

# EPILEPSY AND EEG ABNORMALITIES IN CHILDREN WITH AUTISM SPECTRUM DISORDER

*EPILEPSIA E ANORMALIDADES ELETROENCEFALOGRÁFICAS EM CRIANÇAS COM TRANSTORNO NO ESPECTRO DO AUTISMO*

*EPILEPSIA Y ANORMALIDADES ELECTROENCEFALOGRÁFICAS EN NIÑOS CON TRASTORNO EN EL ESPECTRO DEL AUTISMO*

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## ABSTRACT

**Introduction:** Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder characterized by impaired communication and social interaction, and by restricted and repetitive behavior. Children with ASD are more likely to have seizures than children with normal neurological development. **Objective:** Analyze the incidence of seizures and EEG abnormalities in a cohort of 63 patients with ASD. **Methods:** Children with autism were included in the study, which calculated the incidence of epilepsy and analyzed the main abnormalities in the EEG. All the patients were evaluated by the same physician, and underwent EEG and MRI of the brain. **Results:** A total of 63 patients were included between January 2010 and January 2015; 23 (36.51%) female and 40 (63.49%) male; ages at diagnosis ranged from 17 to 58 months ( $35.97 \pm 11.77$  months); in 16 (25.4%) patients the MRI was reported to be abnormal. All the patients with autism and epilepsy had abnormal EEGs; 11 (17.4%) had a diagnosis of epilepsy ( $n=7$ ; 63.6% female and  $n=4$ ; 36.4% male); and the mean age at diagnosis of epilepsy was  $33.7 \pm 4.3$  months. **Conclusion:** Our findings suggest that in patients with autism, epilepsy rates are higher than in the general population, but there is no unique pattern of discharge in the EEG.

**Keywords:** Autistic disorder, Epilepsy, Electroencephalogram.

## RESUMO

**Introdução:** O transtorno do espectro do autismo (TEA) é um distúrbio de desenvolvimento neural heterogêneo caracterizado por comunicação e interação social deficientes e por comportamento restrito e repetitivo. As crianças com TEA têm maior probabilidade de ter convulsões do que as crianças com desenvolvimento neurológico normal. **Objetivo:** Analisar a incidência de convulsões e anormalidades eletroencefalográficas em uma coorte de 63 pacientes com TEA. **Métodos:** Foram incluídas no estudo, crianças com autismo, a incidência de epilepsia foi calculada e as principais anomalias do EEG foram analisadas. Todos os pacientes foram avaliados pelo mesmo médico e foram submetidas a EEG e RM do cérebro. **Resultados:** De janeiro de 2010 a janeiro de 2015, foram incluídos 63 pacientes, 23 (36,51%) do sexo feminino e 40 (63,49%) do sexo masculino; a idade ao diagnóstico variou de 17 a 58 meses ( $35,97 \pm 11,77$  meses); em 16 (25,4%) pacientes o laudo da RM relatou anormalidade. Todos os pacientes com autismo e epilepsia tinham uma anormalidade no EEG, 11 (17,4%) tinham diagnóstico de epilepsia ( $n = 7$ ; 63,6% meninas e  $n = 4$ ; 36,4% meninos); a média de idade ao diagnóstico de epilepsia foi  $33,7 \pm 4,3$  meses. **Conclusão:** Nossos achados sugerem que em pacientes com autismo, as taxas de epilepsia ainda são mais altas do que as da população de risco geral e não existe um padrão único de descarga no EEG.

**Descritores:** Transtorno Autístico; Epilepsia; Eletroencefalograma.

## RESUMEN

**Introducción:** El trastorno del espectro del autismo (TEA) es un disturbio de desarrollo neural heterogéneo caracterizado por comunicación e interacción social deficientes e por comportamiento restringido e repetitivo. Los niños con TEA tienen mayor probabilidad de tener convulsiones que los niños con desarrollo neurológico normal. **Objetivo:** Analizar la incidencia de convulsiones y anormalidades electroence-

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*falográficas en una cohorte de 63 pacientes con TEA. Métodos: Fueron incluidos en el estudio niños con autismo, la incidencia de epilepsia fue calculada y las principales anomalías del EEG fueron analizadas. Todos los pacientes fueron evaluados por el mismo médico y fueron sometidos a EEG y RM del cerebro. Resultados: De enero de 2010 a enero de 2015, fueron incluidos 63 pacientes, 23 (36,51%) del sexo femenino y 40 (63,49%) del sexo masculino; la edad en el momento del diagnóstico varió de 17 a 58 meses ( $35,97 \pm 11,77$  meses); en 16 (25,4%) pacientes el laudo de la RM relató anomalía. Todos los pacientes con autismo y epilepsia tenían una anomalía en el EEG, 11 (17,4%) tenían diagnóstico de epilepsia ( $n = 7$ ; 63,6% niñas y  $n = 4$ ; 36,4% niños); el promedio de edad en el momento del diagnóstico de epilepsia fue  $33,7 \pm 4,3$  meses. Conclusión: Nuestros hallazgos sugieren que en pacientes con autismo, las tasas de epilepsia aún son más altas que las de la población de riesgo general y no existe un estándar único de descarga en el EEG.*

**Descriptores:** Trastorno Autístico; Epilepsia; Electroencefalograma.

## INTRODUCTION

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder characterized by impaired communication and social interaction and by restricted and repetitive behavior<sup>1</sup>. The diagnosis of ASD is based on clinical criteria; however, some neuroimaging and neurophysiological tests are often performed to establish the etiology and severity of the disease<sup>2,3</sup>. There are some neurological conditions related to ASD, and among those, epilepsy is the best-known comorbidity. Epilepsy is reported to occur in 5 to 46% of individuals with ASD, which exceeds the prevalence of epilepsy in general population (0.7-1%)<sup>2,4,5</sup>.

The increased prevalence of epilepsy and/or EEG abnormality in patients with ASD reinforce the belief that these patients have some basal neurologic condition, but this association is not completely understood<sup>4,5</sup>. There are no seizure type or electroencephalography (EEG) patterns specifically associated with ASD. Some studies have been already reported complex partial seizures (with or without secondarily generalized), absence, and generalized tonic-clonic seizures. Recognition of different EEG types or patterns can be very useful as evidence of cortical dysfunction in ASD, and may reveal some sort of brain damage<sup>5</sup>. The aim of our research is to analyze the occurrence of epilepsy and the main EEG abnormalities in children with ASD.

## METHODS

We retrospectively reviewed the medical records of 63 children with ASD and epilepsy, admitted to the Department of Pediatric Neurology of Pequeno Principe Hospital, Curitiba, Brazil, between January 2010 and January 2015, evaluating them for epilepsy diagnosis. In order to be included in study the participants had to have a diagnosis of ASD based on DSM-V<sup>3</sup> clinical criteria established by and expert clinical evaluation. For the purpose of this study, the definition of epilepsy adopted was the occurrence of at least one epileptic seizure and a brain disorder characterized by persistent predisposition of the brain to generate seizures and by neurobiological, cognitive, psychological and social consequences of this condition<sup>6</sup>.

All patients were evaluated by the same physician, and performed EEG MRI of the brain. The EEG tests were performed in digital equipment Neuropmap EEG-40i, Neurofax Nihon Kohden EEG-1200 or EEG Brain Wave II, lasting as a minimum 30 minutes. The electrodes were placed according to the International 10-20 System of Electrode Placement

(this international system is based on the relationship between the location of an electrode on the scalp and the underlying area of cerebral cortex).

Clinical variables included gender, age of autism diagnosis, age of epilepsy onset, maternal age at pregnancy, perinatal factors (such asphyxia), family history of neurological disease, EEG pattern, MRI findings, and pharmacological treatment. The systematic analysis of EEG abnormalities considered: (a) focal pattern - up to three independent and well-delineated epileptogenic focus; (b) multifocal pattern - more than three independent epileptogenic focus; and (c) generalized pattern - synchronous discharges in large areas of two hemispheres brain.

Data were analyzed using descriptive statistics. The local Ethics Committee on Research Involving Human Subjects (number registration - 44905015.0.0000.0097) approved all aspects of this research.

## RESULTS

### Patients characteristics and neuroimaging

From January 2010 to January 2015, 63 patients with ASD were included in the study, 23 (36.51%) female and 40 (63.49%) male. The age at diagnosis ranged from 17 to 58 months ( $35.97 \pm 11.77$  months). Maternal age at pregnancy ranged from 21.4 to 58 years ( $30.03 \pm 4.27$  years). Prolonged labor and perinatal asphyxia occurred in 5 (7.94%) and premature birth in 6 (9.52%) patients. Family history of neurological disease was reported in 10 (15.87%) patients - 4 siblings with delayed speech development, 2 siblings with neuropsychomotor development delay, 1 sibling with autism, 1 cousin with autism, 1 cousin with delayed speech development and 1 cousin with Down syndrome (DS). All patients included in the study underwent MRI examination of the brain. In sixteen (25.4%) patients the MRI was reported to be abnormal. All patients with ASD and epilepsy had an abnormality of EEG.

### Prevalence and epilepsy classification

Of 63 individuals,<sup>7</sup> (17.4%) had epilepsy diagnosis ( $n=7$ ; 63.6% female and  $n=4$ ; 36.4% male). The mean age at diagnosis of epilepsy was  $33.7 \pm 4.3$  months. We obtained EEG reports for all the 63 patients, as part of their clinical follow-up. The EEG information for 52 (82.54%) participants without clinical seizures did not report epileptiform discharge, but in 50% of these patients showed a mild to moderately disorganized background activity. For the eleven participants with clinical epilepsy, EEG data supported the diagnosis and was useful in the classification

of seizure type: 1 patient (9.1%) had spike and polyspike generalized discharges; 1 patient (9.1%) had sharp wave discharges in the left middle temporal lobe; 3 patients (27.3%) had multifocal sharp waves; 1 patient (9.1%) had sharp wave discharges in the left anterior and middle temporal lobe; 1 patient (9.1%) had spike-wave generalized discharges with irregular morphology and multifocal sharp waves; 1 patient (9.1%) had sharp wave discharges in the left frontal lobe and left anterior temporal lobe; 1 patient (9.1%) had sharp wave discharges in the right frontal lobe and right anterior temporal lobe. In the other two patients the EEG was reported only with mild to moderately disorganized background activity (no epileptiform discharges).

### Clinical treatment

Antiepileptic drugs and/or antipsychotic drugs, such as sodium valproate, lamotrigine, pericyazine, risperidone, clonazepam and clobazam were being prescribed for eighteen patients (28.57%). The majority of them (55.5%; n=10) were receiving only one drug, while 22.2% (n=4) of the patients were under a treatment with two drugs and the other 22.2% (n=4) were using three drugs.

## DISCUSSION

Epilepsy is considered a well-known significant comorbidity associated with ASD, and it causes important disability to individuals.

The mean age of epilepsy diagnosis in this study was  $33.7 \pm 4.3$  months. Epilepsy in ASD has two peaks of presentation, one in early childhood and the other in adolescence, which is believed to be more common<sup>5,8</sup>. In a retrospective British study, 150 individuals with autism were evaluated for onset of epilepsy, and revealed that in the majority of cases, seizures first began after the age of 10 years, consistently with the prevalence founded in other studies, which is 22% to 38% in adolescents and young adults with ASD<sup>4</sup>. The prevalence of epilepsy in individuals with ASD founded in our sample was 17.4%, consistently with previous data, although it is been reported a wide range (5-46%) in epilepsy frequency in those patients<sup>9,10</sup>. This variability has been credited to the heterogeneity of samples with respect to age, sex, comorbidity, intellectual disability, ASD phenotypes and epilepsy diagnose criteria<sup>7</sup>. The founded epilepsy prevalence associated to autism in our sample was not as high as others studies, probably because we included only younger children. It can be hypothesized that after a few years, at adolescence, some of those patients without seizures present with onset of epilepsy, increasing those numbers.

Regarding the gender, the autism sample was formed mainly for males, thus, the association with epilepsy was more prevalent in female (63.6%). It is believed that female gender is more associated with epilepsy<sup>4,11</sup>. A meta-analysis found the male to female ratio in autism with epilepsy was close to 2:1 vs. 3.5:1 in autism without epilepsy<sup>7</sup>. Unfortunately, further information is necessary to determine the risk for epilepsy as a function of gender.

Among the eleven patients with the association between autism and epilepsy, all were associated to neurologic conditions or MRI abnormalities. Some well-known neurological comorbidities associated to ASD, as tuberous sclerosis, fragile X

syndrome and DS, have a high rate of epilepsy themselves, and might be the underlying cause to the increased prevalence in non-idiopathic groups of ASD<sup>7,12,13</sup>. The emerging literature of structural and functional neuroimaging in autism may reveals some underlying central nervous system (CNS) abnormality<sup>(5)</sup>. In tuberous sclerosis, for example, the change that affects the frontal or mesiotemporal structure (limbic system) can be the origin of an autistic phenotype<sup>7,9</sup>. Even though, idiopathic groups of ASD still show a considerable increase of epilepsy rate above general population (1%)<sup>9</sup>. That suggests a possible common pathophysiological alterations between these two conditions<sup>14</sup>. An altered balance between excitatory and inhibitory synapses, that contributes to epileptogenic discharges, could affect learning and social behavior<sup>15</sup>.

The clinical diagnosis of seizure in autistic individuals can be challenging because behavior abnormalities can be attributed to either complex partial seizure and/or to the clinical characteristics of autism itself<sup>5</sup>. No specific seizure type were associated with autism, but there are some reports with higher prevalence of abnormality in temporal region<sup>8,9</sup>, which is consistent with our findings (36.6% - 4/11 children). Although, many reports of background or interictal EEG changes in individuals with autism without seizures, has not being considered evidence of epilepsy, but a sign of cerebral dysfunction, which may leads to behavioral, communicative and cognitive deficits<sup>5</sup>. Recently, high rates of epileptiform EEG in children with autism without a history of seizures or epilepsy had been reported<sup>9,16</sup>. In our study, 50% of the children without clinical seizures had EEG abnormalities at the background activity, but none of them presented with epileptiform discharge.

EEG has an important role at investigation of individuals with ASD and clinical seizures, although there is not a consensus if it should be performed in all children with autism<sup>17</sup>. Occasionally founded discharged usually is treated only in specific cases, such as Landau-Kleffner syndrome and infantile spasm<sup>16,18</sup>. Experimental studies suggest that in the immature brain, interictal spikes may result in alterations in neuronal network function, impaired short and longterm potentiation, and possibly decreased neurogenesis or cell loss of specific populations<sup>19</sup>. Although this hypothesis is not already well established, if further investigations reveal the real causal relationship between epilepsy and autism, a substantial percentage of patients could conceivably benefit from treatment, not only because of seizures control, but also by improving behavioral, language, or cognitive disturbance<sup>5,18</sup>.

The main limitation of our research was the small number of patients studied. However, we believe that our data can contribute to better understanding of the relationship between ASD and epilepsy.

Our findings suggest that in autism samples, epilepsy rates are still higher than the general population risk epilepsy, and there is not a unique pattern of discharge at the EEG. The ASD investigation should include an EEG as instrument for epilepsy diagnosis, especially in children with neurological associated disorders. A large systematic studies and appropriate longitudinal follow-up may better shed light on clinical aspects of the relationship between ASD and epilepsy, and could have a significant impact on outcomes for patients and their families.

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