ORIGINAL ARTICLE

Epilepsy in Children and Teenagers with Autism Spectrum Disorder: A Review of 15 Years

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Abstract

Introduction: Autism spectrum disorder is characterized by persistent deficits in social communication and interaction as well as restricted patterns of behavior, interests, and activities in the early developmental period. It is an increasingly frequent diagnosis. Association between autism spectrum disorder and epilepsy is known. Different studies have reported different predictive factors related to the future diagnosis of epilepsy, such as cognitive impairment, neurodevelopmental regression, and absence of language.

Methods: We conducted an observational, retrospective, descriptive, and comparative study reviewed clinical records of pediatric patients with autism spectrum disorder who were followed up in a child developmental center between January 2006 and January 2021. The data were analyzed using SPSS software (version 23). The level of significance was set at $p < 0.05$.

Results: The present study included a total of 377 children and adolescents with autism spectrum disorder, of whom 41 (10.9%) were later diagnosed with epilepsy. The mean follow-up time was five years. In patients with epilepsy, the most frequent age of the first seizure was determined in two periods: between 2-5 years (53.5%) and during teenage years (25.6%). The most frequent (68.3%) presentation was focal seizures, 56.1% of which were electroencephalogram paroxysms (17.1% in the temporal lobe). The majority (65.9%) were currently treated with antiepileptics, 60% in monotherapy and mostly with sodium valproate (37.2%). Regression (39% *vs* 19.3%, $p = 0.008$) and absence of language (41.5% *vs* 23.8%, $p = 0.022$) had higher association with the development of epilepsy in patients.

Discussion: Based on the obtained results, 11% of patients had both autism spectrum disorder and epilepsy. Neurodevelopmental regression and the absence of language were associated with the development of epilepsy. This may imply the need for specific counselling and anticipatory care in this subgroup of patients.

Keywords: Adolescent; Age of Onset; Autism Spectrum Disorder/epidemiology; Child; Comorbidity; Epilepsy/diagnosis; Epilepsy/epidemiology

Keypoints

What is known:

- Autism and epilepsy share a common neurobiological substrate.
- In our series of children and adolescents with autism, neurodevelopmental regression and absence of epilepsy were associated with the future diagnosis of epilepsy.

What is added:

- This is the first characterization of epilepsy in autism in a national reference center.
- In our study the main electroencephalography finding was temporal lobe paroxysmal activity.
- Most of our children achieved seizure control with monotherapy with either sodium valproate or carbamazepine, however autism persisted.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by the early onset of persistent deficits in social interactions and communication and repetitive and restricted interests and behaviors.[1] In addition to the core issues, patients with ASD frequently suffer from co-occurring conditions, such as intellectual disability, seizures, attention-deficit disorder, sensory integration difficulties, anxiety, obsessive-compulsive

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symptoms, gastrointestinal conditions, and sleep disorders.[2]

Although ASD is a lifelong disorder, variability occurs in the pattern, severity of symptoms, and the timing of diagnosis. It is becoming a more frequent diagnosis, with rising incidence and prevalence rates. This is probably due to an increase in awareness of this neurodevelopmental disorder, changes in the diagnostic criteria, better identification approaches, improvement of screening methods, and complex interaction between genetic and environmental factors.[3] Prevalence also varies between countries. The ASD prevalence is highest in the United States, with 1/54 children diagnosed, according to 2021 data.[4] In Portugal, limited data on ASD from 2007 shows a global prevalence of 9.2/10 000.[5] This high prevalence justifies the recommendations by the American Association of Pediatrics to screen children for ASD at 18 and 24 months of age.[6]

Epilepsy was defined in 2014 by the International League Against Epilepsy as a state of an enduring predisposition to recurrent epileptic seizures. It has been characterized by the occurrence of two unprovoked seizures separated by 24 hours, one unprovoked seizure with a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures over the next 10 years, or the diagnosis of an epileptic syndrome.[7]

Association between ASD and epilepsy is well recognized.[8] Epilepsy and ASD are both heterogeneous clinical disorders, and several studies found that the prevalence of epilepsy in children with ASD varied between 2% and 66% with a median of 12%.[3,9,10] Series with a longer follow-up typically have higher prevalence rates. Several variables in the literature, including cognitive impairment, neurodevelopmental regression, and absence of language, can be associated with the later diagnosis of epilepsy in patients with ASD.[11,12]

This study aimed to characterize the development of epilepsy in patients diagnosed with ASD and identify factors associated with the future diagnosis of epilepsy in this group of children.

Methods

We conducted an observational, retrospective, descriptive and comparative study by reviewing the clinical records of patients with ASD under 18 years of age, who were followed in a child developmental center between January 2006 and January 2021.

The data reviewed in the clinical records included gender, presence of seizures, type of seizure, presence of family history, skin lesions, macrocephaly, dysmorphic features, cognitive impairment, neurodevelopmental regression, absence of language, medication, investigation pursued, namely contrast-enhanced magnetic resonance imaging (MRI), electroencephalography (EEG), and genetic testing.

Autism spectrum disorder

Diagnosis of ASD was defined using Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria.[1]

Teenagers

Teenager age patients were considered to be those in the age range of 10-19 years, according to the definition by World Health Organization (WHO).

Epilepsy

Epilepsy was defined using the criteria from the International League Against Epilepsy classification.[7]

Seizure type

Seizures were classified based on the operational classification of seizure types.[13]

Family history

Family history was defined as the history of a neurodevelopmental or psychiatric diagnosis in a relative until three generations.

Cognitive impairment

Cognitive impairment was considered when the intellectual functioning level and adaptive skills were significantly below the average for the child chronological age as determined by the psychological evaluation (intelligence quotient range < 70).

Neurodevelopmental regression

Neurodevelopmental regression was defined as a loss of previously acquired neurodevelopmental milestones.

Favorable response to treatment

It was defined as a favorable response to treatment when there was at least a 50% reduction in seizures.

Exclusion criteria were the presence of a prior genetic diagnosis that predisposed to epilepsy and the presence of infantile spasms or Dravet syndrome prior to the diagnosis of autism spectrum disorder. The data were collected by consulting the clinical records of patients and our center database. We used Microsoft Excel (version 14) and IBM SPSS Statistics software (version 23) to perform statistical analysis. Descriptive statistics and the chi-square test were adopted to compare nominal variables and multifactorial analysis. The level of statistical significance was set at $p \leq 0.05$.

Results

A total of 377 pediatric patients with ASD met the inclusion criteria, the majority of whom were male (82.1%, n = 310), with median current age of 12 years (2-18 years of age). On average, the age of referral for consultation was 2.6 years (1-17 years), and the mean follow-up time was five years (1-15 years).

Regarding the clinical examination, 16.9%, had macrocephaly (above the 97th percentile, WHO growth curves), 9% had skin lesions and 6.6% had dysmorphic features. Concerning neurodevelopmental issues, 62.9% showed cognitive impairment, 25.9% were non-verbal, and 21.4% presented neurodevelopmental regression. The complete results are presented in Table 1.

In our population, 37.7% of patients had MRI study, of which the main findings were non-specific abnormalities (that is, ventriculomegaly and white matter T2 hyperdensities). Grey matter heterotopies were found in two patients.

In total, 42.7% of patients underwent EEG studies, of which the large majority (83%) included sleep and awake EEG. The EEG were sought for initial investigation of autism in 83.2% of the cases, which included neurodevelopmental regression in 38.8%. In 14.9% of the cases, it was sought after the first seizure.

Paroxysmal activity in the EEG was observed in 21.7% (n = 35) of the patients. The EEG showing paroxysmal activity was sought after the first clinical seizure in 65.7% (n = 23) of cases and during the diagnostic process to suspect autism in the rest (n = 12) of cases.

Table 1. Characterisation of population with autism spectrum disorder (n = 377)

Characteristic	n	%
Male	310	82.1%
Seizures	41	10.9%
Family history	92	24.3%
Skin lesions	34	9.0%
Macrocephaly	64	16.9%
Dysmorphic features	25	6.6%
Cognitive impairment	237	62.9%
Regression	81	21.4%
Absence of language	97	25.9%
Investigation		
MRI	142	37.7%
EEG	161	42.7%
Genetic testing	109	28.9%
Medication		
Anti-epileptic	37	9.8%
Anti-psychotic	109	28.9%

EEG - electroencephalography; MRI - Magnetic Resonance Imaging.

Finally, 28.9% of the patients with ASD were subjected to genetic studies, mainly array-based comparative genomic hybridization (array-CGH) and fragile X. Most of the genetic findings were inconclusive, although three patients presented *1q21.1* duplication which is associated with ASD.

Of all the patients with ASD in our sample, 10.9% (n = 41) were diagnosed with epilepsy during the study period. The characteristics of this subgroup are in Table 2.

The first seizure occurred mainly in two age groups: toddlers and teenagers (Fig. 1). The majority (59%) of these patients were already being followed in our center for neurodevelopmental concerns when the first seizure occurred.

Focal seizures were the most frequent (68.3%) and were mainly described in clinical records as focal seizures with impairment of consciousness, followed by generalized tonic-clonic seizures (24.4%).

In this subset, 73.2% of patients underwent MRI, of which one showed grey matter heterotopias. Regarding EEG studies, 56% showed focal epileptic activity (30% temporal lobe paroxysms, 22% frontal lobe paroxysms), 13% showed generalized activity, and the rest did not show any paroxysmal activity. No patients showed continuous spike wave during sleep in the EEG study.

A total of 27 patients (68%) with seizures were under treatment with anti-epileptic drugs: 37% with sodium valproate, 14% with carbamazepine, 14% with levetiracetam, and 5% with eslicarbazepine. In the epilepsy group, 51% were also managed with anti-psychotic drugs (risperidone or aripiprazole) compared to 27% of patients without epilepsy.

Favorable response to monotherapy was observed in a significant number of patients (60%). Drugs of choice for monotherapy were sodium valproate (n = 8) and carbamazepine (n = 7). In total, eight patients needed a two-drug regimen, one needed three drugs, and another needed four drugs to attain epilepsy control. No patient in our sample underwent epilepsy surgery.

There were 336 patients in the ASD without epilepsy subgroup in our sample (Table 2). The majority of whom were male (n = 277, 82%), 17% had macrocephaly, 10% showed skin abnormalities and 6% had dysmorphic features. In our sample, 63% showed cognitive impairment, 24% were non-verbal and 19% showed neurodevelopmental regression. In this subgroup, 33% underwent MRI studies, with 11 patients showing findings, mainly non-specific abnormalities such as ventriculomegaly and white matter T2 hyperdensities. Regarding EEG studies, 33% were submitted to an electroencephalogram, with 12 (3.6%) patients showing

Table 2. Characterisation of subgroups: with autism spectrum disorder and epilepsy and with autism spectrum disorder without epilepsy

	Autism and Epilepsy		Autism without Epilepsy	
Characteristic	**n**	**%**	**n**	**%**
Total	41		336	
Male	33	80.5%	277	82.4%
Family history	10	24.4%	82	24.4%
Skin lesions	1	2.4%	33	9.8%
Macrocephaly	7	17.1%	57	17%
Dysmorphic features	4	9.7%	21	6.3%
Cognitive impairment	25	61.0%	212	63.1%
Regression	16	39.0%	65	19.35%
Absence of language	17	41.5%	80	23.8%
Investigation				
MRI	30	73.2%	112	33.3%
EEG	41	83.7%	110	32.7%
Genetic testing	9	21.9%	100	29.7%
Medication				
Anti-epileptic	27	65.9%	-	-
Anti-psychotic	21	46.3%	90	26.8%

EEG - electroencephalography; MRI - Magnetic Resonance Imaging.

Table 3. Comparison between the epilepsy and no epilepsy subgroups

	Epilepsy		No epilepsy		*p* value*
	n	%	n	%	
Family history	10	24.4%	82	24.4%	1.000
Male gender	33	80.5%	277	73.5%	0.828
Macrocephaly	7	17.1%	57	17%	1.000
MRI changes	6	14.6%	30	8.9%	0.257
Absence of language	17	41.5%	80	23.8%	**0.022**
Regression	16	39%	65	19.3%	**0.008**

MRI - Magnetic Resonance Imaging.
* Chi-square test.

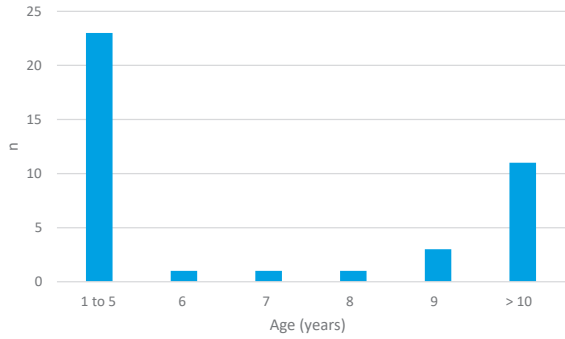

Figure 1. Age distribution in the first seizure (n = 41).

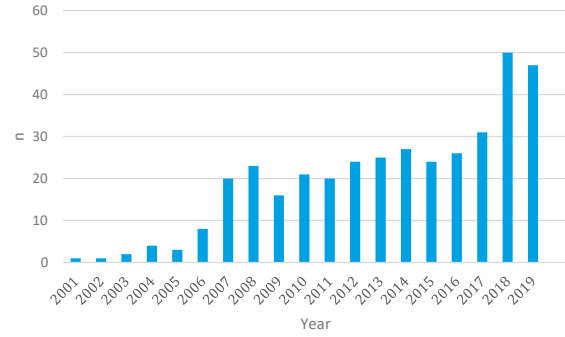

Figure 2. Yearly diagnosis of autism spectrum disorder in our center.

paroxysmal activity, mainly in the temporal lobe.

In this group, 27% of patients were managed with antipsychotic drugs.

The results obtained from the comparison of the subgroups with and without epilepsy showed that the absence of language and regression was associated with the presence of epilepsy (Table 3). Multifactorial analysis adjusted for language and regression showed the

independence of both variables (absence of language $p = 0.048$, neurodevelopmental regression $p = 0.014$).

Discussion

In our center, we have witnessed a rise in both the referrals for suspicion of autism (Fig. 2) and the diagnosis of ASD itself, in the last 15 years. Characteristics such as the age of the included patients and the change in the diagnosis criteria for ASD through the years are factors that can impact the reported rates of autism.

Autism and epilepsy share a common neurochemical substrate. Current evidence suggests that both conditions share a genetic etiology as research links mutations in different genes to epilepsy, autism, or both conditions.[14,15] Both autism and epilepsy could be secondary to disturbances of large-scale neuronal networks of the cortical-subcortical systems,[16,17] and environmental factors such as unidentified toxic substances and increasing parental age may also play a role.

Seizures can contribute to the behavioral changes in ASD through repetitive seizure-induced excitotoxicity that causes permanent injury of the cortical neuronal networks that control behaviour.[18] The sensory perceptual abnormalities in ASD could reflect this change in cortical function which can be manifested in the auditory, tactile and visual, domains.[19] Stereotypies commonly displayed by autism patients can improve sensory processing by regulating brain rhythms, through a rhythmic motor command or the rhythmic sensory feedback created by the movements.[20]

When compared to the healthy population, patients with ASD present an increased incidence of epilepsy. Our results agree with existing studies, with an incidence of epilepsy in 11% of children and teenagers with autism.

The first seizure occurred mainly in two age groups, toddlers and teenagers, similar to other studies.[12,21] The median age of patients in our sample was 12 years old, which explains why the toddler age group outsized the teenager group, as opposed to other studies in which most patients have their first seizure in their teenage years.[12] It is likely that some children might develop epilepsy in the future and fall within the second age group.

Most (59%) patients were already being followed in our center for a suspected or already confirmed autism diagnosis when the first seizure occurred. Therefore, it can be inferred that the neurodevelopmental symptoms that first point to precede the clinical seizures in most cases.

The majority (68%) of our patients showed focal seizures. Although no predominant type of seizure has been specified in the literature, reports are increasingly displaying a preponderance of focal seizures in patients with ASD.[10,22]

An EEG was sought in the vast majority (92%) of the patients with clinical seizures. Studies have suggested that EEG with sleep study is more likely to show paroxysms. We could only get sleep studies in 87% of cases, due to the difficulties in performing EEG in children with behavior problems, sensory integration difficulties, and sleep disturbances. This might explain the presence of EEG paroxysmal activity in only 60% of patients.

In both groups (with and without epilepsy), there was a noteworthy number of ASD patients with temporal paroxysmal activity. The temporal lobes are critical for language and social functioning, and these skills might not develop in the presence of epilepsy syndromes that affect the temporal lobe.[11] The presence of epileptiform discharges in temporal areas before 18 months of age may be linked to the deficits in social development typical of autism.[23] Imaging studies support this, as some patients with temporal lobe epilepsy display anatomic changes in the brain structures that are responsible for social brain functioning.[24,25] In children with ASD and epilepsy, single-photon emission computed tomography (SPECT) studies show hypoperfusion in areas that are likely correlated with reduced function, such as mesial temporal lobes or the prefrontal lobes.[26,27] However, not only temporal, but also paroxysmal activity in the frontal lobe is associated with later diagnosis of epilepsy.[28-30]

In the subset of patients with ASD without epilepsy, 3.6% showed paroxysmal EEG activity, which mainly included temporal paroxysmal activity. Our patients with paroxysmal activity (none of them with continuous spike wave during sleep) without epilepsy will continue follow-up.

Our study comprised patients who were followed for a period of 15 years, during which methods to investigate neurodevelopmental disorders have changed. Furthermore, suspected autism was not always the reason for referral and was a later diagnosis. This might explain why over a third of our patients underwent EEG studies. Currently, the presence of neurodevelopmental regression is the established indication of EEG study in autism spectrum disorder.

In our study, sodium valproate was the main choice of treatment for seizures. The choice of anti-epileptic varies through literature[12,31] and, as of our research, there were not any specific recommendations regarding an ideal drug regimen for epilepsy control in autism spectrum disorder. Sodium valproate might be a good treatment choice for its effects on both seizure and behavioral control, which are often impaired in these patients. It has been demonstrated that antiepileptic

treatment does not impact the improvement of the core ASD symptoms.[31,32] It is important to note that scientific data does not support the use of anti-epileptic drugs in patients without epilepsy.

In our sample, 21% of ASD children showed neurodevelopmental regression, which was lower than that in other studies reporting a rate of 30%-41%.[11,22] In line with other studies, regression, and the absence of language in our sample were associated with the presence of epilepsy in patients with autism spectrum disorder.[33,34]

Some authors suggest association of epilepsy with female gender or the presence of cognitive impairment, which we could not demonstrate in our study.[10,12,35] Moreover, some reports suggest a correlation between the severity of cognitive impairment and the risk of epilepsy.[17]

Regarding the limitations of our study, like other retrospective studies, the data was gathered by reviewing the clinical process of the patients, who are followed by different clinicians, with different methodologies of investigation, which might impact the data collected. Regarding the degree of severity of autism spectrum disorder, the main tests used in our center to evaluate our patients were Childhood Autism Rating Scale (CARS) and Autism Diagnostic Observation Schedule (ADOS-2). However, due to incomplete records, it was not possible to include these data in our analysis and to characterize the cognitive impairment in all patients. Furthermore, we chose not to include the presence of EEG paroxysmal activity in the comparative analysis, as most patients did not have an EEG prior to the beginning of epilepsy. Unfortunately, it was not possible to perform video-EEG on most of our patients.

Finally, some patients included in this study are currently over 18 years old, therefore are not followed in neither child neurology consult, nor, in some cases, at our institution anymore. Data about eventual seizures after the age of 18 might be missing, and true incidence of epilepsy in our sample might be underestimated.

In conclusion, we found that the absence of language and neurodevelopmental regression were associated with the future diagnosis of epilepsy. We understand that diagnosing seizures in ASD patients is difficult due to the behavioral characteristics of this disorder, such as non-responsiveness or motor stereotypies, that might just be the manifestations of autism spectrum disorder. Regardless, we advocate that the possibility of developing seizures in ASD patients should be discussed with caretakers, particularly in cases of patients with such symptoms as neurodevelopmental regression or absence of language. It is of paramount importance to maintain adequate follow-up and have a low threshold to suspect seizures in these patients. Anticipatory measures should be pursued, such as teaching parents to recognize a seizure, and perhaps even address the approach to a seizure, as well.

Our study translates our local reality and cannot be generalized to a national scale. In the future, it would be interesting to develop a multicentric approach to understand the incidence of epilepsy in ASD in our country and to better characterize this disorder.

Author Contribuitions

GB, JM, ACF, JNC, AD, LR, LV, MJF and JPM participated in the study conception or design. GB, JM, ACF, AD, LR, LV, MJF and JPM participated in acquisition of data. GB, JM, ACF, JNC, AD, LR, LV, MJF and JPM participated in the analysis or interpretation of data. GB, JM and ACF participated in the drafting of the manuscript. GB, JM, ACF, JNC, AD, LR, LV, MJF and JPM participated in the critical revision of the manuscript. All authors approved the final manuscript and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki 2013).

Provenance and peer review

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Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

Awards and presentations

Preliminary results of this study were presented at the 15º Congresso da Sociedade Portuguesa de Neuropediatria, held in Lisbon, in May 2021, and received the prize for the “Best Poster”.

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Epilepsia em Crianças e Adolescentes com Transtorno do Espectro do Autismo: Uma Revisão de 15 Anos

Introdução: O transtorno do espectro do autismo é caracterizado por défices persistentes na comunicação e interação social, bem como padrões restritos de comportamento, interesses e atividades no período inicial do desenvolvimento. É um diagnóstico cada vez mais frequente. A associação entre o transtorno do espectro autista e a epilepsia é conhecida. Diferentes estudos relataram vários fatores preditivos relacionados com o diagnóstico futuro de epilepsia, tais como **défic**e cognitivo, regressão do neurodesenvolvimento e ausência de linguagem.

Métodos: Foi realizado um estudo observacional, retrospectivo, descritivo e comparativo da revisão dos registos clínicos de doentes pediátricos com transtorno do espectro do autismo que foram acompanhados num centro de desenvolvimento infantil entre janeiro de 2006 e janeiro de 2021. Os dados foram analisados com o programa software SPSS (versão 23). O nível de significância foi estabelecido em $p < 0,05$.

Resultados: O presente estudo incluiu 377 crianças e adolescentes com transtorno do espectro do autismo, dos quais 41 (10,9%) foram diagnosticados posteriormente com epilepsia. O tempo médio de seguimento foi de cinco anos. Nos doentes com epilepsia, a idade mais frequente da primeira crise foi determinada em dois períodos: entre os 2-5 anos (53,5%) e durante a adolescência (25,6%). A apresentação mais frequente (68,3%) foram crises focais, 56,1% das quais foram paroxismos de eletroencefalograma (17,1% no lobo temporal). A maioria (65,9%) estava sob tratamento com antiepilépticos, 60% em monoterapia, principalmente com valproato de sódio (37,2%). A regressão (39% *vs* 19,3%, $p = 0,008$) e ausência de linguagem (41,5% *vs* 23,8%, $p = 0,022$) apresentaram uma maior associação com o desenvolvimento de epilepsia nos doentes.

Discussão: Com base nos resultados obtidos, 11% dos doentes apresentavam transtorno do espectro do autismo e epilepsia. A regressão do neurodesenvolvimento e a ausência de linguagem foram associadas ao desenvolvimento de epilepsia, o que pode implicar necessidade de aconselhamento específico e cuidados antecipatórios neste subgrupo de doentes.

Palavras-Chave: Adolescente; Comorbilidade; Criança; Epilepsia/diagnóstico; Epilepsia/epidemiologia; Idade de Início; Transtorno do Espectro Autista/epidemiologia