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Association of Epileptiform Discharge and Autism Spectrum Disorder Severity in Children Attending the Outpatient Clinics, Child Welfare Teaching Hospital, Baghdad

Esraa E. Abdulrazaq[1]*, **Ghassan Th. Saeed[1]**
[1]*Department of Physiology, College of Medicine, University of Baghdad, Baghdad, Iraq.*

Abstract:

Background: Subjects with Autism Spectrum Disorder (ASD) have a higher prevalence of seizures than the general population, according to a significant body of research. Also, seizure-free patients with ASD have been found to have a higher prevalence of epileptiform discharge abnormalities compared to healthy controls across investigations. Changes in the electroencephalogram (EEG) can manifest as sharp waves or spikes, sharp and slow waves, generally distributed or general area, or focused, and can manifest in various brain regions. There is a necessity to search for a distinctive EEG characteristic in ASD patients.

Objectives: This study used electroencephalography to investigate the relationship between interictal epileptiform discharges and the severity of ASD in children.

Methods: The study involved a total of 65 children. The first group consisted of 30 children (seven females and 23 males, 2-12 years of age) recruited from the autism center and the pediatric neurology consultancy clinic in the Child Welfare Teaching Hospital / Medical City. The second group consisted of 35 age- and gender-matched normally-developed children (10 females 25 males, 2-12 years of age) recruited from the Pediatrics Consultation Clinics in the Child Welfare Teaching Hospital. The ASD children met the DSM-5 criteria for autism and the Childhood Autism Rating Scale was utilized to determine the severity of autism. The electroencephalography signals were recorded to detect epileptiform discharge. The data was collected during the period from 5th October 2022 to 1st April 2023.

Result: A statistically significant association was found between the epileptiform discharges and the study group (ASD Vs normally developed children). The EEG records were normal in 20 (66.7%), abnormal in the form of focal epileptiform discharge in 5 (16.7%), and in the form of generalized epileptiform discharge in 5 (16.7%) of ASD children. The EEG findings and the CARS-measured autism severity showed a statistically significant association, as the EEG abnormalities increased with the severity of autism.

Conclusion: The degree of autism was found to be associated with the abnormalities of the electroencephalogram and the degree of autism.

Keywords: Autism; Childhood Autism; Electroencephalogram; Prevalence; Rating Scale.

Introduction:

Autism spectrum disorder (ASD) is identified by challenges in social interaction and communication and the manifestation of confined and repetitive patterns of behavior and interests. Additional symptoms include restricted and repetitive behavioral patterns (1)(2). Recent epidemiological research has shown a sharp rise in the number of people with ASD, with boys being affected four to five times more often than girls. (3) It is predicted that the prevalence of ASD is 1% across the board in Asia, Europe, and North America respectively. (4) ASD is present in all races, ethnicities, and socioeconomic categories. (5). Studies of autism frequency have been particularly rare in the Middle East. Saudi Arabia has a prevalence of 18 per 10,000, which is greater than the worldwide incidence of 13 per 10,000(6).
The estimated prevalence of ASD Among all children in the Sultanate of Oman aged 0-14 years was

*Corresponding Author's dr.esraaemad1991@gmail.com.

2.04/1000, which is quite low in comparison to most estimations worldwide (7). In Qatar, from 2015 to 2018, ASD was projected to have a frequency of 11.4/per 1000 children (6-11 years old), which is much higher than the prevalence seen in other Middle Eastern nations (8). In 2014, a study in Lebanon determined the prevalence of ASD in 16–48-month-old children to be 15.3/1000. This is a very high result, in comparison to the expected prevalence in Western nations (9). Recent research has shown about more than 70% of people with autism have concomitant disorders. the abnormal cognitive profiles associated with autism including impaired social cognition and perception, problems with executive function, and peculiar patterns of perceiving and processing information (3).
Patients with ASD have a significantly higher prevalence rate of epilepsy (1.8–60%) than people without ASD (0.0–0.7%). (10). EEG has been the major approach for recording and describing

epileptiform paroxysmal activity that is more prevalent in ASD. High rates of epileptiform electroencephalograms have also been documented in children with autism who do not have a family history of seizures or epilepsy. (11) Even in the absence of a clinical history of epileptic seizures, electroencephalographic Abnormalities have been demonstrated to be present in ASD in several investigations, with estimates ranging from 4–86%. (12) According to published research, electroencephalographic abnormalities in patients with ASD are higher than those in the general population (2% to 8.7%), however in other studies, they appear to decline with puberty (13). Higher frequencies of epileptiform activity have also been documented in sleep investigations; for example, Chez et al found that 61% of people with ASD and no clinical history of seizures had epileptiform abnormalities (11).

Most research reveals a range of epileptiform discharges, suggesting that there is no uniform pattern of these discharges among investigations, including unilateral or bilateral, multi-focal, and focal discharges confined to various distinct brain regions (11). Epileptiform discharges may change brain networks and have long-term effects on seizure vulnerability and learning skills. Because epileptiform activity may have a direct or short-term effect on cognitive processes; treating it may improve autism symptoms (14). In other words, decreasing or stopping epileptiform discharges could prevent the onset of epilepsy (11).

This study aims to detect the relationship between epileptiform discharge and the severity of autism in children.

Patients and methods:
A case-control study was carried out at the Autism Center, Child Welfare Teaching Hospital, Baghdad Teaching Hospital in Medical City for the period from 5th October 2022 to 1st April 2023.

The study was approved by the ethical committee of the College of Medicine / University of Baghdad. A written consent was obtained from the children's parents after the nature of the procedure had been fully explained.

Patients' selection: Children attending the outpatient clinics in the hospital / autism center were randomly selected from the list of patients using a simple random sampling technique as one patient per day.

The study involved a total of 65 children, comprised of 30 children with an age range of (2-12 years) who were recruited from the autism center and Child Welfare Teaching Hospital, Medical City and met the DSM-5 criteria for autism.

The control group consisted of 35 age- and gender-matched normally-developed children with an age range of (2-12 years). They did not fulfill the criteria of any pervasive developmental disorder and were recruited from the children's consultancy clinic in the Child Welfare Teaching Hospital.

A full medical history was taken followed by a physical examination and demographics were recorded. In addition, neurological and psychiatric examinations were conducted for the clinical assessment of ASD according to DSM-5 criteria. ASD severity was assessed by the Childhood Autism Rating Scale score (CARS) which is an observational scale in which each item is given a rating ranging from 1 (within the normal boundaries) to 4 (abnormally severe). Ratings take into consideration the "peculiarity, frequency, and length" of the behavior being rated. It can result in a total score somewhere between 15 and 60. Autism ranging from mild to moderate severity is indicated by a score between 30 and 36.5, while scores between 37 and 60 indicate severe autism (15). The EEG signals were recorded using the 10-20 international system for electrode location. (16) By an EEG machine (Nihon Kohden Company, Japan, and Serial No. VNCT617201). The EEG recording was done during induced sleep with 50mg/kg of chloral hydrate. (17). Nineteen scalp electrodes were attached to the following sites (Fp1, Fp2, F3, F4, Fz, Cz, Pz, F7, F8, T3, C3, C4, T4, T5, T6, P3, O1, P4, O2) utilizing montage (bipolar), with the time of recording varying from 20 to 30 minutes. All electrode impedances were kept <5 Kohm.

EEG data were classified as "Yes" or "No" for two criteria: Normal or epileptiform discharges which are either focal or generalized discharge.

The SPSS statistical software, version 22, was utilized for statistical analyses that were conducted (IBM Corporation, USA).

Normally distributed variables were shown as mean ± standard deviation (SD) and their differences were tested using the student t-test.

The Chi-square and Fisher exact tests was used to determine the associations of categorical variables.

Inclusion criteria
(1) Diagnostic and Statistical Manual of Mental Illnesses, 5th edition, standards of ASD and CARS score of greater than 30.
(2) Both genders, males and females.
(3) Age between 2 and 12 years old.
(4) Any social and economic class.

Exclusion criteria
(1) Other neurological conditions.
(2) Metabolic diseases.
(3) The existence of other mental illnesses or psychiatric conditions.

Results
Out of the 30 diagnosed ASD cases included in this study there were 23 males and 7 females. Out of the 35 were normally developed controls there were 25 males and 10 females.

No significant associations were found between gender and ASD (p = 0. 632) and no significant difference (p = 0.994) was found between the mean

age of children with ASD and their normally-developed controls, Table 1.

Table (1): The demographic characteristics of the ASD cases and controls

Variable	Category /Statistics	ASD (N=30)	Control(N=35)	Tests of significance	p value
Sex No. (%)	Male	23 (76.7%)	25 (71.4%)	χ2= 0.229a	p = 0.632
	Female	7 (23.3%)	10 (28.6%)		
Child's age (years)	X±SD	6.2 ±2.5	6.3 ±2.5	t=1.88	p = 0.994
	Range	2-12	2-12		

A statistically significant association is found between epileptiform discharges and ASD condition, table 2.

Table (2): Distribution of the ASD cases and controls by the epileptiform discharge

Children	Epileptiform discharges		No	Total	p-value
	Yes				
	Focal	Generalized			
ASD	5	5	20	30	p=0.001
Normally developed	0	0	35	35	

According to the autism severity score, 12 cases (40%) had mild ASD, 12 cases (40%) had moderate, and only 6 cases (20%) had severe forms of ASD.
The EEG recordings were normal in 20 (66.7%) of ASD children, abnormal in the form of focal epileptiform discharge in 5 (16.7%), and abnormal in the form of generalized epileptiform discharge in 5 (16.7%), table (3).

Table (3): Distributions of ASD severity score and EEG patterns in autistic children

Variables	Categories	Children with ASD Number (%)
ASD severity score	Mild	12 (40)
	Moderate	12 (40)
	Severe	6 (20)
EEG changes	Normal	20 (66.7)
	Focal	5 (16.7)
	Generalized	5 (16.7)

The EEG findings and the CARS-measured autism severity showed a statistically significant association (P=0.03), as the EEG abnormalities increased with the severity of autism. Table 4 shows the distribution of the EEG patterns for the autistic group by the CARS autism severity classification.

Table (4): Distribution of the EEG patterns by the severity of autism

Autism Severity	EEG patterns (Number)			Total	Chi-square Test significance
	Normal	Focal	Generalized		
Mild	10	1	1	12	χ2=9.37
Moderate	9	2	1	12	p=0.03
Severe	1	2	3	6	
Total	20	5	5	30	

Discussion
The current study showed epileptiform discharges on EEG records in the form of focal spikes or generalized discharges, which were observed both during sleep and on short-term EEG recordings
The rate of epileptiform discharges on EEG recordings in the current study was remarkably lower than the 60% rate shown in other studies. These recordings are seen despite the absence of epilepsy. Such discrepancies may be causally related to the autism phenotype. (18)(19).
Children with autism were found to have epileptiform discharges in sleep studies, commonly characterized as co-morbid conditions with the same underlying pathophysiology as epilepsy (20). Many researchers have concluded that the presence of epileptiform discharges in an EEG recording is an important sign of epilepsy in autistic patients, and the diagnosis of epilepsy is typically made in autistic patients who exhibit recurrent episodes of unresponsiveness, stereotypical repetitive movement, staring, and epileptiform discharges in their recordings (12). Numerous observational studies indicate that many autistic children may exhibit epileptic discharges on their EEG but do not have symptomatic seizures. Epileptiform EEG abnormalities were detected in 35% to 86% of ASD patients with epilepsy and up to 60% of ASD patients without epilepsy (21). Some studies have claimed that the temporal lobe is the most frequent location of epileptiform discharge (22). The prevalence of epilepsy in ASD was reported to be 2.4% - 46% by some studies (21)(22), while others reported a prevalence of almost 50% (18) which is significantly higher than the percentage found in the general population (0.6–1%) (23) (24). This variation is most likely related to the differences of the groups analyzed in terms of age range, gender, the severity of symptoms, the duration of the EEG recording, and the presence or absence of any co-occurring medical problems. (18)
These associations between epileptic EEG results and ASD support the hypothesis that having a single neurological dysfunction may increase a person's risk of developing another neurological condition (25). This high incidence of epilepsy suggests that ASD and epilepsy may have similar pathophysiological basis. Nevertheless, there is no consensus on the neuropathy physiology of ASD (26). Equally, Children with epilepsy are also more likely to be diagnosed with ASD. (18).
The current study demonstrated that EEG abnormalities were significantly associated with CARS-measured autism severity. Autistic children that are severely affected exhibit predominantly generalized epileptiform discharge. These results suggest a possible neurological basis for the intensity of autistic symptoms.
These findings of the current study regarding the association between the severity of autism and the EEG findings, are in accordance with the reports that found EEG epileptic changes to be more frequently associated with lower intellectual performance, and

more significant dysfunctional behaviors, that are often associated with more severe types of autism. (27)(28)(29)(30)

In agreement with the current study, another study found that the prevalence of generalized EEG abnormalities was 9.1% in mild autism, 27.3% in moderate autism, and 63.6% in severe autism. It also found that in severe autism, localized EEG abnormalities happened in 66.7% of the cases. EEG was typically normal in mild cases, while EEG abnormalities were more

prevalent in moderate and severe autism cases (27).

According to several studies, EEG epileptiform abnormality appears to be more prevalent than non-epileptiform abnormalities (19). The presence of an abnormal EEG has been linked to a malfunction in the cerebral cortex (18)(31), which suggests that autism may be a neurobiological disorder (32). It is believed that these epileptic discharges interfere with normal neural processing, further impairing the cognitive function of ASD patients. (31).

Conclusion:
The current found that EEG abnormalities are associated with the degree of autism severity.

Authors' declaration:
Conflicts of Interest: None.
We hereby confirm that all the figures and tables in the manuscript are mine/ ours. Those which are not, have been permitted for re-publication (attached with the manuscript). The authors have signed an ethical consideration's approval-
Ethical Clearance: The local ethical committee had approved the project in the Autism Center, Child Welfare Teaching Hospital, Baghdad Teaching Hospital in the Medical City. according to the code number (44363) on 24.10.2022.

Author's contributions:
Esraa Emad Abdulrazaq undertook a literature review, data collection and analysis, and manuscript drafting. The literature review, data analysis, study design, and manuscript draft revisions   were supervised   by Ghassan Thabet Saeed conducted the planning of patients' recruitment and supervision of data collection. All authors approved the finalized draft of the manuscript.

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Association of Epileptiform Discharge and Autism Spectrum Disorder
Severity in Children.

Esraa E. Abdulrazaq & Ghassan T. Saeed

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تقييم الموجات الصرعية ودرجة شدة التوحد عند الأطفال المراجعين للعيادة الاستشارية في مستشفى حماية الطفل التعليمي، بغداد

إسراء عماد عبد الرزاق¹ غسان ثابت سعيد¹

¹فرع الفسلجة، كلية الطب، جامعة بغداد، بغداد، العراق

الخلاصة:

خلفية البحث: الأشخاص الذين يعانون من اضطراب طيف التوحد لديهم معدل انتشار مرتفع للنوبات الصرعية مقارنة بالأشخاص العامة وفقا لمجموعة كبيرة من الابحاث. أيضا تم العثور على مرضى طيف التوحد الذين لا يعانون من نوبات صرعية لديهم معدلات عالية من موجات صرعية. ويمكن أن تظهر التغييرات في مخطط كهربية الدماغ على شكل موجات أو ارتفاعات حادة، أو موجات حادة وبطيئة، أو موزعة بشكل عام أو منطقة عامة، أو مركزة، ويمكن أن تظهر في مناطق مختلفة من الدماغ. هناك ضرورة للبحث عن خاصية تخطيط الدماغ عند مرضى التوحد.

الأهداف: استخدمت هذه الدراسة تخطيط كهربية الدماغ للتحقيق في العلاقة بين موجات الصرع البيني وشدة التوحد عند الأطفال.

المنهجية: أجريت الدراسة على 65 طفلا منهم 30 حالة (7 إناث و 23 ذكور) تتراوح أعمارهم بين (2-12 سنة) تم شمولهم بالدراسة من مركز التوحد واستشاري أعصاب الأطفال في مستشفى حماية الطفل التعليمي بالمدينة الطبية واستوفوا معايير DSM-5 للتوحد وتم استخدام مقياس تصنيف التوحد في مرحلة الطفولة لتحديد شدة التوحد، و35 طفلا آخر مطابقين للعمر والجنس للحالات (10 إناث و 25 ذكور) مع عمر (2-12 سنة). الذين لا يستوفون معايير أي اضطراب في النمو منتشر يعملون كمجموعة تحكم، تم شمولهم من استشاري الأطفال في مستشفى حماية الأطفال التعليمي.

النتائج: يوجد علاقة ذات دلالة إحصائية في الموجات الصرعية بين الأطفال المصابين باضطراب طيف التوحد والأطفال ذوي النمو الطبيعي. كانت سجلات مخطط كهربية الدماغ طبيعية لدى 20 (66.7%) من الأطفال المصابين باضطراب طيف التوحد، وكانت غير طبيعية لدى 5 (16.7%) من أطفال التوحد على شكل موجات صرع بؤرية وغير طبيعي، لدى 5 (16.7%) من أطفال طيف التوحد على شكل إفرازات صرع معممة. وجدنا أن 33.4٪ من الأطفال المصابين بالتوحد لديهم نتائج تخطيط كهربية الدماغ غير طبيعية. أظهرت نتائج مخطط كهربية الدماغ وشدة التوحد التي تم قياسها بواسطة مقياس كارز وجود علاقة ذات دلالة إحصائية. حيث زادت تشوهات مخطط كهربية الدماغ مع شدة التوحد. (P = 0.05)

الإستنتاجات: وفقا للنتائج هناك علاقة بين تشوهات مخطط كهربية الدماغ ودرجة شدة التوحد.

مفتاح الكلمات: التوحد، مقياس تصنيف التوحد في مرحلة الطفولة، مخطط كهربية الدماغ.