Review

Causes & Prevalence

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Autism with epilepsy: A neurodevelopmental association

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Abstract

Introduction

The association between Autism Spectrum Disorders (ASD) and epilepsy has been extensively documented and the estimated prevalence varies, depending upon the selected population and the clinical characteristics. Children with early-onset epilepsy and early brain damage have a higher risk of presenting ASD compared to those without epilepsy. Genetic abnormalities are likely implicated in the association of ASD and epilepsy, although these abnormalities are currently detectable in only a small percentage of patients. Copy number variants (CNVs) with a low rate of occurrence (so-called rare variants) have been found to be implicated in these conditions as well. Furthermore, some genetic and medical conditions are associated with ASD and epilepsy. Currently the co-occurrence of autism and epilepsy is conceptualized as the result of common abnormal neurodevelopmental pathways. Synaptic dysfunction is likely to be involved in both disorders, as observed in preclinical models. There is no specificity of seizure type to be expected in children and adolescents with ASD compared to other neurodevelopmental disorders or epileptic syndromes. Treatment options include developmentally-based early interventions for ASD and medications for epilepsy. The aim of this article is to provide a brief overview of current research on the association of autism with epilepsy, from molecular basis to clinical characteristics.

Conclusion

Common neurodevelopmental pathways are probably at play in the association of autism with epilepsy. Synaptic abnormalities and genetic variations have been shown to be implicated in this complex condition.

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Introduction

Autism Spectrum Disorders (ASD) and epilepsy are frequently associated and the rates of co-occurrence vary greatly in relationship to the selected population and concomitant predisposing factors[1].

Recent studies have reported significant differences, especially in cognitive levels. In a meta-analysis on this association, epilepsy was concomitant with ASD in 21. 5 % of patients with a type ASD who also had an Intellectual Disability (ID), in a pooled estimate, compared to a much lower prevalence of 8% in subjects without an ID[2].

A later meta-analysis evaluating the occurrence of epilepsy in ASD detected a prevalence of 8.9% in individuals over the age of 12 yrs without an ID, and a higher prevalence of 23.7% in individuals over the age of 12 years with an ID[3]. In the opposite association, children with early-onset epilepsy are also at a higher risk for presenting ASD compared to those without epilepsy.

In a population-based study of children with the onset of epilepsy in the first year of life, an elevated risk of ASD was found in those with infantile spasms secondary to a previous pathology[4]. Another study found that 5% of children with epilepsy in childhood also had ASD. Again, in this study infantile spasms were identified as predisposing factors and an ID was the other relevant factor associated with epilepsy and ASD. Furthermore, in patients with normal cognitive levels, the prevalence of ASD was 2.2%, still higher than that in the general population, thus confirming the pathogenic association between ASD and epilepsy[5].

Currently, the co-occurrence of ASD and epilepsy is seen as the result of common abnormal neurodevelopmental pathways.

There is evidence that shared mechanisms are responsible for the co-occurrence of epilepsy, autism, and ID[6,7] and the mechanisms that lead to epilepsy may also negatively interfere with social development and overall cognition. These basic mechanisms and the pathways involved in social and cognitive dysfunctions in ASD, with or without epilepsy, are still under intense investigation.

The aim of this paper is to describe the association of autism with epilepsy and detail the relevant genetic and synaptic abnormalities that are involved in the complex association of autism with epilepsy.

Discussion

The author has referenced some of its own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed.

All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Genetic underpinnings of ASD with epilepsy

The genetic abnormalities of the association of autism and epilepsy fall within the overall pool of abnormalities of ASD. Cytogenetic studies have identified recurrent, maternally

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inherited duplications of chromosome 15q11-13, which along with other rare chromosomal abnormalities is still considered to be an important cause of ASD. Furthermore, individual genes of major effect, such as NLGN4, NRXN1, and SHANK3, have been identified by array-based methods. Although they collectively account for an estimated 15% of cases, variants at these and other loci are detected in no more than 1% to 2% of children with an ASD. In addition, it must be mentioned that these variants have been observed not only in individuals with ASD but also in patients with an Intellectual Disability (ID[8]. Currently in a large percentage of patients with ASD, with or without epilepsy, there are still no detectable genetic defects and diagnosis is made solely on clinical grounds.

Copy number variants (CNVs; e.g.microdeletions, microduplications, insertions) and single gene disorders have been found to be associated to ASD. CNVs that occur infrequently, so-called rare variants, have been found to be implicated in these conditions[9]. According to a current hypothesis[10], common diseases are the result of multiple rare variants that have great functional effects. This is the case in autism and epilepsy, which both present a marked heterogeneity, and in which a number of rare variants would lead to multiple phenotypes. Further evidence of the importance of the search for rare variants has been found in the disease genes discovered to be closely related to ASD. As many as 103 disease genes have been described as related to ASD, includingSHANK3, CNTNAP2and NLGN4X, and many of them are also implicated in epilepsy[11] (Table 1).

Single gene disorders known to be associated with ASD, such as Fragile X Syndrome (FMR1), 22q13 Deletion Syndrome/Phelan-McDermid Syndrome, Rett Syndrome (MECP2), and Tuberous Sclerosis (TSC1, TSC2), are associated with epilepsy in various but significant percentages[12,13,14,15] (Table 2).

For example, 22q13 deletions/SHANK3 mutations (Phelan-McDermid Syndrome) suggest that the haploinsufficiency of SHANK3 can cause a single gene form of ASD with a frequency of 0.5% to 1%. The clinical phenotype of SHANK3-haploinsufficiency is characterized by neonatal hypotonia, absent or severely delayed language, minor dysmorphic features, gastrointestinal disease, renal abnormalities and ASD. In addition, seizures and epilepsy are present in about 30% of individuals[16].

Although these syndromic ASDs have diverse genetic origins and phenotypes, and they account only for a small fraction (approximately1-2 %) of the whole ASD spectrum, they share common intermediates in the signalling pathways that are probably implicated in synaptic abnormalities and their association with epilepsy.

To further analyse the association of autism with epilepsy, multiplex ASD families were studied, providing significant results. In a recent investigation the prevalence of epilepsy was 12.8% in individuals with ASD and 2.2% in siblings without ASD. The risk of epilepsy in multiplex autism was significantly associated with ID, but not with gender.

In addition, genetic or non-genetic identified risk factors of autism tended to be significantly associated with epilepsy. When children with prematurity, pre- or perinatal insult, or cerebral palsy were excluded, a genetic risk factor was reported for 10.2% of children with epilepsy and 3.0% of children without epilepsy ($P = 0.002$).

Furthermore, the epilepsy phenotype co-segregated within families ($P < 0.0001$). As a result, epilepsy in multiplex autism likely has significant genetic components and it may define a different subgroup of clinical characteristics and genetic risks[17].

Excitation/Inhibition(E/I) imbalance in ASD and epilepsy

The co-occurrence of epilepsy, autism, and ID is probably the consequence of functional abnormalities of neurons disrupting the normal balance between excitation and inhibition, interfering with neural functioning[6,7]. An altered balance between excitatory synapses, mostly expressed by glutamate transmission and inhibitory GABAergic synapses, could affect social cognition during development, as well as a predisposition to epilepsy[18].

Molecular abnormalities in synaptic structures and functions in ASD and epilepsy involve neuroligins and neurexins, proteins that are crucial for aligning and activating synapses along with the SHANK3 scaffolding protein. Multiple genes can contribute to the disruption of GABAergic interneuron development, which may be a point of convergence for both autism and epilepsy. Mutations in GABAA receptor subunit genes have been associated with ASD. The genes coding for the three GABAA receptor subunits α5, β3 and γ3 (GABRA5, GABRB3 and GABRG3, respectively) are located on the 15q11chromosome, and single nucleotide polymorphysms (SNPs) in these genes have been associated with ASD[19].

Neurexins (NRXNs) are presynaptic proteins that bind their postsynaptic counterparts, the neuroligins (NLGNs). NRXN-NLGN signalling is consistently involved in postsynaptic differentiation and it controls the balance of inhibitory GABAergic and excitatory glutamatergic signalling. Mutations and chromosomal rearrangements in NRXN1, one of the three genes coding for neurexins, have been associated with ASD[20].

Recently, it has been shown that NRXNs can bind not only NLGNs but also GABAA receptors[21], with the result of decreasing GABAergic transmission. NLGN1, NLGN4X and NLGN4Y neuroligins are localized at glutamatergic synapses, while NLGN2 is located in GABAergic synapses. Mutations in NLGN1, 3 and 4X genes have been identified in ASD and two X-

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Table 1: Altered genes in ASD with epilepsy. Modified by Amiet 2013 and Betancur 2011.

Gene	Locus	Type of mutation	Transmission	Molecular abnormalities
SCN1A	2q24	Point mutation	De novo	Na-channel
SCN2A	2q23–q24.3	Deletion	De novo	Na-channel
KCNMA1	10q22	Point mutation	Dominant inheritance	K-channel
NLGN4X	Xp22.31	Point mutation	Inherited	Synapse formation
NRXN1	2p16.3	Deletion Point mutation	Recessive inheritance De novo	Synapse formation
CNTNAP2	7q35	Deletion Point mutation	Recessive inheritance De novo	Synapse formation
SYNGAP1	6p21.3	Point mutation	De Novo	Synapse RasGAP
ARX	Xp22.13	Duplication	Inherited De novo	Aristaless-related homeobox protein

linked neuroligin mutations have been associated with familial ASD[22].

All these studies highlighted abnormal synaptic GABAergic signaling, establishing the vanguard of current research on molecular abnormalities in ASD and epilepsy.
Alterations of neocortical minicolumns (namely, morphological changes of GABA interneurons associated with reduced width of minicolumns) have been demonstrated in ASD. Minicolumns are anatomically characterized by vertical arrays of pyramidal neurons with dendrite and axon projections. Pyramidal cell arrays are accompanied by their GABAergic interneurons that establish synapses with pyramidal cell bodies, axons and dendrites. A narrowing of these cortical minicolumns has been demonstrated in ASD patients.

It was hypothesized that this reduced intercolumnar distance was dependent on structural/anatomical defects in GABAergic interneurons surrounding principal pyramidal cortical neurons[23,24]. In addition, a significant decrease in GABAA receptor α4, α5, β1 and β3 subunits[25] in ASD brains has been observed.

GABAB receptors were also reduced in restricted regions of the cerebral cortex from ASD patients. However, current research in humans is still at the stage of preliminary investigations. Advanced neuroimaging techniques are developing this field. For example, ^{1}H-magnetic resonance spectroscopy (^{1}H-MRS) is a non-invasive neuroimaging technique that allows for the estimation of specific in vivo neurochemical metabolites of GABA.

In a recent study, creatine-normalized $GABA^+$ ratios ($GABA^+/Cr$) were measured in a group of 17 children with ASD, and in a control group of 17 typically developing children, for motor, auditory and visual regions of interest. In the ASD group, deficits in $GABA^+/Cr$ were demonstrated at approximately 11% in motor regions and at approximately 22% in auditory regions[26]. These findings support a model of regional brain differences in $GABA^+/Cr$ in ASD with an imbalance in the inhibitory component.

Clinical characteristics of epilepsy in ASD

On clinical grounds, the occurrence of seizures in children and adolescents with ASD is unpredictable, and seizures typically occur in otherwise healthy children/adolescents.

The exception is the occurrence of early onset seizures in infants that have an early epileptic syndrome and who later develop an ASD. Seizures appear as an additional clinical burden to ASD in the first case and, as a rule, neither trigger factors nor concomitant relevant events are identified. Epilepsy is an additional problem in ASD that must be considered by clinicians and family members, since some interventions should be made readily available to the child[1,27]. A set of assistance measures should be explained to the family, including emergency and prophylactic norms that are the same as those used in the general care of children with epilepsy.

In the evolution of seizures, the causes and clinical course remain elusive and they are not helpful in the choice of treatment, nor in clinical consultation. Seizures are heterogeneous and they vary individually, as any kind of seizure may appear in young people with ASD with an unpredictable course.

There is a wide range of possible evolutions, from rare to only one lifetime seizure, or to intractable epilepsy, as is commonly found in epilepsy without autism. Thus, caution is always warranted in management and outcome prediction in each individual case. Epilepsy is a further burden for ASD individuals with already varying degrees of adaptive difficulties, warranting a careful approach by clinicians.

Epileptiform abnormalities without seizures are as frequent as 20-30% in individuals with ASD and epilepsy, however, their role in the development of the nuclear disturbances of autism is controversial[7].

Paroxysmal epileptiform abnormalities are thought to be involved in cognitive disturbances and in the social core difficulties of ASD, but the issue is still unclear. An initial overgrowth of white matter in the first 2 years of life is followed by arrested/abnormal growth of the dendritic tree.

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Table 2: Known genetic syndromes with ASD and epilepsy (modified by Abrahams and Geschwind, 2008).

Genetic Syndrome	Genes	% with ASD	Seizures	Intellectual Disability
Rett	MECP2	80%	++++	yes
Fragile X	FMR1	25%M – 6%F	++	yes
TuberousSclerosis	TSC1, TSC2	20%	+++++	yes
22q13.3(Phelan-Mc Dermid Syndrome)	SHANK3	80%	+++	yes
Angelmann or 15q dup	UB3A	40%	+++	yes
Cortical Displasia Focal epi	CNTAP2	70%	+++++	yes

In ASD, reduced dendritic connections are probably implicated in limiting widespread paroxysms and may be a plausible explanation for the high prevalence of epileptiform abnormalities without seizures[28].

Consistent with this hypothesis, neuroimaging with MRI tensor imaging methods and fMRI investigations have shown reduced/abnormal connectivity between several areas of the brain, further supporting the hypothesis of underconnectivity between cortical areas[29].

The relationship between epileptiform abnormalities and diagnosis, history of regression, communication skills, and other features associated with ASD has been investigated. Interestingly, a higher incidence of epileptiform activity was found in children with stereotypies and aggressive behaviour. The incidence of epileptiform abnormalities was significantly lower in higher functioning ASD individuals compared to autistic patients with ID. In this study, the overall increasing severity of symptoms was associated with a higher frequency of epileptiform abnormalities[30].

Autism with regression and epilepsy

Autism with regression has been reported in one third of children with ASD, in those with previously normal or nearly normal development who later developed the typical social and language impairments of autism. This condition is characterized by the loss of language, usually at the stage of single words, and social withdrawal during the second to third year of age in the absence of apparent concomitant emotional or environmental factors, without antecedents of specific pathologic events.

In a percentage of these children, a so-called autistic epileptiform regression occurs, associated with epileptic disorders. The Continuous Spikes and Waves during Slow-wave Sleep syndrome (CSWSS) and Landau-Kleffner (LKS) syndrome are two rare epileptic encephalopathies that share common clinical features, including seizures and regression with autistic features[31].

Interestingly, many genetic abnormalities found in this study (e.g. CNTNAP2, CTNNA3, DIAPH3, GRIN2A, SHANK3 etc.) are those that have been associated with ASD or language impairment, underscoring the overlapping of these disorders at both the clinical and genetic levels. The relationship of autistic regression to epilepsy or to epileptiform EEG findings is still unclear and needs more research, since some studies have reported higher rates of epilepsy and epileptiform abnormalities in children with ASD and regression, while others did not find significant relationships[30,32].

Interventions in ASD and Epilepsy

With respect to intervention in children with the association of ASD and epilepsy, there is a growing concern about appropriate treatment, especially at a young age. In the global approach to interventions in children with ASD, programs for improving social cognition and social skills should be started quickly after diagnosis since it has been observed that early interventions can consistently modify the development of these children.

Current research on early intervention in ASD has highlighted that children who have received a developmentally-based intervention for ASD (namely, the Early Start Denver Model) have shown significant improvements in IQ, adaptive behaviour, and overall autism symptoms. Conversely, an untreated group showed greater developmental delays, including less adaptive behaviour; improvements in core social abnormalities were also reported in these children, albeit to a lesser extent[33].

In a later study by the same authors, a normalization of EEG brain activity was demonstrated in ASD children, measured by event-related potentials and spectral power analysis[34]. However, this study involved children with ASD who were not affected by epilepsy, thus caution is warranted in extending these results to include children with both disorders. When seizures occur in ASD, antiepileptic medications must be administered according to clinical features and current guidelines for epilepsy. Careful supervision to guarantee treatment compliance and the safety of patients is warranted.

There is evidence that valproate, lamotrigine, and levetiracetam are the most effective and tolerable medications for individuals with ASD. Among the specific treatments for genetic and metabolic syndromes associated with ASD and seizures, there are still only a few studies of the effectiveness of treatments for seizures[35].

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Furthermore, antiepileptic medications have been used for targeting the common epileptiform abnormalities in ASD and for treating some behavioural symptoms of ASD, such as irritability. In a meta-analysis on seven studies, no significant differences were found between medication and placebo in four studies targeting irritability/agitation and three studies investigating global improvement[36]. However, the lack of power and the use of different medications in the examined studies prevent firm conclusions. Additional research is needed, particularly in the subgroup of patients with epileptiform abnormalities.

Conclusion

Current thought regarding the association of ASD with epilepsy considers the overlapping of common neurodevelopmental pathways as a new paradigm, replacing the original concept of two distinct, coexisting major disorders. A growing number of genes that appear etiologically relevant to ASD and epilepsy have been discovered, strengthening the likelihood of a neurodevelopmental association of ASD with epilepsy.

Abnormalities in synaptic plasticity early in development, as the result of either early seizures or genetic variants, may be a common mechanism for the development of autism and epilepsy. The role of CNVs, or structural genomic changes such as deletions and duplications, has been important in reinforcing this developmental association, and it suggests a possible “double hit” mechanism involving more than one gene in the development of the two disorders and co-occurring pathologic determinants, such as early onset epilepsies and/or brain damage.

The impairment of inhibitory neurotransmission and the resulting imbalance in the excitation/inhibition ratio in the developing brain is also likely to be implicated in both ASD and epilepsy. Dysfunctions of GABAergic interneurons and of related mini-columns are thought to be pathogenic mechanisms in the association of ASD with epilepsy.

However, a direct demonstration of GABAergic brain dysfunction is still lacking and it should be promptly addressed. Great efforts are needed to further investigate the complexity of the association of ASD with epilepsy, in order to shed light on the basic mechanisms involved and on the most effective interventions for improving overall outcomes in children with both disorders.

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