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Review

Interictal epileptiform activity and autism

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ABSTRACT

Many individuals with autism have epileptiform discharges on their EEG without having definite clinical seizures. The clinical significance of epileptiform activity in patients with autism is controversial. Some consider it an epiphenomenon of the underlying condition that should be ignored, and others believe that frequent spikes may contribute to the cognitive impairment and advocate treatment. Several studies have reported variable rates of epileptiform activity and variable response to treatment. There is an urgent need to conduct controlled clinical trials to assess the true incidence of epileptiform activity in children with autism, develop a risk assessment model, and study the effectiveness of treatment.

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1. Introduction

The association between autism and seizures has been known since the first described cases [1]. However, the exact prevalence of seizures in children with autism is unknown, with estimates ranging from 5 [2] to 46% [3]. Estimating the prevalence of epilepsy in patients with autism faces several challenges. First, after the diagnosis of autism is made, seizures can start at any point, making the estimation of lifetime risk for seizures difficult, unless patients are followed up for many years. Second, the identification of clinical seizures is not always easy. Children with autism frequently have behaviors that are similar to complex partial seizures, such as staring, repetitive motor activity, and abrupt changes in mood and behavior. Without continuous video-EEG monitoring, it is sometimes difficult to determine if such behaviors result from seizures. Finally, many children with autism who were studied with prolonged EEGs were found to have epileptiform activity without definite clinical seizures. Many authors have concluded that a high percentage of children with autism may have interictal epileptiform activity without clinical seizures [3–6]. However, most clinicians consider the presence of frank interictal epileptiform discharges (IEDs) a strong diagnostic indicator of epilepsy. For example, if a patient without autism presents with recurrent episodes of unresponsiveness, staring, and stereotypical repetitive motor activity, and the EEG reveals frank IEDs, the diagnosis of epilepsy is usually made, and the episodes are assumed to be seizures. However, in some cases, a patient with autism having similar symptoms and EEG findings may not be diagnosed with epilepsy, unless the reported episodes are confirmed to be seizures on video-EEG, despite the presence of frank epileptiform activity. The question of whether a patient with autism has clinical seizures does not always have a simple answer. Many observational studies suggest that a large percentage of children with autism may have IEDs on their EEG and never have clinical seizures [3–6]. As discussed below, most of these studies have limitations, and the conclusion is not necessarily true. Many of the patients reported in various series may either have infrequent seizures that were not recognized by their parents or are likely to develop seizures at some point in the future.

This raises an important question about treatment. Practitioners disagree on this point [7,8], with some advocating aggressive therapy to reduce or eliminate IEDs and others arguing that treatment should only be initiated if clinical seizures are confirmed. Again, this is a situation that is rather unusual. There are only a few clinical scenarios where the presence of IEDs does not necessarily lead to treatment, such as some children with benign rolandic epilepsy and siblings of patients with primary generalized epilepsy. In most other instances, the presence of definite IEDs in the EEG leads to a diagnosis of epilepsy which typically requires treatment. It is quite unusual for the medical community to argue against treatment when a diagnostic test shows definite and sometimes severe abnormalities. The principle of "treat the patient, not the test" may be somewhat misguided here. First, as mentioned earlier, the presence or absence of clinical seizures is not always evident. Second, patients with autism have neurological and cognitive deficits. While many of these patients may not have overt clinical seizures, their neurological function is by no means normal. Therefore, the presence of abnormalities on a diagnostic test that measures the integrity and stability of cortical networks in a patient with impaired cognitive function should be taken seriously. However, the question of causality remains unanswered, i.e., is there a causal relationship between IEDs

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and the symptoms of autism, or are they both epiphenomena of the underlying pathophysiological process? There may not be a simple answer to this question, and the distinction may not be very clear. The two possibilities are not necessarily mutually exclusive.

2. Epileptic encephalopathy

Many patients with epilepsy develop some degree of cognitive or behavioral difficulties [9,10]; however, in some cases when epilepsy is severe, the degree of psychomotor deterioration cannot be entirely explained by the underlying etiology or neurological comorbidities [11]. In such cases, the condition is referred to as epileptic encephalopathy [12,13], and the cognitive impairment is believed to be due primarily to the seizures or interictal epileptiform activity [12]. The concept of epileptic encephalopathy stems from the idea that frequent seizures or epileptiform discharges can interfere with normal neuronal physiology and cause disruption of various cognitive processes, such as plasticity, memory encoding, and language processing.

There are many recognized syndromes characterized by frequent IEDs, especially nocturnal, with infrequent or no clinical seizures, and various degrees of cognitive and behavioral disturbances [14]. In most of these syndromes, the causal relationship between IEDs and the cognitive dysfunction has not been established. Benign childhood epilepsy with centrotemporal spikes (BCECTS) is frequently associated with some degree of learning or cognitive impairment, such as central auditory processing disorder, or behavioral problems, including attention deficit. In one study, the severity of academic problems correlated with the frequency of interictal epileptiform discharges [15]. Other studies revealed that normalization of the EEG after treatment resulted in significant improvement in attention [16] and auditory processing [17].

Conditions typically referred to as epileptic encephalopathies are characterized by severe developmental delay or regression, with very frequent seizures, excessive amounts of IEDs on the EEG, or both [11]. Aggressive medical or surgical treatment frequently results in improved cognitive and neurological development, suggesting that the seizures and IEDs were probably interfering with the normal development of the brain [18–20].

It is possible to demonstrate the impact of a single epileptiform discharge on a cognitive process, and in fact, several studies have shown a one-to-one relationship between the occurrence of epileptiform discharges and a brief disruption of cognitive processes, such as reaction time or memory encoding, supporting the concept of transient cognitive impairment due to the presence of epileptiform discharges [21–25].

However, the question at play here is quite more complicated. The fact that a single spike can cause a transient disruption of a cognitive process does not necessarily mean that frequent epileptiform discharges will cause a more global cognitive decline. Landau–Kleffner syndrome (LKS) is the quintessential condition that specifically addresses this question. Landau–Kleffner syndrome is a syndrome characterized by severe language regression in a normally developing child, associated with severe EEG abnormality in deep sleep. Clinical improvement typically correlates with improvement in the EEG, providing support to the concept that cognitive deficits may be due to epileptiform activity. The key point in LKS is that epileptiform activity occurs only or primarily during sleep, with either rare or absent IEDs during wakefulness. Therefore, the concept of a direct one-to-one disruption of a cognitive process by an epileptiform discharge hardly applies here. In this condition, if we accept the causal relationship between epileptiform activity and language regression, we must then assume that frequent disruptions of normal cognitive processes over a prolonged period of time can lead to persistent disturbance of important functions, such as plasticity and memory encoding, that outlasts the occurrence of the IEDs. In other terms, the deleterious effect of IEDs causes a virtual or physiological "injury" to the networks, preventing them from performing their normal function. Recent animal studies lend support to this hypothesis [26]. This also raises the elusive question regarding the role of sleep in cognitive function and its development. Despite the presence of some animal models of severe epileptic encephalopathies [27], understanding the causal relationship between frequent epileptiform activity and cognitive dysfunction remains challenging [28].

3. Epileptiform discharges in autism

Several series have reported the presence of abnormalities in the EEG of individuals with autism. Reported abnormalities included generalized and focal slowing, epileptiform activity, and seizures. Epileptiform abnormalities are more common than nonepileptiform abnormalities [5,29–33]. Generalized, multifocal, and focal epileptiform discharges have been reported. Focal discharges were reported in many different regions [3,4,30,34–36], with some studies suggesting more common temporal discharges [4,37] but others not supporting this finding [32,33]. The frequency of discharges is also variable [3,33,38], and the reported rate of electrical status epilepticus in sleep (ESES) is very low [33,37,39]. There is no information regarding the frequency of discharges based on the location or type. In the author's experience (unpublished data), generalized discharges tend to be infrequent, and centrotemporal spikes tend to be more frequent, sometimes reaching a very high spike index during sleep.

In general, IEDs are common among patients with epilepsy but are rare (1 to 4%) in healthy individuals [40,41]. Conversely, in patients with autism, there is a high rate of IEDs even in the absence of definite clinical seizures. Reported rates are variable ranging from 6.7 to 61% [4,6,32,35,42–44], with many studies reporting rates in the 30% range [29,31,37] and others reporting much lower rates [30,34,36,39].

Some studies attempted to correlate EEG abnormalities with different subsets of individuals with autism. In one study [33], a significantly lower rate of IEDs was found in individuals with Asperger's syndrome compared to those with more severe forms of autism. In addition, the same study found a higher incidence of epileptiform activity in children with aggressive behavior.

Developmental regression was also addressed in many reports with mixed results. Some studies reported a high incidence of epileptiform abnormalities in regressive autism, from 33 to 68% [45,46], and other studies found higher rates of IEDs in individuals with regression compared to those without regression [37,43], raising the potential similarity with LKS. In fact, some clinicians consider autistic regression an indication to obtain an EEG [47]. However, other studies failed to replicate this finding and found no difference in the rate of epileptiform activity between regressive and nonregressive autism [4,6,38,42,43].

A few studies evaluated the prevalence of IEDs based on intellectual function. Some reports found a high correlation between the presence of IEDs and lower IQ [43,48], but other studies failed to replicate this finding [6,31,37]. In terms of the correlation between behavior and IEDs, studies revealed no difference in behavioral problems based on the presence [49] or severity of IEDs [50]. The more important question regarding an anatomical–functional correlation between the location of spikes and the presence of specific cognitive or behavioral problems has not been properly addressed. For example, nearly all patients with autism have impairment in social skills. Several studies have revealed specific deficits in social cognition in patients with various forms of epilepsy [51–53].

Unfortunately, most studies suffer from major limitations, and the variability in the reported rates is probably due to methodological differences. The most obvious problem is that the majority of studies relied on retrospective chart review. The authors frequently had no access to the raw EEG data and relied on reports that were generated for clinical purposes. Therefore, very important information is usually missing, most importantly a standardized measure of spike frequency. If we consider that IEDs may have a causal effect on cognitive dysfunction, then the frequency of IEDs is of the utmost importance. For example, a clinician might find it easy to consider rare bursts of brief generalized discharges as