

# Epilepsy and autism spectrum disorders

## Relatively related

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For over 30 years, multiple studies have demonstrated that children with autism spectrum disorders (ASD) are at high risk for developing epilepsy, with the highest risk in those with intellectual disability. This risk continues into the second and third decades of life.<sup>1,2</sup> However, not until recently have investigators asked the question: How often does ASD occur in epilepsy? Several studies demonstrated that neurodevelopmental disorders such as ASD occur more frequently in epilepsy, with the highest risk in those with in those with cognitive impairments and frequent seizures. The emerging concept is that there is a bidirectional relationship between epilepsy and ASD. A critical question to understand relates to the mechanisms that link epilepsy to ASD, as this may lead to interventions that can ultimately improve quality of life for individuals with epilepsy associated with ASD.

In children with early-onset epilepsy, the hypothesis is that epileptic seizures and epileptiform abnormalities in the EEG make a large contribution to cognitive and behavioral comorbidities, over and above that caused by the etiology of the epilepsy.<sup>3</sup> This concept of an epileptic encephalopathy has driven aggressive early treatments for children with epilepsies, such as infantile spasms or Dravet syndrome, in an attempt to minimize adverse outcomes.<sup>4</sup> Although this approach may have had modest positive effects on cognition, it has minimally, if at all, reduced the severity or frequency of ASD. This observation strongly suggests that there is at least one other mechanism for children with epilepsy and ASD. The obvious mechanistic candidate is etiology. In an etiology-driven framework, the seizures and the associated neurodevelopmental disorders are a result of an underlying albeit not necessarily identified etiology, and therefore treatment of seizures would not a priori be expected to influence comorbidities.

In this issue of *Neurology*®, Sundelin et al.<sup>5</sup> provide compelling evidence that individuals with epilepsy are at high risk for developing ASD, especially for those in whom epilepsy begins early in life. Furthermore, the authors show that siblings and offspring of people with epilepsy are at increased risk

of ASD, even if those siblings and offspring with epilepsy are excluded. The increased risk in offspring occurs with both mothers and fathers, although the relationship is stronger for women. The investigators use the well-respected and robust population-based Swedish Patient Register to identify patients with epilepsy, their siblings, and their offspring. The sample size was almost 100,000 patients per group. In addition, for each epilepsy patient, they identified 5 individuals who were matched for age, sex, and geographic region. The siblings and offspring of these individuals were controls for the other groups. With this enormous sample size, they show that individuals with epilepsy and no ASD at diagnosis are at increased risk of developing ASD in the future. This elegant study provides a framework to discuss the mechanisms accounting for the association of epilepsy and ASD.

The fact that the highest risk for ASD was in early-onset epilepsies could provide support for the epileptic encephalopathy hypothesis; i.e., that seizures cause the ASD. However, there are several findings that do not fit with that hypothesis. First, this study confirms findings in other studies showing that children with ASD without seizures are at higher risk of developing future epilepsy, and that this may not occur until much later in life. Although this can be explained by arguing that there were unrecognized epileptiform discharges in the EEG at the time of the diagnosis of ASD, with overt clinical seizures only appearing later, there are no data to support that view. In addition, there are now numerous studies that clearly demonstrate that developmental epilepsies and ASD have common molecular mechanisms. This shared pathophysiology viewpoint is clearly supported by the findings of Sundelin et al., given that ASD was more common in siblings and offspring of individuals with epilepsy. As such, the findings in this study strongly argue against the hypothesis that seizures are the cause of ASD in individuals with epilepsy.

This study demonstrates the importance of screening for ASD in epilepsy and, taken together with other epidemiologic studies demonstrating a high risk

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of epilepsy in ASD populations, establishes a strong bidirectional relationship between these 2 disorders. Furthermore, this study provides useful information that serves as a starting point for more detailed studies. For example, the nature of the epilepsies or epilepsy syndromes in the patients in this study is not well-defined. Although a possible weakness of the study, this is expected given the type of data being analyzed. It remains unknown, for example, whether patients with genetic epilepsies are the ones most likely to have siblings and offspring with ASD. This would strengthen the argument for a genetic shared substrate for both epilepsy and ASD.

Although the findings in this study do not directly lead to novel interventions, they open the door for studies to address treatment, and clearly emphasize the importance of early screening for neurodevelopmental disorders in all children with epilepsy, specifically ASD. Early identification of ASD in epilepsy has the potential to tailor treatment strategies that can find the appropriate balance between antiepileptic drug number and dose and frequency of seizures. Furthermore, this study highlights that the comprehensive management of epilepsy is more than treating seizures and should include interventions targeted

at minimizing the consequences of neurodevelopmental disorders related to epilepsy, such as ASD, with the ultimate goal of maximizing quality of life.

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### DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to [Neurology.org](http://Neurology.org) for full disclosures.

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