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Can EEG characteristics predict development of epilepsy in autistic children?

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ABSTRACT

Background: The high occurrence of epilepsy in children with autism spectrum disorders (ASD) is a clear indication that ASD has a neurobiological basis. The current understanding of the association between epilepsy and ASD is still limited, but from a clinical point of view, this association should not be overlooked.
Aims: We investigated the electroencephalogram (EEG) paroxysmal abnormality in children with ASD and the incidence of later development of epilepsy.
Methods: Participants were recruited from University of Yamanashi hospital and 5 satellite hospitals between April 1, 2001 and March 31, 2005. EEG recordings and clinical evaluations were performed every 6 months for at least 6 years, focusing on paroxysmal abnormality. We scored the occurrence and the location of spikes and evaluated the relation with later development of epilepsy.
Results: The prospective study included 21 patients with ASD (12 males and 9 females) between the ages of 3 and 6 years. EEG paroxysmal abnormalities were present in 11/21 patients (52.4%). In addition, six of 21 patients (28.6%) had epilepsy at some point in their lives. The presence of frontal paroxysms was significantly associated with later development of epilepsy compared with centrotemporal paroxysmus ($p < 0.003$). The type of seizure diagnosed was mainly partial; in particular, partial with secondary generalization in 4/6 (66.7%).
Conclusion: The presence of frontal paroxysms may indicate a higher risk of epilepsy in ASD.

1. Introduction

There are few studies on the prevalence of autism spectrum disorders (ASD) in individuals with epilepsy; however, ASD and attention deficit/hyperactivity disorder (ADHD) are two of the most common neuropsychiatric disorders in children with epilepsy.[1] The high occurrence of epilepsy in children with ASD is a clear indication that ASD has a neurobiological basis. Epilepsy is more common in people with ASD than in the general population,[2] and ASD is more common in people with epilepsy than in those without.[3] In recent studies, three factors, age, cognitive level, and type of language disorder account for most of the variability in the reported prevalence of epilepsy.[2]

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The term autism is herein used to describe all ASDs. This broad category includes various types of pervasive developmental disorders according to the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (4th ed., DSM-IV).[4] ASD is a genetically heterogeneous neurodevelopmental disorder with onset in early childhood, characterized by impairments in communication, reciprocal social interaction and restricted and stereotyped patterns of interests and activities.[5] It should be noted that the prevalence of epilepsy in children in the general population is 2–3%, while a conservative estimate of epilepsy in children with ASD is approximately 25%.[2] Therefore, there appears to be a strong association between ASD and seizure disorders that should be further investigated.[6]

Detection of epileptiform activity in children with ASD has been greatly facilitated by advances in electroencephalographic technology. Rossi et al. studied 106 patients with ASD from about 3–31 years of age, finding a 23.6% prevalence of epilepsy and/or febrile convulsions and paroxysmal abnormality without epilepsy in 18.9% of electroencephalograms (EEGs).[7] Some authors noted that seizures frequently arose in adolescence when EEG paroxysmal abnormality without epilepsy recurred at a rate of 14.3–82.9%.[8,9]

The current understanding of the association between epilepsy and ASD is still limited, but from a clinical point of view, this association should not be overlooked. Therefore, we prospectively investigated the EEG paroxysmal abnormality, especially focusing on paroxysmal abnormality, in children with ASD and the incidence of later development of epilepsy.

2. Participants and methods

Participants were recruited from University of Yamanashi hospital and five satellite hospitals between April 1, 2001, and March 31, 2005. The diagnosis of ASD was made according to DSM-IV criteria (299.00 Autistic Disorder), such as qualitative impairment in social interaction, qualitative impairment in communication, and restrictive, repetitive, and stereotypic pattern of behavior, interests, and acivities.[4] Children with a past history of an established seizure disorder or other neurologic disorders were excluded. However, children with a previous history of febrile seizures and those with a clinical suspicion of undiagnosed seizures (e.g., staring episodes) at the time of first evaluation were included in the study group. Children who were receiving any medication at the time of first evaluation were excluded. Also, we excluded patients with autistic syndromes secondary to a congenital or acquired encephalopathy, but we included those with mild non-specific cerebral lesions of unknown etiology (grey and white matter cerebral lesions were not extensive and not related to malformations or degenerative or metabolic pathology).[7]

Mental retardation (MR) is defined as intelligence quotient (IQ) < 70, resulting in functional impairment (Wechsler Intelligence Scale for Children, version III: WISC-III). Mild mental retardation is defined by an IQ 60–69, moderate mental retardation with an IQ 50–59 and severe mental retardation by an IQ < 50.

Epileptic seizures were defined as a clinical manifestation presumed to result from abnormal and excessive discharges of a set of neurons in the brain (the International League Against Epilepsy, ILAE).[10] The type of seizure is divided to four groups; simple partial, complex partial, partial with secondary generalization, and primary generalized. The type of seizure is diagnosed in combination with EEG recordings. Epilepsy was defined as two or more epileptic seizures, unprovoked by any immediate identifiable cause (ILAE) and excluding neonatal seizures.

Patients were studied using digital EEG. EEG studies were coded by number and read independently by two paediatric epileptologists or neurologists blind to the identity of the patients. EEG recordings and clinical evaluations were performed every 6 months for at least 6 years, focusing on paroxysmal abnormality. Paroxysmal abnormalities, including focal spikes, multifocal spikes, and generalized spike and wave complexes were each coded separately. Interpretations of the EEGs were compared for agreement between readers. EEGs were then scored for the location of spikes and evaluated by whether there was later development of epilepsy. Epilepsy features were investigated taking into consideration the type and frequency of seizures, age at onset, antiepileptic treatment and evolution. The statistical significance of differences was evaluated by Chi-square test and Fisher's exact test. $P < 0.05$ was accepted as a statistically significant result.

Informed consent was obtained from the parents of each patient following a full explanation of the planned procedures.

3. Results

A total of 25 children with ASD were performed EEG. Four were excluded because no follow-up EEG was obtained after first evaluation. The study included 21 patients with ASD (12 males and 9 females) from 9 to 12 years of age, at the last observation (mean age: 10 years and 3 months: mean follow-up: 6.5 years from the first to the last observation). There was not the patient with mild non-specific cerebral lesions of unknown etiology in this study. The clinical characteristics of all patients in this study are presented in Table 1. MR, gender, and family history of epilepsy were not significant as risk factors for later development of epilepsy (MR, $p = 0.29$; gender, $p = 0.68$; family history of epilepsy, $p = 0.35$). Our study showed that one peak occurs in pre-adolescence around age 9 years (mean age, 8.8 years; range, 7.5–10.8 years).

EEG paroxysmal abnormalities were present in 11/21 patients (52.4%). The patients with ASD presented with the following sequential EEG results. In the first observation, none of the 21 patients had abnormal EEG findings. Two years after the first observation, two patients had rare sleep-related frontal spikes. Four years after, four patients had frontal spikes and one had centrotemporal spikes. Six years after the initial observations, six subjects had frontal spikes, three had centrotemporal spikes and two had multifocal spikes (Table 2).

The EEG paroxysmal abnormalities without epileptic seizures were present in five of 21 patients (23.8%). In contrast, six of 21 patients (28.6%) had epilepsy at some point in their lives. The ratio of male to female was 1.0. The characteristics of all patients in the psychiatric follow-up study ($n = 21$) and individuals with epilepsy ($n = 6$) and those without ($n = 15$) are