Behavioral correlates of epileptiform abnormalities in autism

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There is a high incidence of epileptiform abnormalities in children with autism even in the absence of clinical seizures. These findings are most prominent during sleep recordings. The significance of these abnormalities is unclear. Although studies do not all agree, there may be some association between cognitive function, behavior, and the presence or absence of epileptiform discharges. Small studies of anticonvulsant treatment mostly suggest an improvement in certain aspects of cognitive or behavioral functioning in these children, but larger and more comprehensive studies are needed to determine the potential relationship between epileptiform discharges on EEG, cognitive and behavioral functioning, and treatment effects in the population with autism.

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1. Introduction

Despite many years of study, there is still limited information regarding the underlying neurobiological substrates associated with autism. One of the potential reasons for this may be the heterogeneous nature of the condition. Autism may be a number of different conditions manifesting as a common clinical phenotype. The core features of impairment in social communication and social interaction; restricted range of interests; and repetitive, stereotyped behaviors define the clinical disorder. Abnormal (either hypo- or hyper-) sensitivity to sensory stimuli is included within the stereotyped behaviors and can include behaviors such as excessive smelling or touching of objects and avoidance of certain textures, sounds, or smells. There are additional commonly associated, although not core, features, such as disturbances in sleep, gastrointestinal problems, and behavioral issues including hyperactivity, attention problems, and aggressive and impulsive behaviors. Seizures are one common associated complication of autism, occurring at a much higher rate than that in the general population, with estimates of 6–46% of individuals with autism having clinical seizures at some time during their lives [1–5]. Moreover, even in individuals with autism without a history of clinical seizures, there is a very high incidence of epileptiform abnormalities on electroencephalographic (EEG) recordings [6–12]. This observation raises several questions. Are the epileptiform discharges associated with underlying behavioral or cognitive problems commonly found in autism? Could treatment of the epileptiform discharges alter the clinical symptoms?

2. Incidence and type of epileptiform abnormalities

There have been a number of reports of the presence of epileptiform abnormalities on EEG in children with autism spectrum disorder (ASD) or pervasive developmental disorder (PDD) [6–12] (see Table 1 for a summary of relevant studies). Most have looked at a possible association between the presence of epileptiform activity and autistic regression, an occurrence in approximately 20–30% of children with autism. In regressive autism, the children appear to be developing normally and then lose eye contact, stereotypies and repetitive behaviors appear, and communication and social behaviors regress. Tuchman and Rapin [1] reported on 585 young children with PDD, 30% of whom had a history of regression in early development. Eleven percent of their population had a history of epilepsy. Of the 392 children in their study who had EEGs performed, 59% of the children with epilepsy had epileptiform abnormalities on EEG, but only 8% of the children without epilepsy had abnormal EEG findings. There was a slightly higher incidence (14% vs. 6%) of autistic regression in the group with epileptiform abnormalities than in the group without epileptiform discharges. Rossi et al. [6] found an 18.9% incidence of paroxysmal discharges on EEG in children and adults with autism who did not have epilepsy. These authors also did not find EEG abnormalities or epilepsy to be associated with autistic regression.

In a large retrospective study, 889 patients with autism (mean age: 5.8 years) with no prior history of epilepsy received 24-hour ambulatory EEGs over a 10-year period [12]. The incidence of epileptiform EEG
abnormalities in their population was 60.7%. As in previous studies, the authors found no difference between children with a history of autistic regression and those without such a history. Interestingly, all of their patients had EEG abnormalities in sleep only. There was not a consistent location found for EEG abnormalities in their population. The most common site for abnormal electrical discharges was the right temporal lobe or the bilateral temporal and central regions, but frontal, occipital, and parasagittal spikes were seen in some patients, and generalized spike–wave discharges were found in 16% of the recordings.

More recently, Mulligan and Trauner [12] identified 101 children with autism (mean age: 7.1 years) who had undergone 24-hour EEGs. We found that 59.4% of children with ASD had epileptiform discharges on EEG and that 21.8% had nonepileptiform abnormalities, primarily slowing of the background activity. When only children without a history of epilepsy were included, 50% had epileptiform abnormalities, whereas 95% of children with a history of seizures had interictal epileptiform discharges. Sixty percent had abnormalities during sleep only, again highlighting the fact that a sleep EEG is essential to detect such abnormalities. Only 3.6% had epileptiform activity in waking only. The presence of epileptiform activity was associated with lower functional levels (intellectual and behavioral) in the children with autism, whereas those with high-functioning autism (HFA; Asperger’s) had only a 20% incidence of such abnormalities. The reciprocal association between intellectual functioning and the presence of epileptiform discharges is also of interest with relation to the question of causality, i.e., do the epileptiform discharges cause the symptoms of autism, do they co-occur as a result of a common underlying brain disorder that causes both, or are they coincident to each other? This reciprocal association has been demonstrated between autism and clinical epilepsy as well [13–15].

The presence of epileptiform abnormalities in the Mulligan and Trauner [12] study was also associated with a higher incidence of motor stereotypes (61% vs. 36% without epileptiform abnormalities). As was found in earlier studies, there was no association between epileptiform abnormalities and autistic regression. There was a markedly higher association of aggressive behaviors with the presence of epileptiform abnormalities, but the numbers were too small to allow for meaningful statistical analysis. However, this study raises the question of whether interictal epileptiform abnormalities may play a role in some of the behavioral difficulties observed in many children with autism.

The studies of Chez et al. [8] and Mulligan and Trauner [12] both found a very high percentage of children with autism with epileptiform abnormalities in the absence of clinical seizures. Most often, the abnormalities were detected during sleep only. These studies highlight the importance of a sleep EEG in this population and, ideally, a prolonged (overnight) EEG in order to capture all stages of the sleep cycle.

Magnetoecephalography (MEG) is a noninvasive technique that utilizes neurophysiological and magnetic resonance imaging paradigms to identify areas of abnormal activity in the brain. Magnetoecephalography studies of children with autism have identified areas of persistent epileptiform discharges primarily in the perisylvian regions [16,17]. Magnetoecephalography may be more sensitive than routine EEG and possibly better able to detect abnormalities than 24-hour EEGs [16].

3. Are the epileptiform discharges reflecting cortical dysfunction in autism, or are they coincidental findings unrelated to the neurobiology?

The above studies raise the crucial question of whether the epileptiform abnormalities found in many children with autism reflect underlying cortical dysfunction and create or add to the clinical symptomatology or whether they are merely coincidental findings that are not in themselves responsible for any of the clinical manifestations. There are a number of studies demonstrating a higher risk of autism with certain types of epilepsy (e.g., infantile spasms, Lennox–Gastaut syndrome) [18–20]. There is also a higher risk of autism in children who have seizure onset under two years of age [21]. However, these observations do not prove causation. More relevant to the current topic is that there is very little information published with regard to the presence of epileptiform EEG abnormalities having a causal role in autism. Several studies have demonstrated transient subtle cognitive impairments in individuals without autism with epilepsy during the time that epileptiform discharges are occurring [22–25]. The possibility that recurrent epileptiform abnormalities may cause permanent cognitive, social, or behavioral impairments is much more difficult to demonstrate. Animal studies [26] have documented that persistent interictal epileptiform discharges in the prefrontal cortex that were initiated during early brain development led to deficits in social behavior in adult rats, even though the epileptiform discharges were no longer present. Such work indicates that early persistent epileptiform discharges can have long-lasting effects on synaptic plasticity and lead to deficits reminiscent of what might be found in individuals with autism.

A relevant study of patients with tuberous sclerosis complex (TSC), a condition associated with a high incidence of autistic spectrum disorders, showed an association between frequency of epileptiform discharges in the left temporal lobe and the presence of autism [27]. The authors conclude that persistent epileptiform activity in specific brain regions, particularly the temporal lobe, early in brain development may lead to long-term social and communication deficits.

Of interest with regard to the above studies is that although epileptiform discharges may be seen in any area of the brain in children with autism.
autism, Chez et al. [8] found the temporal lobe to be the most common site for epileptic discharges, while Mulligan and Trauner [12] described a frontal predominance in their study group. An MEG study of 36 children with autistic spectrum disorder [17] documented subclinical epileptiform activity in 31 of their patients, with foci primarily in the perisylvian regions of the brain. This information adds to the hypothesis that the presence of early epileptiform activity in particularly vulnerable brain regions limits plasticity and prevents adequate neural networks from forming, in turn leading to the cognitive and social impairments observed in autism.

Lado et al. [28] provide an excellent theoretical argument for the idea that persistent epileptiform discharges, even without clinical seizures, may cause permanent adverse effects on the developing brain that may result in cognitive and/or behavioral impairments. Citing evidence from animal studies (e.g., Hernan et al. [26]), they hypothesize that persistent spikes during early brain development inhibit the normal plastic processes that allow networks to be set up for effective cognitive functioning.

Other clinical conditions exist in which persistent epileptiform abnormalities are strongly associated with cognitive dysfunction, again suggesting but not proving a causal connection. One of the most prominent of these is Landau–Kleffner syndrome, in which sleep-activated bilateral, independent, temporal lobe–predominant spikes are associated with severe language and, sometimes, behavioral regression [29,30]. Treatment (with antiepileptic medications or steroids) often reverses the cognitive impairments, again suggesting but not proving a causation between epileptic abnormalities and cognitive dysfunction. Rolandic epilepsy has also been associated with cognitive regression, particularly in the face of more frequent epileptic discharges [31,32]. Both oral and written language deficits have been documented in this condition. All of this information taken collectively strongly argues for a causative role of persistent epileptiform discharges in cognitive and behavioral impairments when the discharges are present during early brain development. However, there is still no direct evidence that such epileptic abnormalities are directly associated with the clinical features in children with autism.

4. Are the epileptiform discharges associated with underlying behavioral or cognitive problems associated with autism?

There is very limited information regarding the possible effect of epileptiform discharges on behavior and cognitive functioning in children with autism. Epileptiform abnormalities are more likely to be seen in children with autism with lower IQ [33] or with more severe forms of ASD (autism and PDD in contrast to Asperger’s [12]). Children with severe EEG abnormalities have been found to have more problems with behavior, sleep, and attention than those with less persistent EEG abnormalities [34]. As mentioned earlier, the study of Mulligan and Trauner [12] showed that the presence of epileptiform abnormalities in children with autism was associated with a higher presence of motor stereotypies and that there was a strikingly higher association of aggressive behaviors with the presence of epileptiform abnormalities. Much more study is obviously required to determine whether the presence of persistent epileptiform discharges in the population with autism has a detrimental effect on cognition or behavioral functioning.

5. Could treatment of the epileptiform discharges alter the clinical symptoms?

One of the most salient questions is whether treatment with medications targeting the epileptiform activity could improve cognitive or behavioral functioning in children with autism. No large-scale controlled studies have been conducted to date to determine whether such interventions have a positive effect [35]. Chez et al. [8] treated 176 patients with autism with abnormal EEGs with valproic acid. The EEGs normalized in almost one-half of those treated, and most of the remaining had improvements noted on repeat EEG testing. No cognitive or behavioral testing was performed, however, so clinical correlations were not possible. A number of small studies using anticonvulsants to treat behavioral symptoms in autism have resulted in inconsistent results. An early open-label study of sodium valproate (VPA) [36] found improvement in aggression in children with autism, but a later placebo-controlled study showed no reduction in aggression using the same medication [37]. An open-label trial of levetiracetam showed significant improvement in emotional lability in children with autism compared with placebo [38]. Hollander et al. [39] conducted a double-blind, placebo-controlled trial of VPA in 27 children with autism, targeting irritability as the primary outcome measure. There was a significant difference between VPA and control groups, with 62.5% of the VPA group showing significant improvement in irritability compared with 9% of the control group. Electroencephalography was not used as an inclusion criterion, although sleep-deprived EEGs were attempted on all subjects enrolled in the study. Exploratory analyses based on very small numbers suggested that those children with abnormal epileptiform EEGs were more likely to have a positive response to VPA than those with normal EEGs. That finding is particularly intriguing in light of the question of causation and also because of the potential implications for identifying children with autism who might be most amenable to treatment with anticonvulsant medications.

One of the difficulties in interpreting results of such studies using VPA is that this medication is commonly used to treat mood disorders. The question arises as to whether any positive response to VPA is related to suppression of epileptiform activity or, merely, to mood stabilization. Obviously, the effectiveness of other anticonvulsants such as levetiracetam, which is not typically used in psychiatry for mood disorders, is suggestive that the positive effects observed were more likely due to suppression of abnormal electrical activity, but too few studies of anticonvulsants other than VPA have been reported to determine whether this is the case.

All of the studies targeting autistic symptoms with antiepileptic medications suffer from the same limitations: small sample size, lack of consistency in inclusion and exclusion criteria, and lack of prospective grouping by EEG findings. Clearly, a large, randomized, double-blind controlled study of medication in children with autism with normal EEG and those with abnormal EEG is necessary to answer the question of possible efficacy of treatment, but several factors, including the choice of medication, behaviors to be targeted, and other issues, need to be worked out for such a study to be meaningful.

6. Where do we go from here?

It is clear that much work is needed to determine the relationship between epileptiform activity and autism and whether treatment of one alters symptoms and/or outcome of the other. Animal models of epileptiform discharges and autistic symptomatology can be expanded and may provide clues as to underlying mechanisms such as neural network disruption, neurotransmitter alterations, and other potential causes. Genetic studies of children with epilepsy and autism may provide information on underlying genetic influences in these mutually occurring cases. As mentioned above, a large, randomized, double-blind controlled study of antiepileptic medication in children with autism with normal EEG and those with abnormal EEG would be beneficial in determining whether early treatment alters autism symptoms as well as long-term outcome.

7. Conclusions

Abnormal brain wave activity is common in children with autistic disorders. Epileptiform discharges, found primarily during sleep, are present in the majority of children with autism and are not necessarily associated with clinical seizures. Persistent epileptiform activity starting early in life may contribute to some of the cognitive and behavioral
issues found in individuals with autism. Whether treatment aimed at suppressing the epileptiform discharges will lead to reduction in problematic behaviors and improved cognition is not known but deserves future study.

Conflict of interest

The author declares that there are no conflicts of interest.

References
