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REVIEW ARTICLE

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Autism: epileptiform discharge in EEG with and without seizure disorder

Abstract

Autism, also known as autistic spectrum disorder, is a neurodevelopmental disorder, characterised by social and communication deficit with repetitive behaviour and restrictive interest. Epilepsy has been found to be highly comorbid disorder though range varies. But epileptiform discharge in autism without history of epilepsy has been reported by various studies. There is no treatment recommendation for abnormal EEG without history of clinical seizure with anticonvulsant in these populations due to the lack of controlled trials. These abnormal EEG may have an important role to explore its association with autism.

Keywords: Neurodevelopmental Disorders. Anticonvulsants. Pervasive Developmental Disorders.

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Introduction

Autism, term coined by Eugene Bleuler in 1912 meaning "aloneness", was adopted by Leo Kanner, who first described this condition. Autism is often considered the prototypic of pervasive developmental disorder (PDD) because it is characterised by significant delay in all three domains of communication, social interaction, and aberrant behaviour.

PDD include autism, Asperger syndrome, Rett's syndrome, childhood disintegrative disorder, and PDD not otherwise specified.[1] But various PDD fall on a continuum of a spectrum, hence the phrase 'autism spectrum disorder' (ASD) has been used to describe the entire broad range of PDD.[2]

Rates of epilepsy and intellectual disability in ASD

Though various investigations have been conducted like pharmacological, pathological, neuroimaging, neurophysiological but exact aetiology still remain unknown for the majority of the ASD children. But due to presence of comorbid neurological disorder and epilepsy suspicion goes toward central nervous system (CNS) or brain dysfunction because autistic children are found to be high risk for epilepsy. The epilepsy may be subclinical, yielding an electroencephalography (EEG) that is epileptiform but without clinical seizure and is particularly frequent in childhood disintegrative disorder.[3] EEG has been used primarily to measure neurophysiological changes related to postsynaptic activity of the neocortex.[4] The age distribution of epilepsy among children with autism appears to be bimodal, with one peak between infancy and five years of age, and the second in adolescence after the age of ten years.[5] Almost one third of the children with ASD will experience at least one seizure in childhood.[6] Some study reported that prevalence of epilepsy in autism is about 46%.[7] The lifetime prevalence of epilepsy in some sample has been reported 38%.[8] In a population of children at tertiary care epilepsy clinic, Clarke *et al.*[9] noted that 32% fit criteria for ASD. Presence of intellectual disability has been found to be confounding factor for propensity to develop seizure in children with autism. Studies have reported that high percentage of children with ASD have comorbid intellectual disability.[10] Because it is seen that intellectual disability itself is an independent risk factor for developing epilepsy.[11,12]

Subclinical epileptiform abnormality in the absence of seizure in ASD

But one of the interesting finding is that the children with ASD show epileptiform discharge without seizure or epilepsy. These EEG findings have been considered to be a cerebral dysfunction in ASD. Prevalence of high rates of epileptiform discharge in ASD without epilepsy has been reported by various studies. One study has reported non epileptiform abnormal EEG in 17.5% and abnormal EEG with epileptiform discharge in 38.1% of autistic children and in the study, epilepsy were found in 22.1%. Same study reported that abnormal development during first year of life was significantly associated with epileptiform EEG.[13] Akshoomoff *et al.*[14] has reported that out of 60 young children with PDD (two to six years)32%

had EEG abnormalities and only two had clinical seizure. We studied the data of 2011 children during the period of 2011 to 2014.[15] Of the four children with PDD who has done EEG, abnormality was found in three of them.

Loss of acquired skills or developmental regression occurs in one third of children with autism. In the children developing normally, this regression is usually seen in between 18-24 months of age.[16] Sleep EEG in 64 young autistic children with and without regression, and no history suggestive of epilepsy has been conducted by Baird *et al*.,[17] and reported that 39 of the children presented with regressive autism and 20 of the participants showed some epileptiform abnormality. But some other reported only four to 22% of epileptiform discharge in children with autism without seizure disorder.[18,19] These EEG changes include slowing or asymmetry and epileptiform discharges, slow waves, generalised spikes and poly spikes. High prevalence of epileptiform EEG abnormalities in children with autism on video-EEG monitoring in the absence of seizure has been reported by Kim *et al*.[20]

Epileptiform discharges are also reported in healthy children. A longitudinal community-based screening reported that epileptiform discharge had been found to be 3.5% in healthy children between six to 13 years and 5.3% of them develop seizure.[21] Language regression has been observed in both autistic regression and Landau-Kleffner (LK) syndrome. LK syndrome is also known as acquired epileptic aphasia. As per the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) criteria,[22] in this syndrome child with previously made normal progress in language development, loses both receptive and expressive language skills but retains general intelligence. Onset is accompanied by paroxysmal abnormalities on EEG and majority of cases by epileptic seizure. Association between epileptiform EEG and occurrence of regression is unclear; but to rule out LK syndrome, EEG has been often advised. In ASD, regression has been found to be important variable associated with high rates of epileptiform EEG (33-68%). Magnetoencephalography (MEG), a non-invasive method identified a subset of children with ASD who demonstrate clinically relevant epileptiform activity during slow wave sleep and activity may be present even in absence of a clinical seizure. The multifocal activity was identified in the perisylvian brain regions and same region has been involved in LK syndrome.[23,24] A retrospective study examined 149 children with language regression who had overnight EEG monitoring and found that those having isolated language regression had a higher frequency of epileptiform abnormality (60%) than those with language regression in the context of autistic regression.[25] Epileptiform discharges are found in EEG using overnight recording or sleep state recording without history of epilepsy in 31% of children with autism.[17]

Genes implicated both in epilepsy and autism

Recently research on genetic study has found the role of CNTNAP2 gene in autism, which was originally discovered in family with epilepsy.[26] Gamma-Aminobutyric acid (GABA) receptor genes have been found to be a candidate autism susceptibility gene.[26] Abnormalities of GABA synthesis and transmission have been implicated in the pathophysiology of most seizure disorders.[28,29]

Role of anticonvulsant drugs

A retrospective review reported that 60.7% children with ASD without history of epilepsy had epileptiform EEG on 24-hour ambulatory digital EEG in sleep and 176 autistic patients were treated with valproic acid. The most epileptiform abnormalities were localised over the right temporal region.[30]

Antiepileptic drugs have been used for the treatment of inter-ictal epileptic discharge in children with epilepsy and to improve behaviour.[31,32] But, treatment of epileptiform EEG discharges in autism has not been routinely practiced. Hollander *et al*.[33] conducted an open trial of divalproex sodium to suppress the EEG discharges in ASD and found improvement in ASD symptoms. Another study reported improvement of communication and behaviour among individual with autism with epileptiform discharge when treated with valproic acid.[34] There is evidence that autism, intellectual disability, epilepsy, and mood disorder share a common neurochemical substrate. The anatomical location of epileptiform activity in sylvian fissure in patients with autism, intellectual disability, and psychiatric comorbidity supports that there is modulation of amygdala kindling by serotonergic mechanism.[35,36]

Could abnormal EEG without seizure be a biomarker?

High rates of epileptiform discharges in autism in the absence of clinical seizure and recent genetic research finding of common genes in both epilepsy and autism indicate that these discharges could be a biomarker of brain dysfunction. GABA-ergic abnormalities can have early developmental consequences, as GABA acts as an excitatory trophic factor prenatally, guiding growth and connectivity of dendrite.[36] Many children with ASD not diagnosed until the age of four years.[38,39] Hence early detection is necessary to implement early intervention of ASD, which may necessitate the importance of biomarker in these population.[40] Resting EEG studies have detected selective alteration which may be identifiable as early as six months.[41,42]

Conclusion

At present there is little evidence or no controlled trials regarding abnormal EEG treatment without history of seizure in ASD. But in light of high prevalence of epilepsy and epileptiform EEG without epilepsy in children with ASD and detection of common genes in both epilepsy and autism, further research is required to understand the aetiopathological mechanism of autistic children. So that evidence-based pharmacological treatment can be implemented following early identification of biomarkers on EEG of children with autism.

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