Autism and Epilepsy: What Has Regression Got to Do with It?

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The relationship among epilepsy, autism, and regression is a poorly understood and controversial subject. In this brief review, examples of epileptic encephalopathies associated with regression of language and behavior and their overlap with autistic regression are discussed.

Autism, like epilepsy, includes a wide spectrum of conditions in children, and the term *autism spectrum disorder* is used clinically to describe a group of behaviorally defined, neurodevelopmental disorders characterized by deficits in verbal and nonverbal communication, poor social skills, a restricted repertoire of interests, and repetitive behaviors. The term *autism* is used throughout this review to include the wider spectrum of autistic disorders in children. Autistic regression refers to children with autism who have a regression or loss in their language, behavior, and social communicative skills. In the same manner, the term *epilepsy* includes a variety of clinical syndromes that are grouped together on the basis of clusters of symptoms or signs. The severity of impairment and the variety of symptoms associated with autism or with particular epilepsy syndromes reflect structural or functional as well as focal or global dysfunction of neuronal networks.

Epilepsy and autism are both heterogeneous clinical disorders associated with an array of etiologies and pathologies, many of which are common to both groups of disorders. There is a paucity of data on how many children with epilepsy have autism. Recent studies suggest that as many as one third of children with epilepsy are at risk of having an autism spectrum disorder and that this risk is highest in those children who have seizure onset at a younger age (1,2). In children with autism, approximately one third have epilepsy, with the highest risk for those patients with severe mental retardation (3–5). Clinical experience and data from the larger studies on autism and epilepsy suggest that severe cognitive dysfunction, motor deficits, genetic risk factors, and severe receptive language impairment are the common risk factors that contribute to the frequency of coexistence of epilepsy and autism (3,6–11). There are several epilepsy syndromes in which regression of language, cognition, and behavior may lead to clinical manifestations that overlap with the behavioral syndrome of autism. In addition, for a subgroup of children with autism who have a history of regression in language and social behavior, the role of epilepsy has been a source of controversy, challenging both researchers and clinicians. Furthermore, there are many case reports demonstrating that epilepsy can directly affect cognition and behavior, and there are several epileptic disorders that may cause behavioral and language regression, with a behavioral phenotype similar to autism (12). Despite the importance of the relationship among autism, epilepsy, and regression, the subject remains poorly understood and controversial.

Regression in Epilepsy

The evidence that recurrent seizures or abnormal electrical activity can cause specific cognitive, language, or behavioral abnormalities is still controversial, even in the epileptic encephalopathies. The International League Against Epilepsy has defined an epileptic encephalopathy as "a condition in which the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function" and includes in their definition disorders such as early myoclonic encephalopathy, Ohtahara syndrome, West syndrome (Infantile Spasms), Dravet syndrome, myoclonic status in nonprogressive encephalopathies, Lennox–Gastaut syndrome, Landau–Kleffner syndrome (LKS), and epilepsy with continuous spike-waves during slow-wave sleep (13). Other than LKS and continuous spike-waves during slow-wave sleep, the epileptic encephalopathies are associated with frequent, though not necessarily severe, convulsive seizures.

As a group, the epileptic encephalopathies are associated with regression or slowing of cognitive, language, or behavioral development; the hypothesis is that the seizures or the interictal epileptiform activity are responsible for the deterioration (14). It is difficult to determine which comes first, the epilepsy or the cognitive and behavioral impairment, even in children exhibiting relatively typical symptoms (15,16). With the epileptic encephalopathies, it may be that there is an underlying impairment in brain function and that the regression in cognitive, language, or behavioral features is attributable to the added effects of the seizures or the interictal epileptiform activity on

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an already compromised brain. However, to date, studies have failed to dissect the effect of seizures per se from the effects produced by the underlying problems in brain function.

Animal and human studies suggest that the age of onset of seizures is an important determinant of cognitive, language, and behavioral sequelae (17). Evidence from animal models suggests that seizures early in life are associated with subtle deficits in behavior and cognition (18). Clinically, seizures or interictal epileptiform activity that start early in life also are more likely to be associated with cognitive deficits and with reduction in brain volume (19). Recent work investigating epileptic risk factors for the development of autism in patients with tuberous sclerosis found that tubers in the temporal lobes predisposed patients to autism spectrum disorders and, more specifically, that temporal lobe epileptiform discharges, a history of infantile spasms, and onset of seizures in the first 3 years of life determined whether or not an individual with tuberous sclerosis complex developed an autistic spectrum disorder (20). Furthermore, among children with epilepsy, at least among those seen in a tertiary care epilepsy clinics, the greatest risk for developing autism appears to be among children whose seizures start around age 2 or before (2).

The epileptic encephalopathy commonly associated with autism is LKS, an acquired aphasia. LKS occurs after 3 years of age, in association with an epileptiform EEG that is predominantly over the temporal regions; yet, in approximately 25% of children, it appears without clinical seizures (21). With LKS, the assumption is that epileptiform discharges in areas concerned with linguistic function are responsible for the language dysfunction, but there is still controversy regarding the etiology and pathophysiology of this presumed epileptic encephalopathy (22). An MRI volumetric study of four children with well-defined LKS demonstrated a significant reduction, compared to controls, in the cortical volume of the superior temporal areas that encompass the auditory association cortex, with volume reduction being the most dramatic in the two children with the most epileptiform activity (23). This evidence does not clarify whether the atrophy is the cause of the LKS or the consequence of the excitoxicity from the epileptiform discharges, but it does provide data to support the concept that the epileptiform activity itself may be responsible for language regression in LKS.

It is reasonable to hypothesize, as in the example of tuberous sclerosis, that there may be multiple variables, such as age of onset of the seizures, interictal epileptiform activity and location, or extent of the epileptiform activity that influence whether or not the full autism behavioral phenotype develops. In fact, there is some evidence that LKS may differ from other conditions associated with acquired aphasia or with frequent epileptiform discharges during sleep because of the dipolar orientation of its spike focus across the sylvian fissure, with negativity found above the fissure and positivity at the temporal side (24,25). This observation remains controversial, as does the issue of whether it is the frequency of the epileptiform discharges that determines if language deteriorates or improves in LKS and other epileptiform disorders associated with cognitive symptoms (26).

Regression in Autism

In comparison to children with LKS, patients with autistic regression have regression of both language and behavior in association with significant social deficits; it occurs in approximately 30% of children with autism (27, 28). The regression in language seen with LKS is more dramatic and the social deficits are less severe than those associated with autistic regression, although the distinction may be clinically difficult to make in young children. Regression associated with autism may be superimposed on prior abnormal development and is usually related to the loss of only a few words but is accompanied by the loss of nonverbal communication skills (29–32).

There is evidence to suggest that in a subgroup of children with autism spectrum disorders and without convulsive seizures, an epileptiform EEG is significantly more likely to be associated with a history of regression in language (33). However, these data must be put into perspective as they represent a very specific subgroup of children with autism, and because at the present time, there are no data regarding the number of children in the general population without seizures who have cognitive and behavioral impairments as well as interictal epileptiform activity (detected by an overnight EEG study). Other investigators have found no differences in regression in those children with epileptiform EEGs and epilepsy and those without seizures and a normal EEG (34). One study suggested that epilepsy, but not EEG abnormalities, was associated with autistic regression (35).

The age of regression of language differs between LKS and autistic regression. Children with autism are more likely to regress earlier, usually prior to age 2, as contrasted to those patients with LKS, who more typically have a regression in language after 3 years of age (36–38). Furthermore, seizures are more likely to occur in children who regress in language after age 3 (36–38). This finding is different from data on children with LKS, as only 12%–14% of these children regress before age 3 years (39), and the peak age of onset of symptoms is between 5 and 7 years (40). McVicar et al. found that children with isolated language regression have a higher frequency of epileptiform discharges and seizures than children with both language and autistic (i.e., social and behavioral) regression (41).

Children with late-onset autistic and cognitive regression, usually occurring after age 3, have been classified under the subgroup of disintegrative disorder; this subgroup has a higher incidence of epilepsy (70% vs. 30%) than other subgroups of children with autism (42,43). The differences between children

with autistic regression (i.e., those who regress prior to age 2) and children with disintegrative psychosis need to be further delineated. Similarly, issues related to why children with autistic regression, early or late, have worse outcomes than children without regression require further study (44).

Clinical Implications

It is clear that despite the overlapping features of autism, epilepsy, and autistic regression, the clinical implications of regression in children with epilepsy are different from the clinical implications of regression with autism. Importantly, in treating children with epilepsy, especially those patients who have a regression of language and behavior, clinicians need to have a heightened awareness that the behavioral phenotype of autism may coexist. When autism and epilepsy coexist, the quality of life of these individuals is severely impacted (45). Furthermore, with some of the epileptic encephalopathies, there may be a causal relationship between the epileptiform activity and the regression. An equally important point is that autism is not an epileptic encephalopathy and that epilepsy and epileptiform activity are more likely to be associated with language regression than with autistic regression.

When managing an epilepsy syndrome whose outcome is associated with cognitive, language, and behavioral deficits, treating only the seizures is not adequate; while seizures generally respond to antiepileptic medications, there is very little evidence that these agents can change cognitive or behavioral outcomes. Addressing the cognitive, language, and behavioral manifestations becomes an important component of the treatment for these individuals. There is no evidence to suggest that epilepsy or interictal epileptiform activity is a cause of autistic regression. In children with autistic regression, there is no evidence that treatment of the seizures or of the interictal epileptiform activity makes a difference in regard to outcome of the language and social deficits. Of course, because the relationship between autism, epilepsy, and regression is complex, the clinician's index of suspicion for epilepsy should be high, and treatment of the epilepsy should be pursued, using the same guidelines applied to any other epilepsy patient, with or without autism.

Despite the need for a high index of suspicion for subtle symptoms of seizures, a recent review that attempted to provide evidence-based guidelines for performing an EEG on children with autism found that there was insufficient evidence to recommend for or against the routine use of screening EEGs with autism (46). For children with autism and regression, an EEG needs to be considered only when there is clinically significant loss of social and communicative functions and a suspicion (based on other clinical variables, such as age of regression or amount of language loss) that abnormal electrical activity may be contributing to the regression. Even then, the clinical implications of the epileptiform activity in autistic regression remain unclear.

The protocol for treatment of LKS is the best available model to use for the behaviors associated with epileptiform EEGs. However despite numerous case reports suggesting that traditional antiepileptic drugs, steroids, intravenous gamma globulin, and surgery can stop the seizures and improve behavior (as in other epileptic encephalopathies), the direct effects on language of any of these interventions is uncertain (25,47–49). All of these clinical case reports used variable measures of language, behavioral, and cognitive outcomes. With no controlled clinical trials and with confusing terminology, such as "LKS variants," and vague end points, it is impossible to determine which child may benefit from treatment with corticosteroids or which one from intravenous gamma globulin. The data suggest that despite success with pharmacologic or surgical treatment of seizures, the ability to modify cognitive, language, and behavioral outcomes of children with autism and epilepsy (or with epilepsy and associated language, cognitive, and behavioral regression) is limited.

For clinical disorders in which regression, epilepsy, and autism overlap, there are multiple variables that can guide clinical management, such as type of regression (language vs. autistic); age of onset of the seizures or epileptiform activity; as well as the location, orientation, and quantity of the epileptiform activity. It is essential to use appropriate descriptive terminology to classify children in whom autism, epilepsy, and regression overlap. Imprecise clinical classification and use of vaguely and arbitrarily defined endpoints (e.g., general descriptions of behavior or social function) will create further confusion.

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