JICNA® | Journal of the International Child Neurology Association
A peer reviewed open access e-journal in Child Neurology

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ORIGINAL RESEARCH

EEG changes and their relationship with intellectual disability in children with autism spectrum disorders in a tertiary care hospital

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https://doi.org/10.17724/jicna.2021.205

Received: February 18, 2021; Accepted: October 7, 2021

Abstract

Background: Autism in children is frequently associated with Intellectual disability (ID) and epilepsy. It is known that lower IQ influences epilepsy rates; however, electroencephalographic (EEG) findings in different grades of intellectual functioning are less well studied. Objectives: This study aimed to evaluate the EEG findings and their association with the degrees of ID in children with autism. **Methods:** Fifty-two children, diagnosed with autism according to the DSM-IV-TR criteria, aged between 2 to 12 years, were included in the study. Participants were recruited from outpatient clinic in the Institute for Paediatric Neurodisorder and Autism (IPNA) in Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. All of them were subjected to physical and neurological examination. Intelligence quotients (IQ) were measured in all the participants. Psychometric tests Bayley Scales of Infant and Toddler Development, Third edition (BSID III) or Weschler Intelligence Scale for Patients-Revised (WISC-R) were used for evaluating IQ. EEG recordings were done in all the participants. **Results:** The frequency of EEG abnormalities were observed in 51.9% participants. Among these abnormalities, 36.5% were epileptiform and 15.4% were non-epileptiform. Majority of the focal discharges, in this study were from temporal and frontal ((50% and 40% of focal discharge). Among generalized abnormalities, 89% were symmetrical spike-wave complexes. EEG abnormalities were associated with epilepsy in 66.7% of participants. ID was present in 84.6% and of them, 77% had moderate to severe ID. Mild, moderate or severe ID did not show significant association with EEG abnormalities ($p>0.05$). However, patients with moderate to severe ID (IQ <50) had a higher rate of EEG abnormalities compared to those without ID or mild ID (81.5% versus 18.5%) ($P=0.03$). *Conclusion:* Relatively large number of children with autism and ID had EEG abnormalities and there was a significant association with moderate to severe ID (IQ <50) and EEG abnormalities.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder of social reciprocity and communication, as well as restricted interests and a repetitive pattern of behaviour [1]. These symptoms occur in the early stages of child development, which leads to functional impairment [1]. ASD is frequently associated with intellectual disability (ID), electroencephalographic (EEG) abnormalities and seizures [2]. The prevalence of ID has been reported in a varying range from 16.7% to 84% in ASD [3, 4, 5, 6, 7, 8] .

It has been established by researchers that a group of common genes are associated with either ID or ASD and are involved in many of the same molecular and biological functions [5, 6, 8, 9, 10]. As both ID and ASD are disorders of neurodevelopment, this is a rationale for this commonality of pathophysiology [9]. Epilepsy is also a common comorbidity in ASD, and their prevalence ranges widely from 5% to 46% in quite many studies [11, 12, 13, 14, 15, 16].

An EEG evaluation is usually made when there is a history of seizure or epilepsy. In addition, it is also done frequently in ASD to evaluate and assess the children as they often present with a delay/regression of language and behavioural abnormalities. An abnormal EEG is a common finding in ASD. The epileptiform abnormalities found in ASD children ranging from 35% to 85.8% were associated with epilepsy [11, 15, 17, 18]. But varying rates of discharges from 8% to as high as 60% had also been reported, even in the absence of epilepsy [11, 15, 17, 19, 20, 21, 22, 23].

An abnormal EEG is considered as a biomarker of cortical dysfunction [14, 10, 19, 23, 24, 25, 26] and provides evidence that autism is a neurobiological disorder [19]. Interictal discharges (IED) are thought to interfere with normal neural processing which may further impair cognitive function [14, 22, 27, 28, 29].

These discharges are often more common when there is a history of autistic regression, even if there is no history of seizures or epilepsy, and there is concern about behavioural and cognitive problems being caused by these discharges [28].

One study has aimed to explain how the various cognitive processes, like plasticity, memory coding, and language processing is being interfered with by IED. They have mentioned the detrimental effect on intrinsic connectivity networks in the brain, resulting in the deficient organisation of functional networks, followed by abnormal neurocognitive development [30]. The same

study also reported three main findings from functional magnetic resonance (FMR) imaging, which are that: (1) large-scale changes in networks precede and follow IED, (2) resistance to the specific area of the IED network is associated with a network at rest with the strongest connectivity, and (3) vulnerability to IEDs are associated with poorer neurocognitive results.

Studies have reported an association of lower IQ with epilepsy rates in ASD, [18, 31, 32, 33, 34] but the effect of ID on epileptiform EEGs is less well studied, and the existing data are conflicting. Baird et al. [35] found no relationship between ID and epileptiform discharges, while more recent studies [17, 18] reported that an epileptiform EEG was significantly more common among individuals with ID. Stefanatos [36] mentioned the inverse correlation of ID of ASD with the frequency of epileptiform activity.

However, treatment of abnormal EEG discharges with antiepileptic drugs (AED) without clinical seizures remains a controversial issue [14]. The same authors also commented that these abnormalities could simply be an epiphenomenon of neuropathological processes responsible for autism and have no relevance to intervention. However, a number of authors are in favour of using AEDs with the rationale that, even in the absence of epilepsy, these discharges could interfere with normal neural functioning causing deleterious transient cognitive impairment (TCI) [14, 26, 37, 38]. Aldenkamp and Arends [38] mentioned that frequent TCI might result in permanent cognitive decline. Another author, Braun, suggested that strict control of IED with AEDs might prevent the worsening of cognitive function [39]. And Frye et al. [40], in their study with a small group of children, suggested that a trial of AED with those affected by epileptic discharges might be of benefit to children with autism having cognitive disorders.

This study aims to evaluate the EEG findings and their association with the degree of ID in children with autism, which is still unknown in this population in Bangladesh. This might contribute to deciding whether AED could be tried in cases where EEG abnormalities are present but educational therapies are not helping to reduce the symptoms.

Patients and methods

In this cross-sectional and non-experimental study, children consecutively attending the outpatient clinic at the Institute of Paediatric Neurodisorder and Autism (IPNA) in Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh between June 2017 and June 2018 were considered as study participants.

All patients in the age range of 2–12 years were diagnosed as having autism/ASD by using the Diagnostic and Statistical Manual of Mental Disorders DSM-IV TR criteria [41] by assigned paediatric neurologists or pediatricians, as our practitioners were not trained enough on DSM-5 at that time. Previous studies comparing DSM-IV and DSM-5 had shown that children with higher IQs were less likely to meet the new diagnostic criteria [42]. We included 97 children fulfilling the criteria for 'classical autism', as it is the most severe form of autism and is usually associated with cognitive impairment. Since DSM-5 states that individuals with well-established DSM-IV diagnosis should be given the diagnosis of ASD, we have used this term to ensure the updated information in our research. Of 97 children diagnosed, 52 children were enrolled in this study.

Exclusion criteria included inability to complete psychometric testing and/or to record EEG activity during sleep. Children having acute neurological disorders were also excluded from the study group. Data on demography, birth-related history, language ability and a thorough history of epilepsy/seizures were also taken from these children.

Intelligent quotient

The intelligent quotient (IQ) and developmental quotient (DQ) were evaluated by clinical psychologists of the same institution, using standardised psychometric tests, and taking a thorough history. The psychometric tools used were the Bayley Scales of Infant and Toddler Development, third edition (BSID III), [43] the Wechsler Preschool and Primary Scale of Intelligence, third edition (WPPSI-III), [44] and the Wechsler Intelligence Scale for Children, revised (WISC-R) [45]. These three scales were used depending on the child's age and ability. The BSID III evaluates the functioning of infants and young children from one month to 42 months of age and assesses cognitive, language and motor, as well as social, emotional, and adaptive behaviour. Children aged four to six years and six months, without a severe language impairment, were evaluated using WIPPSI-III and WISC-R after six years and up to 16 years. WIPPSI III and WISC-R both measure verbal and performance IQ.

The average DQ from BSID and the average IQ from WIPSSI-III and WISC-R were taken and an IQ $\geq$ 70 was taken as average and borderline, an IQ 50–69 as mild, 35–49 as moderate and less than 35 as severe.

ID is a condition characterised by below average intellectual functioning (IQ < 70) in conjunction with significant limitations in adaptive functioning [9]. 9 Our participants were grouped into non-ID (average and borderline IQ with ID $\geq$ 70) and ID. The ID group was again categorised according to severity into mild (IQ 50–69), moderate (IQ 35–49), and severe (< 35).

Electroencephalogram (EEG)

EEG recordings were done in all the participants according to the 10–20 system. Since all patients were on the severe autism spectrum and most of them were intellectually disabled, EEGs were performed in their sleep and the monitoring time was about one hour.

Abnormalities were classified into epileptiform and non-epileptiform types. Epileptiform abnormalities were defined as either focal, generalised or multifocal spikes, or sharp and slow wave discharges. Non-epileptiform abnormalities were defined as generalised, intermittent, or rhythmic theta/delta slowing, excessive beta activity or asymmetry. The recordings were interpreted by an assigned paediatrician of the same institution with expertise in clinical neurophysiology.

Statistical analysis

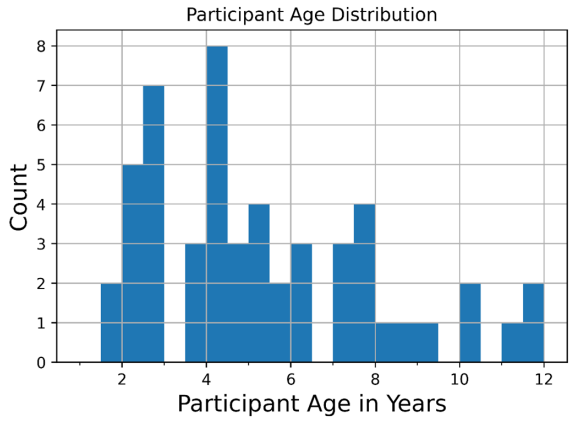
A descriptive statistics analysis was done using IBM SPSS statistics (version 26.0, 2019; Armonk, NY: IBM Corp) for data analysis. The data were compared using Chi-square test or Fischer's exact test, with $P < 0.05$ considered statistically significant.

Ethical permission was taken from the Institutional Review Board of BSMMU (IRB number: 184 Date: 05/02/2018) and informed written consent was taken from all parents of the participants.

Results

A total of 97 children with a diagnosis of ASD were recruited initially. From these, 52 children completed the protocol. Forty-five children were excluded because their sleep EEG and/or psychological assessment tools could not be completed. Figure 1 shows the age range of 20 months–12 years, as well as the distribution of children enrolled. The mean age of the patients was 63 years ± 33 months and male:female ratio was 3.7:1. Epilepsy/history of seizures were present in 10/52 (19.2%) of the patients and a condition of 'no meaningful words' was present in 26/52 (50%) of children with ASD at the time of study (Table 1).

Figure 1. Histogram showing age distribution of participants in years. Each bin size is six months.



Intellectual functioning

ID was present in 44/52 (84.6%) of children with ASD, of which 26/52 (50%) were moderate, 15% were severe and 19% had mild ID, and 15% were in the non-ID group (Table 2).

ID was associated with all the participants having epilepsy, but this was not significant when compared with those who did not have epilepsy ($p = 0.328$, table not shown).

EEG abnormalities

Abnormal EEG recordings were observed in 27/52 (51.9%) of participants. Among those that were most frequent were epileptiform discharges, 19/52 (36.5%) followed by non-epileptiform discharges in 8/52 (15.4%) cases (Figure 2).

Table 1. Demographic variables and associated conditions of the enrolled population with ASD.

N (%)	
Enrolled children	97
Included children	52
Excluded children	45
Gender (M/F)	41 (78.8%)/11 (21.2)
Mean age ± SD	
Mean age (months)	63 ± 33
Age range	20 months–12 years
Residence	
Urban	33 (63.4)
Rural	19 (36.5)
Consanguinity	
Present	4 (7.7)
Absent	48 (92.3)
Place of delivery	
Home	17 (32.7)
hospital	35 (67.3)
Type of delivery	
Term	34 (65.4)
preterm	18 (34.6)
Associated conditions	
Language ability	
No words	26 (50)
Speak in words	9 (17)
Speak in phrases	9 (17)
Speak in sentences	8 (15)
Epilepsy/history of seizures	
Present	10 (19.2)
Absent	42 (80.8)

N, number; SD, standard deviation.

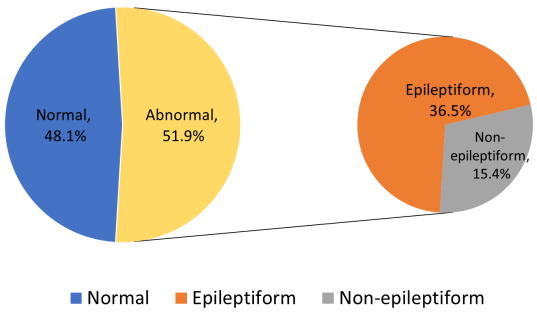
Table 2. Distribution of participants according to intellectual functioning level (n = 52).

Level of intellectual functioning	N	%
Non-ID	8	15.4
ID	44	84.6
Mild	10	19.2
Moderate	26	50
Severe	8	15.4

N, number.

Of the 27 participants with abnormal EEG findings, epileptiform abnormalities were found in 19/27 (70.3%) of patients; these were focal in 9/27 (33%) and generalised in 10/27 (37%). Focal sharp waves involved various regions of the brain. Most of the focal discharges were from frontal and fronto-temporal regions of the brain. Another 2/27 (7.4%) had multifocal sharp waves, defined as sharp-wave foci occurring independently in the left and right cerebral hemispheres in at least three topographically distinct areas (Table 3).

Figure 2. EEG findings of the participants among 52 children.



Generalised discharges were comprised of high voltage generalised spike–wave complexes in 8/10 cases. More of these were from frontal/fronto-temporal/fronto-parietal areas, followed by centro-temporal and temporo-occipital areas. It is observed here that maximum discharges, including both focal spikes and generalised spike-wave complexes, were from temporal areas (11 in number), followed closely by the frontal area (nine in number). Discharges from the posterior regions were fewer in number.

The most common nonepileptiform abnormality was slowing of the background of varying severity, followed by intermittent generalised high voltage slow waves and excessive beta activity. Excessive beta activity was likely to be secondary to concurrent AED use, as were found from their history. One patient had a lateralised asymmetry of his EEG rhythms (decreased alpha rhythm amplitude in the left hemisphere (Table 3).

Table 3. EEG abnormality types in children with autism (n = 27).

Types of abnormalities	Frequency	%
Epileptiform abnormalities	**19**	**70**
Focal		
Frontal/fronto-temporal	3	
Centro-temporal	1	
Fronto-central independently	1	
Centro-temporo-parietal	1	
Occipital	1	
Mid-central parietal	1	
Multifocal sharp waves	2	
Generalised		
Spike-wave complexes	8	
Fronto-temporal and fronto-parietal	4	
Frontal	1	
Occipital	1	
Centro-temporal	1	
Temporo-occipital	1	
Paroxysmal fast activity/polyspikes	1	
Non-epileptiform abnormalities	**8**	**29.6**
Background slowing	3	
Generalised intermittent slow waves	2	
Excessive beta	2	
Lateralised asymmetry	1	

Children with epilepsy showed EEG abnormality in 9/10 (90%) of cases. Out of them, 8/9 (88.9%) were epileptiform abnormalities and 1/9 (11.1%) were non-epileptiform. However, the epileptiform and nonepileptiform discharges present were not significant ($p \geq 0.05$) when compared with total EEG discharges of all enrolled ASD children in this study group of 10/27 (table not shown).

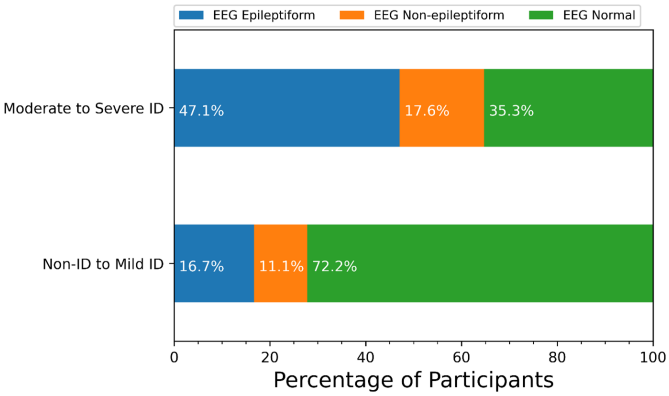
EEG findings and intellectual functioning

Among 44/52 (84.6%) of the participants having ID, the EEG was abnormal in 24/44 (54.5%) and normal in 20/44 (45.5%) cases. This shows no significant association between ID and EEG abnormalities ($p = 0.46$) (table not shown).

Table 4 shows the number and proportion of the type of EEG findings for the various levels of intellectual functioning [45]. The data shows a higher proportion of abnormal EEG findings in participants with more severe ID. However, limitations in the sample size mean the statistical significance is not sufficient to assert a significant association between intellectual functioning levels and different types of EEG abnormalities ($p = 0.06$).

However, grouping intellectual functioning into two groups — those with non-ID or mild-ID (i.e., IQ $\geq$ 50) and those with moderate or severe ID (i.e., IQ < 50) — reveals a significant association with EEG abnormalities ($p = 0.019$) (Table 5). Similarly, the grouped ID levels show a significant association with the different types of EEG findings ($p = 0.041$) (Figure 1).

Figure 3. Proportion of type of EEG findings of participants by grouped intellectual functioning levels.



The p-value is 0.041 (based on a two-sided Fisher's exact test). Significant at $p < 0.05$

Discussion

A sizable amount of literature has reported the association of ID and ASD in a varying range [3, 4, 5, 6, 7, 8]. Epilepsy and EEG abnormalities in ASD are also reported in many studies. While it is common to have EEG abnormalities in ASD, the association of EEG abnormality and ID which is present in ASD is reported less. The aim of this study was to find out the

Table 4. Association of intellectual functioning levels with different types of EEG findings (n = 52).

Level of intellectual functioning	Total	EEG Findings		
	n(%)	Normal n (%)	Epileptiform n (%)	Non-epileptiform n (%)
Non-ID	8 (15,4)	5 (20.0)	1 (5.2)	2 (25.0)
ID	44 (84.6)	20 (80.0)	18 (94.8)	6 (75.0)
Mild	10 (19.2)	8 (32.0)	2 (10.5)	0 (0.0)
Moderate	26 (50.0)	10 (40.0)	13 (68.4)	3 (37.5)
Severe	8 (15.4)	2 (8.0)	3 (15.8)	3 (37.5)
Total	52 (100)	25 (100.0)	19 (100.0)	8 (100.0)

The p-value is 0.061 between individual ID levels. Not significant at p < .05. N, number.

EEG changes and their association with the degree/severity of ID among children with autism. Fifty-two Bangladeshi children with an average age of 63 months were enrolled here.

Table 5. Association of ID levels/degrees with EEG findings (n = 52).

ID	EEG findings		*p-value
	Abnormal	Normal	
Mild to Non-ID	5	13	0.019
Moderate to severe ID	22	12	
Total	27	25	

**Fisher's exact test was done to measure the level of significance. Significant at p < .05.*

Age distribution of the children with ASD shows that most of them were 3.6 to 5.4 months followed by 2.5 months. This shows the level of concern that the participants' parents had when they first noticed ASD symptoms (Figure 1). Demographic variables show the number of male children were almost four times higher than female children, as found in most of the studies (Table 1). This study also shows very high urban representation. ID has been found in 84.6% of cases in this study (Table 2). The Centers for Disease Control and Prevention (CDC) in the US estimated ID to be 31% (IQ $\leq$ 70) in their recent prevalence study [4]. The finding of a relatively high percentage of ID in ASD in our study can be explained by the fact that this study was performed on hospitalised patients, such as the one by Pacheva et al., [11] who found the prevalence to be 90% in their study. Srivastava and Schwartz [9] put emphasis on genetic causes for both ASD and ID. According to them, single gene mutations, as well as copy number variants (CNVs), either duplications or deletions, are associated with both conditions.

'EEG abnormalities' were broadened in this study, and included not only epileptiform discharges (e.g., spikes and spike-wave discharges) but also less obvious abnormal features, such as 'diffuse theta', 'low-voltage fast' and 'amorphous background' as non-epileptiform discharges [46, 47]. A few other studies have also focused on both epileptiform and non-epileptiform abnormalities in children with autism [2, 23, 24, 31, 48, 49].

In this study, 51.9% of the participants had EEG abnormalities, with 36.5% being epileptiform (Figure 2). This corresponds with the average frequency of 30.8–40.5% by a group of investigators [46, 50, 51], but not with rates as high as 60.4%–66.6% reported by other investigators [25, 26, 43, 46]. These variations might be due to inclusion or exclusion of children with epilepsy in the population, age of participants, length of EEG recording [52], their IQ, and the techniques used in different studies [51].

As in many other studies [23, 27, 29, 46, 48, 49], EEGs with epileptiform abnormalities were more common than those with nonepileptiform abnormalities. Non-epileptiform abnormalities were found in 29.6% of total EEG abnormalities (Table 3). These were slowing of the background, followed by generalised intermittent high voltage slow waves and excessive beta activity. This corresponds with Amira et al.[53], Samra et al. [24] and Gabis et al. [49], who found a higher percentage in excess slow waves among their non-epileptic discharges.

An abnormal EEG in 66.7% of cases was associated with epilepsy, but in 28%, no epilepsy or history of seizure was found. Our findings are similar to that of 15%–20% of those by Tuchman and Rapin [54] and Rossi et al. [55].Chez et al. [26] and Canitano et al. [51] added that the abnormal EEG in children with ASD without clinical seizures may have a role in their marked deficit with regard to their cognitive, language function, and behavioural profile.

Table 3 shows the different types of discharges, where focal were slightly lower than generalised (33% and 37%, respectively), whereas Elkholy et al. [25] found an equal number (36.6%) of focal and generalised discharges. Most of these discharges were from temporal and frontal regions (50% and 40%, respectively), and most of these were overlapping in their location. Among generalised abnormalities, 89% were symmetrical spike-wave complexes. This finding is consistent with previous studies, where abnormalities were detected mostly from the right and left temporal cortex and adjacent cortical structures [2, 26, 31, 55].

Epileptic discharges from fronto-temporal regions and temporal areas might play an important role in the pathophysiology of autism and may be associated with delayed or regressed language development [56]. This study found EEG abnormality in 88% of ID patients and 11% of non-ID patients. EEG abnormal-

ity was also present in 84% of non-ID patients and no significant association/relation with EEG abnormalities with ID (p = 3747) was found in our study. This finding is inconsistent with that made in some previous studies [26, 55]. An underlying cortical dysfunction might be the cause of these discharges and might be the clue for an underlying neurological abnormality [14].

This study did not show a significant association between different degrees of ID, and epileptiform and non-epileptiform, when considered separately (p = .6149) (Table 4). However, a significant association with abnormal and different types of EEG abnormalities were found when moderate to severe ID children, combined, (i.e., IQ < 50) were compared with that of children with average IQ and mild ID, combined, (p = .019 in Table 5, and p = .041 in Figure 1, respectively). It is in partial agreement with the studies by Ozcan et al. [2] and Gabis et al. [49] which showed a significantly higher rate of EEG abnormalities (p = 0.03) in patients with ID with mild to moderate degrees of ID. The association of more severe ID could be explained as the 'severity-dependent' association found in previous studies [38]. Lower rates of EEG abnormality with average and borderline intellectual functioning can be explained as a more preserved neural function.

Limitations

Our findings must be interpreted with certain limitations. The first was the relatively small number of cases. Secondly, we could not follow the IQ and adaptive functioning levels over time as our samples were taken from the out-patient department. We had no scope of doing ambulatory EEGs, or video-EEG monitoring and magnetoencephalography, which would have been better in localising EEG changes and correlating those with cognition of the participants. Unfortunately, very few centres in Bangladesh can perform long-term EEGs and it is not cost-effective. Another drawback was that we could only do sleep-EEGs. The lack of a control group may be considered a limitation of the study as well.

Controlled double blind studies are needed to observe the clinical improvement of symptoms of autism following AED therapy, especially for taking decisions about AED therapy.

Conclusion

A significantly higher proportion of EEG abnormalities are found in children with autism having moderate to severe ID (IQ < 50) compared to those with average or mild cases of ID (IQ 50 and above). Keeping this association in mind, a trial for AED could be tried where other therapies (such as educational therapies) are not working. But this decision should be corroborated with further long term multicentred trials.

Acknowledgements

The authors are grateful to Dr Nahid Nabi, Consultant (Clinical Neurophysiology), IPNA as well as the Psychologists, EEG technologists of IPNA and parents of the children who helped us by giving their valuable time.

Competing interests

None.

Author contributions

Shaheen Akhter: conceptualisation, methodology, writing – review & editing. Jannatara Shefa: conceptualisation, methodology, data collection and statistical support. Muzharul Mannan: conceptualisation, data collection and statistical support.

Cite this article as:
Akhter, S. et al. (2021). EEG changes and their relationship with intellectual disability in children with autism spectrum disorders in a tertiary care hospital Journal of the International Child Neurology Association, 21(1). https://doi.org/10.17724/jicna.2021.205

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