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Convulsing toward the pathophysiology of autism

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Abstract

The autisms and epilepsies are heterogeneous disorders that have diverse etiologies and pathologies. The severity of impairment and of symptoms associated with autism or with particular epilepsy syndromes reflects focal or global, structurally abnormal or dysfunctional neuronal networks. The complex relationship between autism and epilepsy, as reflected in the autism–epilepsy phenotype, provides a bridge to further knowledge of shared neuronal networks that can account for both the autisms and the epilepsies. Although epilepsy is not a causal factor for autism, increased understanding of common genetic and molecular biological mechanisms of the autism–epilepsy phenotype has provided insight into the pathophysiology of the autisms. The autism–epilepsy phenotype provides a novel model to the study of interventions that may have a positive modulating effects on social cognitive outcome.

Keywords

Epilepsy; Autism; Pathophysiology; Neurobiology; Genetics; Phenotype

1. Introduction

The unique relationship of autism to epilepsy has been a topic of scientific inquiry since the 1960's [1,2]. These early studies identified a high rate of seizures and EEG abnormalities in children with autism and helped foster research into the neurobiological basis of autism. The decade of the 70s saw several intriguing observations, including an association between infantile spasms, hypsarrhythmia, and autism [3] and autism–epilepsy and tuberous sclerosis [4]. These observations, as well as the increased risk of seizures in autism at puberty [5], raised important and as yet unresolved questions regarding the relationship of autism to epilepsy.

It is now established and widely recognized that children with autism are at high risk for developing epilepsy [6] and some of these risk factors have been identified [7]. Recent developments in our understanding of the genetics and molecular biology of autism [8] have provided new insights and tools that have kindled renewed scientific inquiry into the

relationship of epilepsy to autism. We propose that children with both autism and epilepsy offer a unique model to further our understanding of the pathophysiology of autism.

2. Autism and epilepsy: Conceptual framework

The discussion of the relationship between autism and epilepsy and how this relationship has contributed to our current understanding of the pathophysiology of autism needs to be considered within our present definitions of autism and epilepsy. Autism includes a heterogeneous number of conditions that affect the developmental trajectory of social cognition and verbal and non-verbal communication [9]. Repetitive behaviors and narrow interests are characteristic of individuals with autism. Autism spectrum disorders (ASD) or pervasive developmental disorder (PDD) are the common terms used to include children with autistic disorder (AD), pervasive developmental disorders not otherwise specified (PDD-NOS) and those with Asperger syndrome (AS). Children with disintegrative disorder (DD) and Rett syndrome (RS) are also included under the umbrella term of PDD but have features, specifically when discussing the relationship of epilepsy to autism, that distinguish them from children with AD, PDD-NOS, and AS [10]. With the exception of RS, these disorders are all behaviorally defined and most recent studies use the term autism interchangeably with that of ASD to include children with AD, PDD-NOS, AS, and DD, but not RS.

Epilepsy is a paroxysmal disorder characterized by abnormal electrical brain activity associated with a variety of behavioral manifestations. Seizures have been classified into different epilepsy syndromes based on the semiology of the symptoms experienced and characteristics of the convulsive or motor manifestations, and also on the specific EEG patterns associated with the behaviors. The term sub-clinical or non-convulsive seizure is used to refer to electrographic seizure patterns without clinically recognizable cognitive, behavioral, or motor functions or apparent impairment of consciousness; it requires a concurrent EEG with behavioral testing. Epileptiform abnormalities is a term used to describe spikes or spike and wave discharges on an EEG [11].

Autism and epilepsy are not single diseases or disorders. There is no single etiology for autism or for epilepsy. It is, therefore, more accurate to refer to these disorders as the autisms and the epilepsies. The core clinical feature that defines autism and related disorders and differentiates autism from other developmental disorders is a disturbance of social interaction. The hallmark of epilepsy is recurrent seizures, i.e., clinical events characterized by paroxysmal, stereotyped, relatively brief interruptions of ongoing behavior, associated with electrographic seizure patterns [11]. Both autism and epilepsy are associated with a range of behavioral manifestations, cognitive strengths and weaknesses, and variable outcomes.

Autism and epilepsy are not rare disorders, as the estimated prevalence per 1000 children is 5.8 for autism and 7.1 for epilepsy [12]. Approximately 30% of children with autism have epilepsy [13] and 30% of children with epilepsy, at least those seen in a tertiary epilepsy clinic, have autism [14]. Children with both autism and epilepsy have a worse developmental trajectory than those with either autism or epilepsy alone [15].

3. Autism–epilepsy phenotype

A broad look at the literature on autism and epilepsy suggests a seizure occurrence rate of 5–39% [13]. Issues such as referral bias, age of the individuals included in the study, and degree of cognitive impairment, all of which affect rates of epilepsy in the general population [16–18], are factors that individually or in combination impact reported rates of epilepsy in autism. Understanding how these variables influence the autism–epilepsy phenotype yields insight into the pathophysiology of the autisms.

3.1. Cognition and related variables

The severity of cognitive impairments (mental retardation-MR) and accompanying motor deficits is the most extensively documented risk factor for the development of epilepsy in autism, with the higher risk in those children with autism and moderate to severe MR [6,7]. The prevalence of epilepsy in individuals with autism and MR is as high as 40% [7], and in studies of autism that provide rates of epilepsy, the highest reported rates were in those that included a large number of individuals with both autism and mental retardation [19–22].

In individuals without disability the prevalence of epilepsy is approximately 1%. The prevalence of epilepsy in individuals with disorders known to be associated with cognitive impairments is significantly higher. For example, in individuals with cerebral palsy or Down syndrome the prevalence is approximately 13%, in autism or MR approximately 25%, and it is as high as 40% in adults with both cerebral palsy and MR [23]. In a series of 72 children with autism, age range 4–21 years, 4 of 54 (7.4%) children with no known brain pathology to account for their autism—‘primary autism’ group—had epilepsy, compared to 10 of 18 (54%) of those with epilepsy in the ‘secondary autism’ group, i.e., in those with known brain pathology to account for their autism. In addition, in the primary group, those with severe MR had a higher rate of seizures (20%) than those with moderate MR (12%), suggesting that epilepsy was related to the severity of the underlying brain pathology and MR [24]. In children with autism without severe MR or significant motor deficit and with no family history of seizures or other known risk factors for epilepsy, the rate of epilepsy was 6%, which is similar to a control group of children with language impairments without autism [7].

The relationship of epilepsy, MR and autism is complicated. Autism rarely if ever has a causal role in the development of epilepsy [25], but in many instances epilepsy precedes the autism, raising the issue of the effect of the seizures themselves on the developing brain and, specifically, on cognitive and social skills [26]. In addition, recent reports suggest that mesial temporal lobe epilepsy may be associated with deficits in higher order social cognitive abilities in adults [27,28]. Furthermore when epilepsy co-exists with autism, poorer cognitive, adaptive, behavioral, and social outcomes are more likely than in those with autism without epilepsy [29].

3.2. Developmental age at the onset of epilepsy in children with autism

Studies suggest that there are two peaks of seizures in autism, one in early childhood, and one in adolescence [6]. In studies that include younger preadolescent children with autism, the reported rate of epilepsy is, in general, less than 10% [30–32]. In studies that include a high number of adolescences and adults with autism rates of seizures are as high as 39% [20,33]. In those that include a mixture of infants, children, adolescents, and adults the prevalence of epilepsy is 10–20% [7,34,35].

3.3. Autism–epilepsy: Early peak

There is evidence from both animal and human studies that age at onset of seizures is an important determinant of cognitive and behavioral sequelae. Animal studies demonstrate differences in seizure-induced injury which are dependent on age [36], with the immature brain being more prone to seizures but more resistant to seizure-induced damage, especially hippocampal pathology [37]. Despite lack of cell loss, specific processes affected by early onset seizures include synaptic reorganization, a decrease in neurogenesis in the hippocampal dentate gyrus [38], and a permanent increase in epileptic potential that persists into adulthood [39–42]. Recurrent seizures in rats during the first weeks of life are associated with later cognitive impairment indexed by lower performance in tasks of visual-spatial memory and spatial learning ability [43,44]. The clinical relevance of these findings to humans is unclear [45]. Despite the limitations of the data and the lack of overt neuronal loss or structural neuronal

damage, evidence from animal models suggests that seizures in early life are associated with subtle later deficits in behavior and cognition [46].

Children with seizure onset prior to age 5 years are at highest risk for poor outcome, as the younger the age of onset of seizures, the higher the association with lower intellectual functioning [47]. In children with epilepsy, the greatest risk for developing autism appears to be among children whose seizures started around age 2 years or earlier [14]. One study of 246 children with autism ages 4–15 years found 16 children (6.5%) with seizures, of which 80% had their seizure onset in the first year of life [48]. From an epilepsy perspective it is estimated that approximately 6–7% of children with epilepsy whose seizure onset is in the first year of life go on to develop autism with mental retardation [26]. Children with autism who have a history of epilepsy at an early age probably represent a subgroup associated with more significant insults to the developing brain manifested as epilepsies of early childhood such as infantile spasms [49,50].

3.4. Autism–epilepsy: Late peak

The basis for the second peak in epilepsy during adolescence and adulthood is unknown and may be unique to children with autism, as compared to other developmental disabilities. In a prospective population-based study of adolescents and adults with epilepsy and autism ages 18–38 years, all with moderate to severe mental retardation, almost 50% of those with severe MR had epilepsy by early adult life, as compared to 20% of those with moderate MR [15]. The study included individuals with autism and epilepsy with congenital or acquired disorders such as tuberous sclerosis complex and Rett syndrome. Their inclusion most likely biased the study toward early onset seizures because this population differs from most of those in studies that report a secondary peak [33]. That study did find that more than 10% of individuals developed epilepsy after age 18 years.

The prevalence of epilepsy in cerebral palsy and in adults with MR was stated to decline with advancing age, whereas it increased in individuals with Down syndrome and autism [23]. On the other hand, in girls with Rett syndrome the severity of epilepsy tends to decrease with age, both in terms of seizure frequency and severity, as the girls approach adulthood [51]. Perhaps the secondary peak is found mainly among individuals with autism and mental retardation without known etiology. We suggest that a secondary peak in seizures in ‘primary’ autism, i.e., unassociated with MR, should make clinicians consider further work up, including a search for causes such as an insidious progressive disease or a disorder of energy metabolism like mitochondrial dysfunction, although clearly more research in this area is needed.

3.5. Regression and the autism–epilepsy phenotype

The language and social regression that occurs in a sub-group—approximately a third—of children with autism has been termed autistic regression. Because it occurs early, prior to age 3 years and in most instances prior to age 2 years, it is usually characterized by the loss of only a few words, but it is accompanied by the loss of non-verbal communication skills [52–55]. Autistic regression may or may not be superimposed on prior abnormal development [56]. There has been a suggestion that regression in autism is associated with a higher rate of epilepsy [32,57], and a recent study found that children with autistic regression had more disrupted sleep and a higher likelihood of epilepsy than those without regression [58].

The relationship of autistic regression to epilepsy or to epileptiform EEG findings remains controversial, with some studies reporting higher rates of epilepsy in children with autism and regression [34,59] and others showing no relationship between autism, epilepsy, electroencephalographic abnormalities, and regression [60]. Studies suggest that children with isolated language regression differ from children with both language and autistic regression in

that children with isolated language regression are more likely to have seizures and epileptiform discharges, particularly focal spikes, than those with both language regression and a more global autistic regression [61].

There is a group of verbal children with autism whose late-onset autistic and cognitive regression, usually occurring after age 3 years, can include motor regression and loss of bowel and bladder control. This subgroup is classified as disintegrative disorder (DD) [62–66]. The prevalence of epilepsy in DD is reported to be as high as 77% [19] and EEG abnormalities are significantly more common in children with DD than those with infantile autism [67]. Children with DD regress at a later age than those with autism, lose more than just language and sociability, have significant cognitive impairment, and have higher rates of seizures than children with autism, including those with mental retardation and regression.

The other disorder presently classified under pervasive developmental disorders (PDD) with a rate of seizures compatible with DD is Rett syndrome [51]. Both Rett and DD are associated with regression and severe mental retardation. To what extent the high rate of seizures is secondary to the severe degree of cognitive impairment present in both Rett and DD, or what influence other specific metabolic or molecular factors like MECP2 have in the development of seizures remains unknown.

4. The Autism–epilepsy phenotype and the pathophysiology of the autisms

The characteristics of the autism–epilepsy phenotype suggest that there are underlying etiologies and pathologies responsible for both the seizures and the socio-cognitive and communicative behaviors that define autism. Our present understanding of neuronal networks and the role of cellular dysfunction, and genetic and molecular derangements common to both autism and epilepsy support this argument.

4.1. Neural networks

Both epilepsy [68] and autism [69,70] may be consequences of disorders of large-scale neural networks with alterations in cortical-subcortical systems connectivity [71]. In autism alterations in neocortical minicolumns [72], abnormal trajectory of head growth, atypical functional MRI (fMRI) activation, and atypical diffusion tensor imaging (DTI) of white matter tracts during early development [73] all support the working model of autism as one of brain underconnectivity [69]. Alterations in subcortical systems such as basal ganglia-substantia nigra connectivity, may lower the seizure threshold, contribute to cognitive impairments and to the motor stereotypies commonly found in autism [74]. There are other influences on cortical and subcortical systems connectivity in the developing brain such as testosterone that have been implicated in both autism and epilepsy [75,76]. These observations have shifted the focus from fixed anatomy to function within a developmental framework. Within this vantage point we view epilepsy in autism as both a byproduct of the underlying network dysfunction and as a contributor to further disruption of this network and, as such, as responsible for greater cognitive and socio-communicative impairments.

Two general scenarios can be invoked to account for epilepsy, autism and the autism–epilepsy phenotype. The first is aberrant connectivity between neurons otherwise normal in function, the other a defect intrinsic to neuronal function in the context of normally wired and fully operational circuits [77]. Either cellular/molecular abnormalities of neurons or network abnormalities would eventuate in the epileptogenesis or aberrant cognitive and socio-communicative impairments of autism by upsetting the normal physiological balance between excitation and inhibition in the brain [78].

Malformations of cortical development (MCD), in which focal structural lesions unequivocally point to disruption of normal cortical organization and circuitry, are examples of network disruptions that commonly lead to epilepsy [77]. These disruptions can also lead to autism, as is highlighted in tuberous sclerosis in which both autism and epilepsy co-exist. In autism, it is alteration in cortical minicolumns with selective sparsity of GABAergic interneurons that is likely responsible for the increased seizure susceptibility [72,79]. A disorder in which abnormalities of interneurons is hypothesized and in which both autism and epilepsy commonly coexist is infantile spasm [80].

Several reports have highlighted an association between mitochondrial disorders and autism [81–83]. They provide an example of cellular/molecular level dysfunction of energy metabolism that may lead to either epilepsy or autism or both. Disordered mitochondrial function is more common than appreciated among children with childhood epilepsies, including a number of the epileptic syndromes associated with autism [84]. The relationship of mitochondrial disorders to children with autism, hypotonia, mental retardation, and epilepsy is in need of further research [85]. It would also be of interest to explore the relationship of mitochondrial disorders to adolescents and adults with autism who develop epilepsy as part of the secondary peak previously described.

4.2. Genetic and molecular abnormalities

Gene defects can influence numerous processes in brain development such as, for example, molecular derangement of ion channels, aberrant cortical neurogenesis leading to malformed cortical development, or abnormal specific protein products, all of which have been implicated in the development of both epilepsy and autism [86–90]. Genetics may be responsible for both the EEG pattern and the cognitive dysfunction in children with epilepsy or autism [91,92], and the seizures themselves may alter neurotransmitter release and gene expression [93]. The role of genetics and molecular biology common to the epilepsies, EEG abnormalities, and autism is just beginning to be understood [8,94].

Mutations in a specific gene such as *MECP2* can lead to a complex neurodevelopmental disorder such as Rett syndrome and to other deficits arising from the improper silencing of other genes [95]. Studies of fragile X syndrome indicate that deficiency of fragile X mental retardation protein is associated with alterations of synaptic spines and leads to increased neuronal excitability and susceptibility to epilepsy [96]. A susceptibility locus for autism has been found on chromosome 2 in the vicinity of the genes *SCN1A* and *SCN2A* that are susceptibility genes for seizures [97].

Altered expression of another gene (*MET*) has been hypothesized to alter circuit formation and affect neocortical and cerebellar development, with disruption of interneuron development which contributes to the pathophysiology of both autism and epilepsy [98,99]. Multiple genes can contribute to disruption of GABAergic interneuron development, which may be a point of convergence for both autism and epilepsy [100]. The role of GABA in the developing brain [101] and especially its role in epilepsy and autism is complex [102]. The relationship of GABA to autism and epilepsy is highlighted in studies on Angelman disorder [103] and in work suggesting that stratifying for seizures in autism may aid in identifying susceptibility genes for autism [104].

4.3. Autism–epilepsy: From synapse to treatment

Abnormalities of synaptic structure and function are at the forefront of current investigations of the brain basis of autism [105]. There are increasing numbers of reports of families or individuals with autism who lack genes important in synapse development and maintenance of synapse function [106], including mutations in the gene encoding the synaptic scaffolding

protein SHANK3 [107], and in neuroligins which are synaptic cell adhesion molecules [108]. The present working hypothesis, posits that deficits in activity-dependent gene expression disrupt synaptic development and contribute to the autism phenotype [109,110]. This hypothesis provides a framework for considering new therapeutic interventions for both autism and epilepsy.

Genes controlling circadian rhythms may modulate protein complexes important in synaptic development and in the normal balance between excitation and inhibition in brain circuits [111]. Disorders of the sleep–wake cycle in autism have been documented since 1989 [112] and recent studies confirm that melatonin plays a crucial role in cognitive and behavioral development [113]. Low melatonin levels secondary to a defect in a gene encoding for an enzyme crucial to melatonin synthesis, the *ASMT* gene, is a risk factor for development of autism [113]. Conditional deletion of *PTEN*, a gene associated with macrocephaly and autism, in a mouse model is associated with abnormalities in circadian rhythms, seizures, and social interaction deficits [114]. The clinical role of sleep in the epileptic encephalopathies and in autism [58,115,116] may be at the level of the synapse. Understanding the role of melatonin in regulation of sleep and its relationship to autism and epilepsy through common clock genes and neurotransmitters should provide new targets for therapeutic interventions [117].

Disrupted synaptic development has been hypothesized to be central to the pathophysiology of both Fragile X [118,119] and Rett syndrome [120], both examples of the autism–epilepsy phenotype. It is likely that abnormalities in synapse formation and modulation contribute to higher rates of seizures and regression in both autism and Rett syndrome [121]. Both *MECP2* mutations, and mutations in *CDKL5* which is associated with early onset epilepsy, infantile spasms, MR, and an autism phenotype [122–125] cause disruption of synapses [126,127]. Mouse models provide hope that future treatments for clinical disorders in which the autism–epilepsy phenotype occurs may be devised. For example, a mouse model of tuberous sclerosis was developed in which treatment with the mTor pathway inhibitor rapamycin has been reported to reverse learning deficits [128]. There are also mouse models of Rett syndrome [129] and Fragile X [130] in which reversal of neurological symptoms have been demonstrated.

There has been a paradigmatic shift in our thinking about the relationship of epilepsy to autism. Consideration of common genetic and molecular mechanisms that account for the pathophysiology of the autisms and epilepsies has replaced the concept of epilepsy as a causal factor in autism. The hope is that therapeutic interventions that target common mechanisms that lead to the autism–epilepsy phenotype will have a broader symptom-modifying effect with benefits to all children with either autism or epilepsy.

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