Autism Spectrum Disorder

Subjects: Neurosciences

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Autism spectrum disorder (ASD), schizophrenia, and bipolar disorder are genetically complex and heterogeneous neurodevelopmental disorders (NDDs) resulting from genetic factors and gene-environment (GxE) interactions for which onset occurs in early brain development.

Keywords: autism spectrum disorder ; environment ; immune system

1. Definition and Prevalence

ASD is an increasingly common neurodevelopmental disorder, symptomatically and etiologically heterogeneous, defined by core deficits in social communication and the presence of restricted and stereotyped behaviors [1][2]. In children under the age of five, ASD is the leading cause of disability [3]. Boys are three to four times more prone than girls to developing ASD [4][5].

World-wide large-scale investigations estimate that the global prevalence of ASD is 1–2% [6][7]. More specifically, based on the most recent available statistics from the U.S. Centers for Disease Control and Prevention (CDC), tracking for this since 1996, ASD in the United States affects 1 child in 44 (2021 figure for the year 2018) [8], while the prevalence of ASD in Europe varies from 0.44% to 1.97% of children aged 7–9 years old (i.e., from 1 in 51 children to 1 in 227 children), with an average calculated prevalence of 1.22% (i.e., 1 in 89 children) [9]. In Asia, a meta-analysis of published data found that the pooled calculated ASD prevalence is growing, calculated at 0.36% (i.e., 1 in 278 children) [10].

Apart from current prevalence values, monitoring studies report a rapid rise in ASD prevalence over the past several decades [11]. Indeed, current U.S. data are more than three times higher than the first prevalence estimation of 1 in 150 children between 2000 and 2002 [8]. This increase is not fully explained by the evolution of diagnostic criteria, and the age at which children are diagnosed with ASD remains unchanged, at around 50 months [11]; the increase is rather in favor of a role played by environmental risk factors [5][9].

2. Genetics

Over the past 20 years, despite the extraordinary degree of etiological heterogeneity, the search for ASD genes has been remarkably successful. More than 100 large-effect, rare (often de novo) mutations have been identified in the coding genome. At present, microarray and whole-exome sequencing studies focus on rare variants with convincing statistical support for the association of about a dozen copy number variants (CNVs) and more than 100 genes, a number which is rapidly expanding. More recent studies involving extensive case-control cohorts successfully identified associations with common risk alleles of modest effect, making possible the quantification of cumulative common genetic risks (polygenic risk score) to address polygenic inheritance. Moreover, substantial evidence shows that certain environmental factors could lead to altered epigenetic marks, increasing the risk of neurodevelopmental outcomes associated with ASD and their comorbidities [12][13].

3. Immune Dysfunction

The link between immunogenetics, inflammation, and ASD is particularly well substantiated. For instance, perinatal maternal infections have long been recognized as a prominent risk factor for the development of ASD in the child [14][15][16], raising the potential contribution of early immunological activation [17]. Immune compounds such as cytokines and chemokines and the cells that produce them in the central nervous system (CNS), particularly microglia, are known to have an important function in normal brain maturation [18]. Furthermore, a causal link is demonstrated between ASD and increased cellular production of Interleukin-6 (IL-6) [19][20] and IL-17 [21][22][23] upon immune activation. Increased levels of inflammatory cytokines in cerebrospinal fluid of ASD patients as well as neuroinflammation in post-mortem brain from ASD individuals were also described [19]. In this context, a subset of 35 adult patients with high-functioning ASD present a

chronic natural killer cell inflammatory/activation process, suggestive of cellular hyperactivation [24]. In addition, upregulation of NLRP3 inflammasomes and overproduction of pro-inflammatory cytokines (IL-1β and IL-18) have been described in peripheral blood mononuclear cells (PBMCs) of ASD children compared to controls [25].

Despite existing limitations between human and animal models, preclinical studies significantly contribute to shedding light on molecular and cellular mechanisms that mediate immune-related aspects of normal and pathological brain development [26]. In addition, rodent studies demonstrated that immune dysfunction, including central and peripheral inflammation during perinatal periods (neuroinflammation, increased production of inflammatory cytokines or antibodies, immune cell activation and autoimmunity), impacts the neurodevelopmental trajectory of key circuits in the pathophysiology of ASD [20][27][28][29][30][31][32][33][34]. More recently, both clinical and preclinical studies highlighted the implication of the complement system—a key player in innate immunity—in NDDs, including ASD [35][36]. As a result, a new paradigm has emerged in the field of “immuno-neuropsychiatry”, describing a persistent immunological dysregulation in the pathogenesis of a wide range of neuropsychiatric disorders (for a review, see [37]).

4. Immune System and Environment: A Convergent Point

Recent major breakthroughs in ASD suggest that the immune system acts as a convergence point between ASD-related genetic and environmental risk stressors [38]. The immune system is the connection with the outside world and, as a result, environmental influences that affect the maternal, fetal, and/or neonatal immune pathways could cause distinct neuroimmune alterations in the developing individual [18]. Immune system activation resulting from exposure to pro-inflammatory external compounds during critical periods could cause permanent effects and increase the risk of NDDs, suggesting that inflammation itself represents an early environmental stressor [39].

This leads to the question of how inflammation-related pathways, including autophagy (see below), might be responsible for the impacts of early environmental factors in ASD, especially in the context of genetic susceptibility.

5. Autophagy Disruption and ASD

Converging clinical studies suggest a role for autophagy in ASD etiology:

1. Enrichment analysis indicated that in genome-wide association studies, risk genes for brain disorders, including ASD, are over-represented in autophagy-related pathways identified in gene ontology biological processes [40]. Another observation is the implication of functionally relevant polymorphisms in autophagy-associated genes in the vulnerability to autoimmune and inflammatory disorders known to be associated with ASD [41][42].

2. Whereas no differences were observed in dendritic spine density of childhood post-mortem ASD versus control brains, the decrease in spine density through adolescence was greater in controls (~45%) than in ASD patients (~16%), demonstrating a developmental defect in net autophagy-related spine pruning in ASD [43]. These endophenotypes resemble the “intense world syndrome” describing the autistic brain as hyper-reactive with a hyper-connectivity of local neural circuits. Such complex connections are characterized by exaggerated neural information processing and storage within the brain microcircuits, caused by a higher number of synaptic connections and increased spine density [43][44].

Similarly, in preclinical studies:

1. Impaired microglial autophagy pathways studied in mice led to defective synaptic pruning, which becomes visible by an abnormally high dendritic spine density [45].

2. Interestingly, rapamycin, an autophagy inducer, rescued social interaction impairments in adolescent mice exposed to in utero valproic acid (an inducer of autism-like behaviors) [46]. Indeed, rapamycin also rescued altered gene expression, highlighting the role of autophagy and the mammalian target of the rapamycin (mTOR) pathway in ASD, suggesting the interest in new therapeutic targets involving autophagy modulation [46].

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