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Review article

Epilepsy associated with autism and attention deficit hyperactivity disorder: Is there a genetic link?

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Abstract

Autism Spectrum Disorders (ASDs) and Attention Deficit and Hyperactivity Disorder (ADHD) are the most common comorbid conditions associated with childhood epilepsy. The co-occurrence of an epilepsy/autism phenotype or an epilepsy/ADHD phenotype has a complex and heterogeneous pathogenesis, resulting from several altered neurobiological mechanisms involved in early brain development, and influencing synaptic plasticity, neurotransmission and functional connectivity. Rare clinically relevant chromosomal aberrations, in addition to environmental factors, may confer an increased risk for ASDs/ADHD comorbid with epilepsy. The majority of the candidate genes are involved in synaptic formation/remodeling/maintenance (*NRX1, CNTN4, DCLK2, CNTNAP2, TRIM32, ASTN2, CTNTN5, SYN1*), neurotransmission (*SYNGAP1, GABRG1, CHRNA7*), or DNA methylation/chromatin remodeling (*MBD5*). Two genetic disorders, such as Tuberous sclerosis and Fragile X syndrome may serve as models for understanding the common pathogenic pathways leading to ASDs and ADHD comorbidities in children with epilepsy, offering the potential for new biologically focused treatment options.

Keywords: Epilepsy; Autism spectrum disorders; ADHD; Comorbidity; Genetics; CNVs; Tuberous sclerosis; Fragile X syndrome

1. Introduction

Epilepsy is one the most common neurological disorders of childhood, occurring in 3.5–6.5 per 1000 children [1], and may be associated with several neurodevelopmental disorders, including intellectual disability (ID), attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASDs) [2].

ASDs symptoms may occur in 15–35% of children with epilepsy [3–5]. Epilepsy is estimated to affect 7–46% of patients with ASDs [6–8], occurring more frequently in those subjects presenting also an ID [9]. All seizure types have been reported in ASDs, but focal epilepsy seems to be prevalent [10]. Children and adolescents with epilepsy tend to show an increased risk of ADHD, which is present in 12–70% [11–13]. Overall, these findings suggest a strong interrelationship between the ASDs/ADHD phenotype and childhood epilepsy. Despite current classification systems (ICD-10, DSM-IV) [14] do not allow for a comorbid diagnosis of ASDs and ADHD, in the ASDs population 40–70% of individuals meet full ADHD diagnostic criteria [15,16]. Autistic-like communication and social deficits are evident in 28–62% of ADHD children [17]. These rates of co-occurrence are higher than expected for coincidental findings, making it unlikely that ASDs and ADHD are two independently occurring conditions.

The co-occurrence of an epilepsy/autism phenotype or an epilepsy/ADHD phenotype has a complex and heterogeneous pathogenesis, resulting from several

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altered neurobiological mechanisms involved in early brain development, and influencing synaptic plasticity, GABA transmission and functional connectivity [2]. It is likely that rare clinically relevant genetic aberrations, in addition to environmental factors, may confer an increased risk for ASDs/ADHD associated with epilepsy [2,18].

We reviewed the pathogenic mechanisms behind the high rate of comorbidity between epilepsy and ASDs/ADHD and provided an overview of new data from genetic models that have the potential to clarify this co-occurrence.

2. Search strategy and selection criteria

Information in this Review is mainly based on peer-reviewed medical publications from 1974 to 2012 (PubMed). The selection criteria utilized were the novelty and importance of studies, and their relevance to general medical doctors and child neurologists. Only articles published in English were reviewed. The filters included "epilepsy", "autism", "autism spectrum disorders", "attention deficit hyperactivity disorder", for the identification of studies reporting on a comparison of these neurodevelopmental conditions, and "molecular genetics", "CNV", "SNP" for the genetic data.

3. Genetic links

Different alterations of genes involved in neurodevelopment may result in common biological mechanisms that lead to complex neuropsychiatric phenotypes. Conceptually, during intrauterine brain development or at an early stage in life, common molecular pathways may disrupt developmental trajectories leading to abnormalities in neuronal migration, cortical organization and, finally, in synaptic and dendritic functions [19]. An example is represented by in the *AUTS2* locus, involved in neurodevelopment, in which nucleotide changes could lead to several neurological diseases, including autism, ADHD, epilepsy, dyslexia, motor delay, language delay, visual impairment, microcephaly, and alcohol consumption [20].

Candidate genes associated with childhood epilepsy and ASDs/ADHD comorbidity are reported in Table 1. The majority of these genes are involved in synaptic formation/remodeling/maintenance (*NRX1* [21–23], *CNTN4* [24], *DCLK2* [25,26], *CNTNAP2* [27–29], *TRIM32* [25], *ASTN2* [25], *CTNTN5* [25,30], *SYN1* [31,32]), neurotransmission (*SYNGAP1* [33], *GABRG1* [34], *CHRNA7* [29,34–36]) or DNA methylation/chromatin remodeling (*MBD5* [37,38]).

GABAergic interneurons are involved in maturation and wiring of proper networks, in the regulation of critical period experience-dependent cortical plasticity, and in the control of minicolumns functions [39–41]. Alteration in neocortical experience-dependent maturation leads to an abnormal plasticity, and may significantly contribute to cognitive and behavioral impairments. This process is severely impaired in *Ube3a* deficient mice models of Angelman syndrome (OMIM #105830), a genetic entity characterized by ID, ASDs in one-half of cases, epilepsy, and ADHD [42,43]. Altered [GABA]/[glutamate] ratio has been evidenced in the frontal lobe of autistic patients, with respect to controls [44]. Moreover, SPECT studies showed a GABAergic system disturbance in the superior and medial frontal cortex, brain regions involved in several aspects of the Theory of Mind [45]. Hyperglutamatergia and other neurometabolic abnormalities have been demonstrated in pregenual anterior cingulate cortex of pediatric ASDs patients, with possible right-lateralization [46]. Moreover, Dopamine D(4) receptors seem to control the excitatory synaptic strength in local-circuit neurons and GABAergic inhibition in the prefrontal network, underlining the role of D(4) receptors cognitive processes associated with ADHD [47]. Abnormal excitability and disrupted synaptic plasticity in the developing brain may account both for epilepsy and its comorbidities [48,49].

Decreased cortical expression of the two isoforms of glutamic acid decarboxylase (GAD), GAD65 and GAD67, has been observed in autistic brain samples [49,50]. The importance of GAD65 for synthesis of GABA destined for extrasynaptic tonic inhibition, regulating epileptiform activity, was demonstrated in knockout mice models [51].

Dlx homeobox genes, including *Dlx1* and *2*, encode for transcriptor factors important for specification, maintenance, and migration of interneurons in the adult brain. $Dlx^{-/-}$ mice shown a selective alteration in the dendritic morphology of interneurons and their progressive death, with onset of generalized electrographic seizures [52]. *DLX1* and *DLX2* genes are located in 2q32 band, a region associated with autism susceptibility; Single Nucleotide Polymorphisms (SNPs) of these genes have been documented in multiplex ASDs families [53].

ARX mutations, related to ID, epileptic encephalopathies and, rarely, autism [54] is essential for GABAergic interneurons migration, and is a direct downstream target of Dlx2 [55]. A decreased GABA receptor signaling has been documented in Fragile X syndrome, with a consequent imbalance between excitatory and inhibitory systems [56]. Finally, a selective ablation of Mecp2 from interneurons, causes many features of Rett syndrome and autistic behaviors in mice models [57].

With the advent of whole-genome association studies, several single nucleotide polymorphisms (SNPs) and copy number variants (CNVs) have been associated to ID, ASDs, ADHD, epilepsy and a constellation of other neuropsychiatric disorders. A list of several syndromic conditions associated with chromosomal aberrations are summarized in Table 2. The co-occurrence of