Brain-Derived Neurotrophic Factor Role in Autism Remains Elusive: A Flashback on the Route That Has Brought Us Here

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Autism is a neurobiological developmental disorder, characterized by an array on neurobiological findings as well as a wide range of somatic co-morbidities that justify a close neurophysiological and clinical follow-up on them. The DSM-5 suggests a dyad for Autistic Spectrum Disorders (ASD), the deficit in social communication and restricted interest or repetitive behaviors. The most common neurologic findings in terms of CNS are repetitive movements, motor stereotypies and impaired cerebral functioning and muscle tone. These are often exacerbated by anxiety, depression, sleep disorders, communication impairments and accompanying medical problems, even drug interactions.

Cognitive impairment and intellectual disability is seen in up to 80% of ASD patients and are considered a result of generalized developmental delay but not restricted to it. In fact, the presence of cortical electrical aberration commonly manifested as epilepsy or subclinical epileptiform discharges is associated with cognitive deficit in these patients (1). There is strong genetic evidence for an underlying common mechanism for epilepsy and ASD that could explain the concurrence of these conditions and the frequent appearance of both in syndromic mutations like, fragile X syndrome and tuberous sclerosis.

Attention Deficit Hyperactivity Disorder (ADHD) is a common co-existing condition in ASD patients with overlapping symptoms like difficulty paying attention and deficit in social interaction and in some case of ADHD even repetitive movements. It is even possible that ADHD and Autism are overlapping traits of a more comprehensive pervasive dysfunction.

Autonomic dysfunction in ASD patients is a major culprit, often missed, for anxiety, mood disorders, and even GI symptoms. Disruption of the hypothalamic-pituitary-adrenal (HPA) axis can precipitate the hyper sympathetic symptoms. The HPA axis, often affected by environmental toxins, is implicated in neural development in fetal brain development.

Metabolic abnormalities in terms of mitochondrial disorders and channelopathies are increasingly recognized as the underlying cause or contributory factor in epilepsy or the ASD itself. Mitochondrial activities crucial for immune function further put a spin on the notion as maladaptive behaviors tend to aggravate during episodes of inflammation/infection.

The result of a GWAS study in the Lancet 2013 revealed single nucleotide polymorphisms (SNPs) of four loci to be associated with five major neuropsychiatric disorders, ASD, ADHD, bipolar disorder (BD), schizophrenia (SCZ) and major depressive disorder (MDD) (2). The current opinion is now moving beyond descriptive approach to neurobiological disorders, finding common genomic, proteomic or metabolomics backgrounds for groups of disorders.

The Brain-Derived Neurotrophic Factor (BDNF) is a member of neurotrophin growth factor family with molecular and anatomical associates in the regulation of brain plasticity and early brain development, especially in the hippocampus and prefrontal area. The hippocampus pre-epileptic spikes and dysfunction of the prefrontal cortex are responsible for seizures and affective disorders observed in ASD. Binding of BDNF to the TrkB on both presynaptic and postsynaptic sites augments signal propagation and synaptic plasticity in the long run. The excitatory activity of BDNF is counter-regulated by FMR1/FMRP and TSC1/2 mutated genes of interest in Fragile X syndrome and Tuberous Sclerosis. This explains the prevalence of epileptic symptoms in ASD patients. The p75 pathway culminates in NF-kB activation and can trigger apoptosis signals in neuronal cells. Evidence supports the role of neuroinflammation in ASD with the presence of maternal anti-fetal brain antibodies, elevated proinflammatory chemokines in brain specimen and CSF and elevated microglial expression of NF-kB in anatomically affected brain

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regions.

BDNF polymorphism Val66Met (rs6265) at exon 66 has been widely investigated in ASD, epilepsy, anxiety, ADHD, MDD, BD, and SCZ. This variant modulates BDNF secretion by upsetting the release of mature protein.

While many studies have found elevated levels of BDNF in ASD (3), some have reported non-significant or lower levels (4). The sensitivity and specificity of BDNF in early ASD detection is 81.7% and 66.9%, respectively (4). We demonstrated by meta-analysis, a significant higher BDNF level subgroup of ASD patients with severe or atypical form of the disease (5). BDNF downregulation might be responsible for the extensive loss of dendritic spines in prefrontal cortex in mouse models of SCZ (6).

As outlined above, increased serum levels of BDNF might account for the increased prefrontal cortex volume. In fact, an asymmetry in prefrontal to occipital cortex function has been proposed as a neuro-psychosocial signature for early ASD even in the absence of increased prefrontal white matter volumes. Moreover, polymorphisms in this region reflect differently in hippocampus developmental delay caused by antenatal maternal anxiety (7). We are thus able to postulate that BDNF levels during infancy and early childhood, affect neuronal development.

Serum BDNF levels are also associated with the severity of epilepsy. The Val/Val haplotype of the Val66Met variant is associated with elevated BDNF serum level and disease severity in ASD and epilepsy and is particularly associated with intellectual disability, a feature attributed to epileptiform cortical discharges, are ASD patients.

BDNF overexpression can structurally modify dentate mossy fibers, creating a pro-epileptic circuit in mouse hippocampus (8); further supporting the above notion of common underlying pathogenesis for ASD and epilepsy. The Val66Met variant might also confer risk for developing benign epilepsy with centrotemporal spikes (BECTS) (9).

The BDNF can shade a light over common pathological aspects of other associates of ASD phenotype. Early reports found the Val66Met variant to affect the risk of hypoxia-induced schizophrenia, as an obstetric complication. Elevated BDNF levels, hinders synaptic maturation and affects brain plasticity mechanisms associated with the onset of SCZ as mentioned above (6). While ASD and childhood-onset SCZ may appear to have discrete clinical features, a mouse model of neuroinflammation suggested shared initiating mechanism of ASD and SCZ with non-specific prenatal inflammation by gram-negative or viral infections, yields to an inflammatory phenotype in maternal blood and amniotic fluid. Meanwhile, persistent inflammation rather than latent inflammation favors the evolution of ASD rather than SCZ (10). Although the concurrence of ASD with childhood-onset SCZ is rare, research shows that up to 61% of adult SCZ patients have autistic-like traits (10). The prevalence of autistic traits in bipolar disorder is even lower (about 50%) than SCZ, and the results of meta-analyses indicate a lack of genetic polymorphism association of BDNF in BD and SCZ in meta-analyses (11), with low plasma serum levels of BDNF as a rather consistent finding in SCZ and BD patients (12). Meanwhile, the minor, low yield allele of Val66Met confers a risk for the early-onset bipolar disorder. BNDF variants can, however, affect predisposition to antipsychotic weight gain in both SZC and BD (12). Autonomic dysregulation is a common comorbidity is ASD patients with a preponderance of sympathetic modulation, which renders them susceptible to orthostatic changes. The Val/Val variant of BDNF correlates with the male hyperfunction of the HPA axis while female lower serum BDNF associates with aberrant stress-induced HPA hyperfunction. Interestingly, BDNF knockdown mice represented the increased basal tone of HPA activity (13). The HPA axis, in turn, provides a link for epistatic interactions of environmental stress stimuli in favor of reduced brain plasticity in the hippocampus (7). These inconsistent results should be further interpreted, in terms of male/female and early adulthood homeostasis vs. early life/infancy role of BDNF expression, to clarify a possible underlying BDNF related pathology for HPA axis dysregulation in ASD.

According to the DSM-5, autism is no longer an exclusion criterion for diagnosing ADHD+ASD and overlapping ADHD occurs in up to 30% of patients with ASD (14). A higher serum BDNF level has been reported in ASD patients with only trend significance in females. Cadherin-13 is a negative regulator of hippocampal inhibitory synapses and can provide additional insight into the common pathogenesis of ADHD and ASD (15).

These lines of evidence are suggestive of an underlying common pathological mechanism; involving brain neurotrophins; by 1- Disrupting early neuronal and synaptic maturity in hippocampus and prefrontal cortical as well as other brain areas. 2- Induction of aberrant prenatal cortical development with pre-epileptiform circuits and defective visual attention and interpretation 3- Aberrant hypothalamic and adrenal response to environmental stimuli which in turn disrupts brain development in response to stress.

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