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RESEARCH ARTICLE

Epilepsy and electroencephalographic abnormalities in patients with diagnosis of idiopathic autism spectrum disorder in Medellín

Epilepsia y anormalidades electroencefalográficas en pacientes con diagnóstico de trastorno del espectro autista idiopático en la ciudad de Medellín

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Abstract.
The objective of the present study was to make a clinical and electroencephalographic characterization of the electrical findings and types of seizures in patients with idiopathic autism. Pediatric patients of any age, with the diagnosis of idiopathic ASD, contained within the database of the research "Genetic in autism" were included. An electroencephalographic recording with epilepsy protocol was performed in all the patients. 20 pediatric patients were included with an age media of 10.5 years, SD 5.48 years. The median age for the diagnosis of ASD was 53 months, and epileptic seizures were documented in 45%. 66.6% of patients with epileptic events had anti-epileptic treatment, and only 33.3% had achieved seizure control with medication. Interictal abnormal EEG records were found in 8 patients (40%), with 6 of them having epileptic seizures. The abnormal EEG activity was multifocal in 62.5%, focal in 25% and generalized in 12.5% of the cases. The most frequently compromised location was the temporal lobe.

Resumen.
El objetivo del presente estudio fue caracterizar desde el punto de vista clínico y electroencefalográfico los hallazgos eléctricos y los tipos de crisis en pacientes con autismo idiopático. Se incluyeron pacientes de cualquier edad, con diagnóstico de TEA idiopático y pertenecientes a la base de datos de la investigación "Genética del Autismo". A todos los pacientes se les realizó electroencefalograma de rutina (EEG) con protocolo de epilepsia. Se recolectaron 20 pacientes en edad pediátrica con edad media de 10.5 años, DE de 5.84 años. Para la edad de diagnóstico del TEA, la media era de 53 meses. Se documentaron crisis epilépticas en 45% de los pacientes. De todos los pacientes con crisis, 66.6% tenían tratamiento con medicamentos antiepilépticos, y solo 33.3% habían logrado control de las crisis con el tratamiento. El EEG interictal fue anormal en 8 pacientes (40%), de los cuales 6 tenían crisis epilépticas. La actividad anormal fue multifocal en 62.5% de los pacientes, focal en 25% y generalizada en 12.5% de los casos. La localización más frecuente de las anomalías fue en el lóbulo temporal.

Keywords.
Autism; Epilepsy; EEG; Seizure.
Palabras Clave.
Autismo, epilepsia, electroencefalograma, crisis epiléptica.

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1. Introduction

The autism spectrum disorder (ASD) is a neurologic development alteration characterized by deficiencies in social communication and reciprocal interaction, accompanied by restricted, repetitive, and stereotyped behavioral patterns (American Psychiatric Association, 2013).

The relationship between ASD and epilepsy has been subject of interest since 1943, when the initial description by Leo Kanner reported autism linked with epilepsy. This association has generated discussion, and it has been debated if there is a causal relation, or if the two conditions result from the same biologic bases. It is not likely that the co-occurrence of ASD and epilepsy has a single explanation. It is probable that there may exist common genes to both diseases, and this debate needs to be analyzed in the frame of molecular and genetic knowledge (R. Tuchman et al., 2009). There are not many articles in the Spanish literature concerning both these topics, and most of them come from Spain. This work pretends to alleviate this lack of information, at least in Latin-America.

The electroencephalographic findings in patients with autism and epilepsy in the 1960s were the first to suggest autism as a possible neurobiological disorder (Hutt et al., 1965). Spence and Schneider found that the estimated prevalence of epilepsy in ASD is between 5-46%, with epileptiform abnormalities in 60% of patients with ASD (Spence & Schneider, 2009).

Several studies have attempted to describe such association, and recently Wirrell et al. (2017) described that comorbid autism spectrum disorder affects approximately 7.4% of children with epilepsy and found that coexisting intellectual disability is the most significant correlation. Nicotera et al. (2019) also described that EEG abnormalities are present in patients with ASD and correlate with several phenotypic features, such as autism severity, hyperactivity, anger outbursts, aggressive behavior, even in patients with no clinical evidence of seizures. Portnova et al. (2019) described a relationship between an increase in beta and frontal theta amplitude in patients with autism, and tactile hypersensitivity. Such findings encourage the consideration of making electroencephalogram in patients with autism, even in the absence of seizures.

The aim of this study was the clinical and electroencephalographic characterization of interictal EEG abnormalities and the Electro-Clinical types of Seizures in patients with diagnosis of idiopathic autism.

2. Method

This is a transversal, cross-sectional, descriptive study with a consecutive, non-randomized, at convenience sample. Pediatric patients, with diagnosis of idiopathic ASD, contained within the database of the research "Genetic in autism", belonging to the Pediaciencias and molecular genetics research group of the Universidad de Antioquia, who fulfilled the inclusion criteria, and whose parents or legal guardians accepted to participate on the research, were included. An electroencephalographic recording with epilepsy protocol was performed in all the patients.

The sample was collected between January 2010 and May 2011. The information was obtained through telephonic interview, clinical records. A routine EEG analysis was performed in each patient. The performance of an EEG that included sleep was obtained in most patients, without use of sedatives. It allowed the evaluation of sleep characteristics, with an emphasis on the presence of sleep spindles, and normal background rhythms. Both findings could be associated with better control of epilepsy. The EEG records were reviewed for one of the authors. Their information was recorded in a form, which included all demographic data, age of onset and diagnosis of ASD, presence or absence of epileptic crisis and their semiology, pharmacologic treatment, EEG findings and sleep characteristics.

Inclusion criteria: Pediatric patients contained within the described database, who had filled an informed consent formed, signed by a parent or legal guardian accepting to be part of the study.

Exclusion criteria: Impossibility to perform an EEG, presence of secondary ASD or absence of an EEG including sleep in the cases that had history of seizures.

3. Results

20 patients were included with an age media of 10.5 years, SD 5.48 years. The male to female ratio was 8.5:1.5. The onset age of autistic symptoms, such as social impairment, limited initiation of social interaction and abnormal responses to social overtures, and deficit in verbal and nonverbal social skills, was between 4 and 60 months, with a media of 17.6 months, SD 12.5 months. The median age for the diagnosis of ASD was 53 months, SD 28 m. Table 1.

Epileptic seizures were documented in 9 patients (45%), resulting in a global prevalence of 0.45. The seizure semiology was evaluated in the group of patients who presented epileptic crisis. 7 patients had focal seizures with impaired awareness (77.7%), with 3 of them being focal to bilateral tonic-clonic seizures. 3 patients had generalized onset seizures. One of the patients with focal onset seizures also had isolated generalized seizures, which were considered at the final percentage analysis. All the patients with focal to bilateral seizures had impaired awareness.

Additional developmental regression (autistic regression) was seen in 7 of the 20 patients (35%), through clinical evaluation of the attending neurologists, without the requirement of an IQ test. All the patients with

Table 1

Age range distribution for symptom onset and ASD diagnosis in patients with idiopathic autism. Medellín, Colombia. 2010-2011

Age range. Symptom onset (months)	*n*	*p*	**Age range for diagnosis (months)**	*n*	*p*
1 to 6 months	3	15%	1 to 6 months	0	0%
7 to 12 months	7	35%	7 to 12 months	0	0%
13 to 24 months	8	40%	13 to 24 months	2	10%
25 to 36 months	1	5%	25 to 36 months	7	35%
37 to 48 months	0	0%	37 to 48 months	3	15%
49 to 60 months	1	5%	49 to 60 months	3	15%
			Older than 60 months	5	25%
TOTAL	20	100%	TOTAL	20	100%

autistic regression were male, and 5 of them suffered of epileptic seizures, which had started between the ages of 25 and 36 months in 35% of them.

Of all the patients with seizures, 66.6% had anti-epileptic treatment, and only 3 of the 9 patients (33.3%) had achieved seizure control at least during 12 months with medications. The most used anti-epileptic drug was valproic acid (33.3%).

3.1 Interictal activity

Abnormal EEG records were found in 8 patients (40%), with 6 of them having epileptic seizures. The abnormal EEG activity was multifocal in 62.5%, focal in 25% and generalized in 12.5% of the cases. The most frequently compromised location was the temporal lobe (62.5%), followed by the frontal lobe (50%), central region (37.5%), occipital lobe (25%) and parietal lobe (12.5%). It is important to emphasize that the only locations with exclusive affection were the temporal and frontal lobe, each of them corresponding to a 12.5% of the abnormalities. Focal interictal abnormalities were not always related with the presence of focal seizures in these patients.

3.2 Type of electroencephalographic abnormalities

The electroencephalographic abnormalities corresponded, in order of frequency, to focal spikes, sharp waves, and spike slow wave, mainly in the temporal and frontal lobes.

4. Discussion

In the present study, a predominance of male gender was found in patients with ASD, coherent with a broad reported findings on several previous national and international publications, in which a male to female ratio could vary from 1.4:1 to 15.7:1, depending on the analyzed samples, (Fombonne, 2005; Gabis et al., 2005; Lai et al., 2015; Mottron et al., 2014; Ozonoff et al., 2011). Some hypotheses have been elaborated trying to explain the lower prevalence in female gender, such as the theory of the extremely masculine brain, the female protection factor, cerebral plasticity variants, as well as genetic and epigenetic factors, among others (Johnson et al., 2007).

In contrast with other studies which have documented a higher incidence of epilepsy in women with autism (Johnson et al., 2007), the present study found a bigger number of affected males; nevertheless, this study had a small sample size, which could have contributed to such results.

Most children with ASD show the first symptoms of social impairment, limited initiation of social interaction and abnormal responses to social overtures, and deficit in verbal and nonverbal social skills, between the 12 and 18 months of age, or before, (Filipek et al., 2000). In our sample, the age of onset of autism symptoms was between 13 and 24 months in 40% of patients.

In relation to the age of diagnosis of ASD, it is well known that most children with ASD do not reach a diagnosis until the age of 3 or more (CDC 2016; Matson et al., 2012; Shattuck et al., 2009). In the present study, the age of diagnosis was around 53 months, similar to other author's findings. Research shows that early detection and precocious intervention improve results, highlighting the importance of an active search for ASD symptoms Olsson et al., 1988. Our study found a high prevalence of epilepsy in patients with ASD, indicating that 45% of patients included in the study had epileptic seizures, in contrast with Olsson and collaborators (1988), who reported 20% of epileptic seizures in idiopathic autistic patients. Wong (1993) made a prospective study with 246 children with ASD and found an increased prevalence in early onset seizures, mostly before the first year of life, 5% of epileptic seizures in the infantile autism group; those findings are far below our epilepsy prevalence. One systematic review reported a non-based population prevalence of epilepsy in autistic patients of 13.8%, being lower to our findings (Lukmanji et al., 2019).

This difference in prevalence could be explained by the fact that our sample was based on clinical grounds.

Epilepsy prevalence in that population has been reported to be between 8 and 42%, (Canitano et al., 2005). However, results are related with several factors: the age groups of the studied population, with a higher seizure percentage in teenagers and young adults; and the cognitive level, with a higher incidence of seizures in the studies, including individuals with a lower functionality level (Jokiranta et al., 2014). From a pathophysiologic point of view, it has been proposed that the defects in GABAergic signaling could be a common pathway for the autism and epilepsy comorbidity (Collins et al., 2006).

The seizure semiology in our study was mainly focal (77%), and less commonly generalized (33%). Similar findings were reported in a major population study about ASD in which focal seizures were reported in 73% of the patients, while primarily generalized seizures were seen in the remaining 27% (Christensen et al., 2016). In 1995, Rossi et al. studied 25 patients with epilepsy and autism, including febrile seizures and Interictal Abnormalities. They described one case with idiopathic neonatal convulsions (BINC); 8 patients with febrile seizures with or without partial epilepsy during the follow up; 5 cases (20%) with idiopathic partial epilepsy (BCECTS); 12 patients (48%) with partial epilepsy and three cases (12%) with generalized epilepsy. Those findings are not different from our study, in which 73% of our patients have partial seizures and 27% were generalized. Related to the type of seizures, Rosii et al. described a group of 25 patients, 8 with focal seizures, 11 with focal seizures with secondary generalization (bilateral motor generalization), and hemi-convulsive status epilepticus in 2 of them, similar to what was found in our study 1995.

In 2004, Hrdlicka et al. found epilepsy in 22.1% of patients with autism. Epileptiform abnormalities on EEG are even more frequent than clinical epilepsy in youngsters with autistic spectrum disorder. In contrast, we found 40% of interictal activity and 45% of epilepsy in our sample. That finding could be explained because we did not obtain sleep EEG in some of our patients, and there were some patients with epilepsy and a low charge of interictal abnormalities. Another explanation concerning the highest number of patients with clinical epilepsy could be related with our sample characteristics, because they were part of a deep evaluation inside one genetic study of genetic autism. Baird et al., 2006, who carried out one study of sleep EEGs in 64 children with autism, none of whom had a history suggestive of epilepsy, found that thirty-nine of the 64 children had autism with loss of skills, and 20 of them had epileptiform abnormalities with no evidence of clinical epileptic crisis. Those findings are close to the ones in our sample.

The discharges can be focal, being present in the temporal area in 30% of the cases, central area in 28%, frontal area in 23%, and occipital area only in 8% of the patients (Christelle et al., 2015). Those finding are similar to our study. This epileptiform discharges in the EEG of children with ASD in absence of clinical history of seizures is a poorly understood phenomenon so far, and arises questions such as: Is this epileptiform activity related to a higher risk of developing clinical epilepsy? Is there any relationship between EEG findings and behavioral disturbances in ASD? Should such findings be treated? (Sansa et al., 2011).

Parmeggiani et al. (2010), studied 345 patients with autism and they only found 2.6% of patients with discontinuous and continuous interictal EEG abnormalities during sleep. In our study, interictal findings were mostly multifocal abnormalities. There were no cases of continuous spikes in sleep suggesting epileptic encephalopathy, in this case referring to Landau Kleffner syndrome or continuous spike-wave in slow sleep syndrome (Parmeggiani et al., 2010).

Christensen et al. found a clear increase in risk of epilepsy and ASD in siblings, which suggest that genes or environmental factors shared by family members could play a role in the co-occurrence of both disorders, which also implies that such abnormalities should be searched (2016).

Currently, there are no guidelines for the treatment of seizures in patients with autism spectrum disorders. The decision is based on several criteria, with one of the most important criteria being the determination of a base genetic etiology. Likewise, the type of crisis and adverse effect profile must be considered (Rossi et al., 1995).

Some studies have demonstrated a good control of epilepsy with the use of one or two anticonvulsive drugs (Canitano et al., 2005; Tuchman & Rapin, 1997; Wong, 1993). Wirrell et al. (2017) suggest that ASD does not adversely impact prognosis of epilepsy, and most patients achieve long-term seizure control with AED, even though Sansa et al. had previously reported a treatment refractory rate of 34%. In our study we found only 3 of the 9 patients with control of epileptic seizures; nevertheless, our sample size was not big enough to allow significant conclusions on that matter.

The main limitations of these type of studies are related to the small number of patients and the difficulties concerning the exact timing of EEG abnormalities beginning, as well as how they are related with the increase of autistic severity or decrease in their global developmental behavior.

Given the type of study, it is even more complex to find a clear relation between the interictal EEG abnormalities and the grade of autistic regression or additional behavioral compromise. As we did a retrospective analysis of data, we could not clearly resolve such questions. The follow up of these patients was difficult because our health system, as it constantly changed our

patients to different healthcare centers.

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