortex, elevated NF-κB expression in the orbitofrontal cortex and increased 3-chlorotyrosine concentrations in the cerebellum and temporal cortex. Additionally, the levels of cytokines IL-1β, IL-6, IL-17 and TNF-α are increased in the brains of autistic children [49].

The enlargement of many brain areas, which is typical for children with autism [50], was shown not to be overgrowth but rather cerebral swelling (encephalitis) as a result of persistent neuroinflammation [51]. The increase in brain volume during the early period of development is explained by the proliferative and hypertrophic astrocytes, while the decrease of the brain volume by the time the first autistic symptoms are manifested may be explained by neuronal death as a result of sustained inflammation [51].

ASD is Inflammatory

The increasing number of scientific publications shows evidence that inflammation plays a major role in ASD. In a systematic review by [52], the discussion on the etiology of autism along with an assessment of the strength of evidence was analyzed. The largest number of publications showed an association between ASD and an inflammation/aberrant immune system response (416 out of 437 publications, 95% showed positive association). Apart from being prevalent in number, the articles, which linked ASD to inflammation, also had strong evidence. In this paper, we infer that ASD is an inflammatory disease.

First, oxidative stress, which causes DNA damage, is the consequence of inflammation [53]. It was found in vitro that inflammatory cytokines induce the production of nitric oxide and nitric oxide synthase, which inhibit DNA repair. At the sites of inflammation, macrophages and neutrophils produce reactive oxygen and nitrogen species, resulting in oxidative stress [54]. These species can increase the inflammatory state, inducing additional production of pro-inflammatory cytokines [55]. Additionally, there are studies that link inflammation to particular types of genetic alterations discussed previously in this paper. For example, the association between inflammation and copy number variations in patients with inflammatory breast cancer was shown [56].

However, the main site of inflammation should be the brain, since it is the brain function that is impaired in ASD. Neuroinflammation (as well as systemic inflammation and immune abnormalities) is a common feature in children with autism [52]. A minimum of 69% of ASD children had neuroinflammation and microglial activation [51]. In a 2011 review article, the hypothesis was that autism was the result of genetic defects with contributory effects of advancing parental age and/or inflammation of the brain. As well, the inflammatory state of the brain is supported by the overwhelming number of pro-inflammatory cytokines over-expressed in the brain (reviewed in Rossignol and Frye 2014). Moreover, it was shown that many of the abnormal immunological parameters in ASD individuals were associated with increased disruption in behaviors [31].

Inflammation has been implicated in several other studies as the major cause of ASD. One study proposed that fetal inflammation due to viral or bacterial infections may lead to damage of the CNS, which may result in various neurological disorders such as schizophrenia, cerebral palsy or ASD [57]. In other publications, it was hypothesized that perinatal neuroinflammation may lead to further appearances of autistic symptoms in a child [58-60]. These findings support the idea that genetic changes predisposing a child to ASD may result from inflammation and are likely to appear in the prenatal period.

Apart from oxidative stress causing DNA alteration, neuroinflammation may directly cause atypical brain development by formation of plaques, abnormal neuron growth, increased tau phosphorylation, abnormal neuron growth and proinflammatory cytokine release in the brain [61]. In another study that collected samples of cerebrospinal fluid and serum in children with autism and in healthy controls, autistic children had abnormal levels of neopterin, biopterin, cytokines and cytokines receptors, implicating the role of neuroinflammation in the development of ASD [62].

Neuroinflammation can result from systemic inflammation in three possible ways [63]. First, the inflammation in the body signals the brain through vagal-nerve sensory afferents. Second, cytokines and inflammatory mediators enter the blood through macrophages in organs that lack a blood-brain barrier and the inflammation spreads into the CNS. Third, since the blood-brain barrier was shown to be more susceptible when a systemic infection is present, inflammatory mediators or products may affect the brain endothelium through the induction of a lipid mediator and may cross the blood-brain barrier [64]. Additionally, inflammation in the brain caused by the attempts of the host to combat a viral infection could be the major cause of different neurodegenerative and neural dysfunction processes [65]. All these findings demonstrate that oxidative stress and inflammation are among the major mechanisms producing alterations in the DNA of brain cells.

Moreover, the analysis of the publications on anatomo-physiological alterations in the brains of ASD children indicates the presence of neuroinflammation. It was observed, that autistic children are likely to have a reduced number of neurons in the facial nucleus and superior olive [66]. The increased number of neurons along with the increased volume of the brain may be explained by the findings in the other two studies [67,68]. Apart from the aforementioned changes in the brain, autistic children have brain swelling, particularly in white matter. Increased brain volume and autistic phenotype were shown to be associated with maternal inflammation during pregnancy [69].

Although it was never stated directly, ASD children have brain swelling, based on several facts that indicate brain swelling. First, ASD children were shown to have abnormalities in the ocular fundus [70,71]. Second, children with autism often possess optic nerve hypoplasia [72]. Third, brainstem hypoplasia was observed in autistic children [67].

Infection and maternal immune activation

Inflammation, in turn, can be induced by various factors, but infections are considered the most important factors. The overwhelming number of publications show a wide variety of infectious agents that are suspected to play a role in the initiation and promotion of ASD: herpes simplex virus 1/2 (HSV) [73], Epstein-Barr virus (EBV) [74], Cytomegalovirus (CMV) [75,76], human herpesvirus 6 (HHV 6) [77], rubella virus [78], *Chlamydia* spp. and *Mycoplasma* spp. [77]. Since the initiating event of ASD was shown to begin in the prenatal period [31], it is very likely that the chain of events starts from a maternal viral/bacterial infection.

In a recent large Swedish study published this year, in which 1,8 mln children participated, it was shown that any viral infection during pregnancy significantly increases the risk of ASD in children [79]. In a Danish study that analyzed all children born in Denmark from 1980 to 2005, admission to a hospital due to a maternal viral infection in the first trimester and a maternal bacterial infection in the second trimester was associated with the diagnosis of ASD in the offspring [80]. Another large study conducted in Israel in 1996 revealed a positive correlation between the birth of autistic children and epidemics of measles and viral meningitis [81].

Genetic changes in the murine brain cells similar to those in ASD and schizophrenia were shown to be the result of maternal immune activation (mIA) as a result of inflammation caused by a viral infection [82,83]. It was proposed that the interleukin-6 (IL-6) is a critical cytokine resulting from mIA, which negatively affects CNS development leading to ASD or schizophrenia [84]. Newborn rats inoculated with Borna disease virus intracerebrally manifested an autistic phenotype and had similar blood content alterations with increased TNF-α, IL-1αand IL-1β [85]. Additionally, it is important to state that in addition to the example described above, there was another mechanism reported in a publication [86], which shows the direct impact of viral infection on the upregulation of 21 genes and downregulation of 18 genes in the brain. According to this study, these genes alterations resulted in patterns of autism and schizophrenia. Some viruses, life cytomegalovirus have additional ability to directly damage brain cells when infect them. In a murine study by [87], infectioning of the brain cells with CMV resulted in cerebral atrophy with reduction of neuronal cells and cystic lesions, due to ischemic vascular changes.

Although the immune system's function is to suppress the infections, since in ASD children the immune system is aberrant because of genetic alterations, infection persists, and the chain of events described above negatively influences each other. The cascade of the inter-inducing events observed in ASD is represented in the Figure 1.

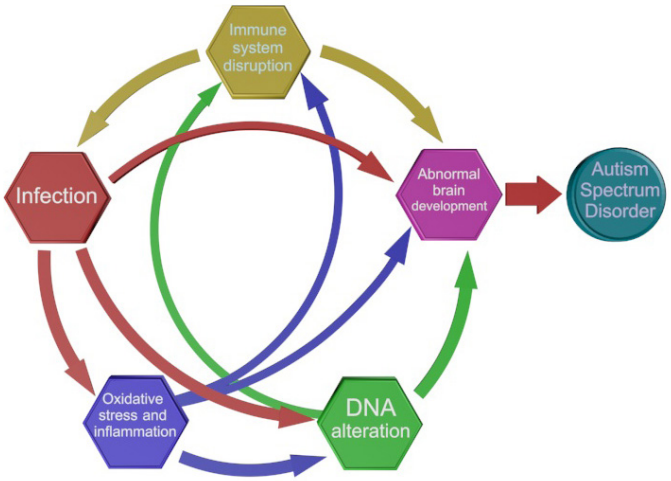

Figure 1: The Figure illustrates the chain of negative events and interconnections between these events leading to ASD and continuing to negatively influence each other. The color of the arrows corresponds to the color of the figure, where the source of the impact is indicated. The suspected inciting events in ASD are a maternal infection, inflammation, and immune activation/disruption which take place in both a pregnant mother and a child in utero. These changes continue in the child in the prenatal and postnatal periods triggering the child's cascade of events leading to the disorder through several alterations. The disorder persists due to the inability of the immune system to fight the infection and a significant number of other pathologies negatively influencing each other.

Maternal autoantibodies to fetal brain

Another possible inflammatory pathway is the autoimmune reaction of the maternal organism to the fetal brain [88-90]. Animal studies showed that injections with autoantibodies to pregnant animals result in offspring behavior abnormalities, cognitive impairments and other symptoms similar to those in ASD children [91-93]. However, autoimmunity is often triggered by a viral infection, because a pathogenic organism can mimic the host proteins as a protective mechanism against the immune system [94,95]. Thus, this pathway does not contradict to the infectious pathway but supports it.

Parental health conditions

There are many parental conditions associated with ASD in children that are consistent with the proposed model of ASD. For example, there is a positive correlation between parental age and the risk of ASD in a child [96]. However, there is evidence that the immune and endocrine systems experience dramatic changes with aging that increase susceptibility to infectious diseases, while DNA instability also increases with age [97-98]. Age itself is not the risk factor for ASD development in a fetus but rather how vulnerable the maternal immune system is to infection.

Other hypotheses of ASD etiology that increase the risk of ASD in a child include: maternal diabetes, obesity, allergies and autoimmune disorders during pregnancy [99-101]. However, all of the listed conditions are associated with an inflammatory response in the body [102-104], which has been discussed previously as a major factor that increases the risk of ASD. So, these conditions are not the root cause of the pathology in a child, but instead, it is a chain of inflammatory reactions caused by these conditions. Moreover, there is indication that the risk of some of these diseases is increased by infection [105,106], and obesity increases the susceptibility to infectious diseases [107]. These examples show that infections and inflammation could be the underlying factors playing a significant role in ASD development.

Heavy Metals Exposure

The theory about the exposure to heavy metals as a risk factor for ASD is controversial. There were several studies that show no association between heavy metals exposure and ASD incidence [108-110]. Moreover, the analyses of the levels of some of these metals in the environment, as well as the mean concentrations of these in the blood children and adults, shows that exposure has been steadily decreasing over time in the USA [111-114]. Particularly, the level of Hg in blood of children aged 1-5 has decreased in the period from 2003 to 2012 by 21% [113]. Another example is the lead level in the blood in a population, which starting from 1960, the level was 60 µg/dL, but it has been constantly decreasing, reaching 5 µg/dL in 2012 [111]. This data does not correlate with the ASD incidence rate, which is reported to have increased exponentially. These findings indicate that lead and mercury concentrations in humans cannot be considered as major etiological factors of ASD.

Focus on Aluminum

Aluminum, which is an adjuvant in some vaccines, is also claimed to be an etiological factor of autism. Several studies showed that the level of aluminum is elevated in patients with ASD compared to healthy controls [115,116]. Although healthy children receive more vaccines than children who later develop autism [117], there are some more arguments against the causal inference between aluminum (from any source) and autism.

First, a certain hematological picture characterizes aluminum toxicity. Namely, it includes decreased levels of hematocrit, hemoglobin, MCV and MCH, low red cell count and elevated iron and calcium concentrations in blood. [118-120]. Studies that include subjects diagnosed with ASD show that autistic children usually have increased red blood cell counts, hemoglobin levels and MCV, normal values of MCH and iron and calcium deficiencies [121-125].

Additionally, most patients with ASD have low serum ferritin levels. Non-autistic patients with low serum ferritin levels, after 2 weeks of oral aluminum load, had significantly increased accumulations of aluminum, while the patients with high serum ferritin did not show any increase in the serum aluminum [126]. This effect is explained by the interconnections of aluminum and iron in the organism; they are carried by the same serum proteins and are stained in bone with the same compounds. Therefore, these elements share some common biological pathways [118]. Nevertheless, this effect does not work in the opposite direction; an increased level of aluminum does not alter serum ferritin level [127]. So, the author concluded that the accumulation of aluminum in body tissues is possible only in patients with low ferritin levels [118].

However, low serum ferritin does not always indicate iron deficiency but usually indicates chronic inflammation [128-130]. This is consistent with the fact that some viral infections result in increased accumulation of aluminum in tissues and blood [131-133].

Additionally, some of the medications often prescribed to children with ASD contain aluminum oxide (e.g. Risperidone) [134]. This, combined with low serum ferritin, may contribute to the difference of aluminum levels observed in ASD children and healthy controls.

ASD is congenital

According to the CDC, “critical period for developing ASD occurs before, during, and immediately after birth” [135]. There are currently several theories regarding the etiology of ASD, but most of them are linked to pregnancy, indicating that the main processes affecting the autistic phenotype occur prenatally.

In a study in which all children born in Denmark from 1980 to 2005 were included, admission to a hospital due to maternal viral infection in the first trimester and maternal bacterial infection in the second trimester was associated with the diagnosis of ASD in the offspring [80]. The diagnosis of ASD in the children studied was determined through nationwide registers. These results support the hypothesis that an early prenatal viral infection increases the risk of ASD and shows the possible role of bacterial infections in the prenatal period as well. This finding was confirmed in a murine study [136]. Pregnant mice were injected with poly (I:C), a substance that induces a similar immune response

to a viral infection. As a result, poly (I:C) injections significantly increased the rate of autism in the offspring, indicating the role of infection during pregnancy and the ensuing maternal immune reaction in the development of ASD.

The broad spectrum of the theories considered shows that the initiation of ASD occurs during pregnancy. Both behavioral and clinical signs and symptoms of ASD manifest in the first months of an infant's life, rejecting the common hypothesis that ASD is a disorder developed by the age of 4 [137,138]. Also, some of the brain alterations commonly observed in ASD children can only be initiated during prenatal brain development. For instance, ASD children have a decreased number of PCs with the absence of empty baskets. PCs are developed only in the prenatal period, so this alteration could take place only in prenatal period.

Conclusion

In this article, we reviewed the studies that supported the role of infection and inflammation in prenatal ASD initiation. Dozens of the papers that describe conducted research find that these different factors of ASD are consistent with each other, and that each of these factors are interconnected to create one comprehensive model of ASD etiopathogenesis. This model explains many of the features observed in ASD, such as atypical brain formation, gene alterations, inflammation, early symptom manifestation and statistical correlations of seemingly unrelated risk factors of the disorder. Overall, we infer that ASD is a congenital disorder resulting from maternal infection during pregnancy, and thus, leading to chronic neurological and systemic inflammation that sets off a chain of events that accumulate into the symptoms that can be observed in ASD children. This etiological understanding of ASD would lead to a more thorough development of preventative measures, early diagnostic tools, and effective treatment to those who are at risk of being afflicted by ASD and those who are already afflicted.

Compliance with Ethical Standards

The study was funded by FLAASK, LLC.
The authors declare that they have no conflict of interest.
This article does not contain any studies with human participants or animals performed by any of the authors.

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