Autism Spectrum Disorder (ASD)

Subjects: Clinical Neurology
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Autism Spectrum Disorder etiopathogenesis is still unclear, no effective preventive and treatment measures have been identified. Research has focused on the potential role of neuroinflammation and kynurenine pathway. Pre-natal or neonatal infections would induce microglial activation, with secondary consequences on behavior, cognition and neurotransmitter networks. Peripherally higher levels of pro-inflammatory cytokines, and anti-brain antibodies have been identified. Increased frequency of autoimmune diseases, allergies, and recurring infections have been demonstrated both in autistic patients and in their relatives. Genetic studies, also, have identified some important polymorphisms in chromosome loci related to human leukocyte antigen (HLA) system. The persistence of immune-inflammatory deregulation, would lead to mitochondrial dysfunction and oxidative stress, creating a self-sustaining cytotoxic loop.
Chronic inflammation actives kynurenine pathway with increase in neurotoxic metabolites and excitotoxicity, causing long-term changes in glutamatergic function, trophic support and synaptic function. Furthermore, overactivation of kynurenines branch, induces depletion of melatonin and serotonin, with ASD symptoms worsening.
According to those findings, in subjects genetically predisposed an aberrant neurodevelopment derives by a complex interplay between inflammatory process, mitochondrial dysfunction, oxidative stress, kynurenine pathway overactivation.
To validate the previous hypothesis a new translational research approach is necessary.

Keywords: ASD ; Neuroinflammation ; Kynurenine pathway

1. Introduction

The prevalence of ASD has dramatically increased during the last two decades from 2–5/10,000 to 1:59 children[1][2] with high social and economic impact.

Although ASD etiology has not yet been defined, significant genetic, epigenetic and environmental determinants have been identified.

In particular, genetic analyses have revealed not only a strong genetic basis for ASD, but have also highlighted the complexity of such disorders that cannot be simplistically explained by the paradigm “one mutation-one disease”. Moreover, numerous genome-wide studies have suggested multigene interactions and/or rare as well as noncoding mutations as main players in the autistic thaumatological scenario[3].

In parallel, analyses of the genotype to phenotype relationships in ASD[4], identification of the sequences that co-localize with cell-type-specific regulatory regions[5] and the application of bioinformatics tools[6] have paved the way to proteomic analyses in autism. Today, numerous autism-related proteins have been identified and are the object of intensive research efforts in order to understand the phenotypic risks for autism. Examples are MeCP2 protein (methyl CpG binding protein 2)[7], reelin protein[8], and CNTNAP2/CASPR2 (Contactin-associated protein-like 2 protein)[9][10].
Immune activation and prenatal exposure to toxins such as thalidomide and valproic acid have been considered environmental factors contributing to idiopathic ASD[11]. Advanced parental age, low birthweight, preterm delivery, and low Apgar scores were also reported to be the few factors more consistently associated with autism [12].

Clinically, altered neurodevelopment during the first and second trimesters of prenatal life is believed to be an underlying neuropathological cause of ASD. Post-mortem studies have unveiled neuroanatomic and cytoarchitectonic aberrations in various brain regions, including cerebellum, hippocampus, inferior olivary complex, amygdala, entorhinal cortex, fusiform gyrus, and anterior and posterior cingulate cortex, with increased growth of the frontal lobes, thinner cortical minicolumns, and increased dendritic spine density[13]. These aberrations appear to be related to alterations occurring during early pregnancy, such as reduced programmed cell death and/or increased cell proliferation, altered cell migration, abnormal cell differentiation with reduced neuronal body size, abnormal neurite sprouting, and pruning, that cause atypical wiring into the brain. In addition, because neurodevelopmental processes are still active into late prenatal and postnatal life, aberrations involve reduced synapse formation and delayed myelination[14]. The observed abnormal neuronal wiring was

previously thought to be characterized by long-range hypo-connectivity and local hyper-connectivity. Recent studies have, instead, shown that abnormal neuronal wiring is characterized by a highly individualized combination of hyper- and hypo-connectivity specific to each ASD patient[15][16].

Despite years of studies, the etiopathogenesis still remains unclear. Consequently, no effective preventive and treatment measures have been identified. In the last decade, an increasing body of research has focused on the potential role of inflammation, oxidative and nitrosative stress, mitochondrial dysfunction and dysregulation of the tryptophan catabolite (TRYCATs) pathway in the onset of psychiatric disorders[17][18][19]. Although the association between inflammation, oxidative stress and mitochondrial dysfunction has been repeatedly demonstrated, understanding the primary mechanism and the predominant pathway associated with specific psychiatric symptoms remains uncertain.

2. Immune System and ASD

The immune system plays an important role in neurodevelopment at multiple neurobiological levels. An aberrant inflammation response, in the very early stage of brain development, determines focal or diffuse neurological damage, and leads to subsequent mental disorder.

Researchers propose ASD to be the result of a complex interplay between genetic susceptibility and environmental predisposition. Researcher's model is based on the hypothesis that, in individuals genetically predisposed and in the presence of specific environmental conditions, a new infection or a reactivation during gestational and/or perinatal age would trigger an abnormal inflammatory response. The inability of the immune system to reduce itself (either because it is immature or because genetically predisposed not to be self-tolerant), induces a cascade of events, which involves, like a domino effect, other biological pathways. The net result is the chronicity of the inflammatory process, through activation of a self-sustaining and self-amplifying “auto-toxic loop” between mitochondrial dysfunction, oxidative stress, and Kynurenine pathway leading, eventually, to an aberrant neurogenesis. As broadly reported, an increased release of pro-inflammatory cytokines mediates:

(1)a cascade that “sensitizes” the immune system with subsequent changes in cellular proliferation, activation of microglia and further increases in pro-inflammatory cytokines downstream;

(2)increase of ROS and RNS, which leads to oxidative stress and further tissue damage;

(3)mitochondrial dysfunction responsible for bioenergetic impairment and consequently neural suffering;

(4)activation of Kynurenine pathways with an increase in neurotoxic metabolites and excitotoxicity causing long-term changes in glutamatergic function, trophic support and synaptic function.

These considerations may have therapeutic implications since it is already possible to interfere with TRP metabolism with medication that has already been found to be effective (high dose melatonin, memantine) or by experimenting with KP enzyme inhibitors to lower QUIN levels as new potential symptomatic drugs[20]. Enzymes in the KP are indeed druggable, IDO inhibitors are in various stages of development to treat cancer, and KMO inhibitors have already been found to be effective in preclinical models of neuropathic pain[21].

However, as outlined in the introduction, ASDs refer to a complex and heterogeneous pool of molecules and conditions and it is likely that additional factors play a secondary role in modulating the severity of disorders. Why do individuals develop a specific disease rather than another? Is it possible that the development of a specific psychiatric symptom is associated with a massive involvement of a specific biological pathway?

The major or minor involvement of one or more brain areas is probably responsible for the huge symptom variability observed in affected individuals and it is also conceivable that the role of each pathway in the pathogenesis of mental disorders is potentiated when they act simultaneously.

To better interpret the role of neuroinflammation and Kynurenines in neurodevelopment and to validate the hypothesis previously described, a wide translational research approach is necessary to examine, collectively and simultaneously, epidemiology, genetics, oxidative stress, mitochondrial dysfunction, Kynurenine metabolism and immune deregulation. Such an approach could be able to obtain robust data to clarify underlying pathological processes and identify specific therapeutic targets.

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