Bangladesh Medical Res Counc Bull 2022; 48: 112-119 DOI: 10.3329/bmrcb.v48i2.62296

RESEARCH PAPER

Autism Spectrum Disorder in Children with Epilepsy: A Case-Control Study in a Tertiary Care Hospital in Bangladesh

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Abstract

Background: Autism spectrum disorders (ASD), a neurodevelopmental deficit, is often associated with epilepsy. Previous literature suggested that ASD and epilepsy share a common pathophysiological basis. Considering the scarcity of studies regarding ASD in children with epilepsy, this study was conducted with an aim to evaluate the association of ASD with epilepsy.

Materials and Methods: This case-control study was conducted in the Department of Pediatric Neurology, Institute of Paediatric Neurodisorder and Autism, Bangabandhu Sheikh Mujib Medical University, Dhaka, from September' 2018 to December 2019. In total, 68 epileptic children, age ranged from five to 16 years, were enrolled as case. Similar number of non-epileptic, age, sex and socio-demographic status matched children were enrolled as control. Parent, teacher and self version of Bangla Development and Well-Being Assessment were used to assess the psychiatric disorders particularly ASD and diagnosis was assigned as Diagnostic and Statistical Manual of Mental Disorders (DSM-V).

Results: The mean age of cases and controls were 9.66±3.13 and 9.26±3.11 years respectively with slight male predominance in both groups (64.7 and 57.35%, respectively). Focal seizure was predominant seizure type (51.5%) among cases. Higher proportion of psychiatric illness was found among the cases compared to controls (83.82 vs 20.59%; p<0.001). Neurodevdevelopmental and emotional disorders were significantly more frequent among cases than controls (29.42 vs 1.5%, and 50 vs 8.82%, respectively, p value <0.001). ASD was prevalent among 8.83% epileptic children, while none of the controls had ASD. Most common types of seizure in ASD children was focal epilepsy .

Conclusions: This study observed the significant association of ASD with epilepsy in studied children. However, further larger multicenter study is recommended.

Keywords: Autism spectrum disorders (ASD), Epilepsy, Diagnostic and Statistical Manual of Mental Disorders (DSM-V), Neurodevelopmental disorder.

Introduction

Epilepsy is a chronic disease identified as a manifestation of the abnormal, excessive hyper-synchronous firing of cortical neurons.[1] It has been reported to be one of the most prevalent neurological disorders, affecting approximately 0.6% of children ageing seventeen years or younger; while varying in degree of severity. Epilepsy impacts over 50 million people globally; nearly 85% of the people with epilepsy live in developing countries.[2]There is a relationship between psychiatric disorders and epilepsy. Psychiatric comorbidities like Autism Spectrum Disorder (ASD) are either the complication of epilepsy or the underlying neurological insult that causes epilepsy or both. Patients with epilepsy have a higher prevalence of psychiatric comorbid disorders.[3]

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ASD is a neurodevelopmental disorder which is associatied with epilepsy commonly. It is charachterized by impairment of social reciprocity and communication . It is suggested that ASD and epilepsy might share a common pathophysiological basis.[4,5]The prevalence of epilepsy among children with ASD ranges widely. It is estimatesd from 2 to 46% in children with ASD .[6] Furthermore, epilepsy seems to be a major factor contributing to the severity of behavioral problems in ASD and is strongly correlated with worse cognitive functioning.[7]Intellectual disability is more common in the subset of epilepsy is children with ASD. Previous studies showed that 8% of individuals with ASD had intellectual disability in the absence of epilepsy.[8] With these increasing recognition of clinical overlap in patients presenting with epilepsy and ASD, a great deal of new information is also available regarding the genetic causes of both disorders. Several biological pathways appear to be involved in both disease processes, including gene transcription regulation, cellular growth, synaptic channel function, and maintenance of synaptic structure.[9]However, the relationship between epilepsy and autism continues to be debated.[10] This relationship is tantalizing from the scientific point of view and challenging from the management point of view.

It is anticipated that a greater understanding of the relationship between these two conditions could have profound effects on the management of patients with ASD.[11] Children with autism and epilepsy represent a unique group of children with special health care needs, and the general pediatrician needs to establish a medical home for this population. Early diagnosis and early interventions are the key elements in providing a medical management for children with autism and epilepsy.[12]

There is very few studies assessing the prevalence of ASD among children with epilepsy, which makes it difficult to establish the valid and reliable association of this co-occurrence. There is little evidence in causal relationships between ASD and epilepsy.[13] While previous data have explained the presence of co-occurring ASD and epilepsy, there remains a pressing need for more research in this sector.[13–16]

Therefore, the aim of this study was to evaluate the association of ASD with epilepsy in children, as well as to determine the frequency of ASD among children with epilepsy.

Materials and Methods

This was a case-control study conducted from September 2018 to December 2019 in the outpatient department of Pediatric Neurology, Institute of Paediatric Neurodisorder and Autism (IPNA), Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. Sixty eight (68) children with epilepsy aged 5-16 years without any diagnosed premorbid psychiatric disorder were recruited as cases and another 68 age and sex-matched children without epilepsy and known neurological problems were recruited as control. Cases were selected consecutively from study center. Controls were also selected from the outdoor of pediatric department randomly who either came as attendants or came to receive treatment for minor ailments.

Sample size was calculated using following formula[17]

$$n=\frac{(r+1)}{r}\frac{P(1-P)\,(Z\beta+Z\frac{\alpha}{2})}{(P1+P2)^2}$$

Here, r= 1, $Z_{â}$= 1.036 for 85% power, $Z_{á/2}$ = 1.96 at 5% significance level, P_1= 0.1222 (expected proportion of ASD in cases) and P2=0.0023 (expected proportion of ASD in controls). P1 and P2 were calculated from the study of Zhang et al.[18]

Before the commencement of the study, formal ethical approval was taken from the Institutional Review Board (IRB) of BSMMU. Informed written consent was taken from the parents or care givers of the study participants. They were interviewed face to face by the researcher using a structured questionnaire designed by the researcher which contained socio-demographic, relevant cultural variables like beliefs and attitude of parents regarding child's disease and variables related to epilepsy. Then the standardized and validated Bangla Development and Well-Being Assessment (DAWBA) tool was used for the diagnosis of ASD. All parents were interviewed by using the parent version of DAWBA. Adolescents of 11 or more years of age were also interviewed by using the self-version of DAWBA. It's teacher version was given to the parents of all school-going children and adolescents with a request letter to the teacher to fill up the questionnaire. It was collected from the parents in subsequent visits. The home teacher filled-up the questionnaire for the non-goers. Then one of the author (MM) who is an international ratter of DAWBA subsequently reviewed both the verbatim accounts and the answers to structured questions and did the clinical rating and

then assigned psychiatric hermonised the diagnoses according to the Diagnostic and Statistical Manual of Mental Disorder (DSM-V) criteria.[19]

Detailed history containing the socio-demographic variables including age, sex, religion, educational status of the child and parents, monthly family income , cultural variables and other related information were taken. Detail history related to epilepsy such as duration of illness, age of onset, type of epilepsy (according to seizure origin), seizure frequency, family history of epilepsy and psychiatric disorders and antiepileptic therapy at the time of assessment was also recorded.

Development and Well-Being Assessment (DAWBA): It is a well-accepted method consisting of questionnaires, interviews, and rating techniques designed to generate International Classification of Diseases (ICD) - 10 and DSM - V psychiatric diagnoses among children and adolescents of 2 to 17 years of age. This instrument was translated in Bangla and standardized and validated byMullick SI and Goodman.[20] The primary purpose of including the DAWBA or any other the social dysfunction index (SDI) in a clinical assessment was to make psychiatric diagnoses more accurate.[21]The interviews were administered by the interviewers who also recorded the verbatim accounts of any reported problems, but did not rate them. Experienced clinicians subsequently reviewed both verbatim accounts and answers to the structured questions before assigning diagnoses according to DSM-V criteria.

The statistical analysis was carried out by using the Statistical Package for Social Sciences version 22.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Qualitative variables were expressed as frequency and percentage and Quantitative variables were expressed as mean ± standard deviation. Test of significance were performed by unpaired t-test and/or chi-squared test. The level of significance was defined asa p-value of <0.05.

Result

The mean age of cases were 9.66±3.13 years.and controls were 9.26±3.11 years. Age of the children ranged from 5 to 16 years. Most of the participants in both groups aged between 8 to 10 years. Both cases and controls showed a male predominance, 64.71% and 57.35% . The majority of the cases came from a rural area (48.53%), whereas the majority of the controls belonged to urban area (50%) without any significant difference (p value >0.05). Higher proportion of children did not attend school at all in the cases (10.29 vs 1.47, p=0.062). The monthly incomes of a family of cases were lower than that of controls (Table I).

Table-I: Socio-demographic characteristics of respondents. (N=136)

Characteristics		Case(n=68) No. (%)	Control (n=68) No. (%)	p-value
Age in years	5 – 7	18 (26.47%)	24 (35.29%)	0.569
	8 – 10	26 (38.24%)	20 (29.41%)	
	11 – 13	15 (22.06%)	17 (25.00%)	
	14 – 16	9 (13.24%)	7 (10.29%)	
	Mean±SD	9.66±3.13	9.26±3.11	0.459**
Sex	Male	44 (64.71%)	39 (57.35%)	0.379*
	Female	24 (35.29%)	29 (42.65%)	
Residence	Rural	33 (48.53%)	25 (36.76%)	0.374*
	Urban	27 (39.71%)	34 (50.00%)	
	Semi urban	8 (11.76%)	9 (13.24%)	
Enrollment in school	Never went to school	7 (10.29%)	1 (1.47%)	0.062***
	Goes to school	61 (89.71%)	67 (98.53%)	
Monthly family income (Taka)	Up to 10000	8 (11.76%)	2 (2.94%)	0.017*
	10001 to 20000	25 (36.76%)	20 (29.41%)	
	20001 to 50000	29 (42.65%)	28 (41.18%)	
	More than 50000	6 (8.82%)	18 (26.47%)	

Values are expressed asMean±SD and within parenthesis percentage (%) over column in total.
*Chi-squared Test (χ^2) was performed. ** Student t-test was performed. ***Fisher's exact test was performed

Focal seizure was predominant seizure type (51.5%). GTCS was the next common type (44.1%). Absence seizure, myoclonic seizure and epileptic encephalopathy were found one in each group. The onset of seizure was between 1 and 156 months with a median of 38 months. Before starting treatment, most patients had up to 10 episodes of seizures (64.7%). During enrolment, 38.2% of epileptic children were seizure-free for the last 6 months. At enrollment most of the children were on monotherapy (63.2%) (Table II)

Among cases 83.8% had psychiatric illness while among controls 16.2% had psychiatric illness (p<0.001). Neurodevelopmental disorders, emotional disorders and behavioral disorders were present 29.42%, 50% and 19.1% respectively in the cases and 1.5%, 8.82% and 10.29% similarly in the controls. All types of psychiatric illness were significantly more common among the cases. Attention Deficit Hyperactive Disorder (ADHD) were significantly higher proportion among cases in comparison to control (p<0.05). The frequency of autism spectrum disorder was 8.8%, while none of the control had ASD. (Table III)

Table-II: Description of seizure characteristics of children with epilepsy (N=68)

Characteristics	Frequency	Percentage	DurationMedian (min-max)
Types of seizure			
Focal	35	51.5	
GTCS	30	44.1	
Ascence	1	1.5	
Myoclonic	1	1.5	
Epileptic encephalopathy	1	1.5	
Age of onset ofseizure (in months)			38.00 (1-156)
No. of seizures before starting treatment			
Up to 10	44	64.7	
11 to 20	15	22.1	
More than 20	9	13.2	
Seizure free in last 6 months			
Yes	26	38.2	
No	42	61.8	
Number of antiepileptic drugs taken			
Monotherapy	43	63.2	
Polytherapy	22	32.4	
None	3	4.4	

Table-III: Distribution of psychiatric disorders among study groups. (N=136)

	Case (n=68) No. (%)	Control (n=68) No. (%)	p-value
Psychiatric disorders	<0.001		
Present	57 (83.82%)	14 (20.59%)	
Absent	11 (16.18%%	54 (79.41%)	
Catagory of psychiatric disorder			
Neurodevelopmental disorders*	20 (29.42%)	1 (1.5%)	<0.001
Emotional disorder*	34 (50%)	6 (8.82%)	<0.001
Behavioral disorders*	13 (19.1%)	7 (10.29%)	0.146
The specific type of neurodevelopmental disorder			
ADHD	14 (20.6%)	1 (1.5%)	<0.001
ASD	6 (8.83%)	0 (0%)	0.028**

*Multiple responses considered.
Values are expressed within the parenthesis percentage (%) over the column in total.
P-value was determined by Chi-squared Test (c^2).

In children with ASD the pattern of seizure was recorded. Most common type of seizure was focal epilepsy observed in 4 children (66.67%). Other type of seizue was epileptic encephalopathy (16.67%) and generalized tonic clonic seizure (16.67%). (Figure 1)

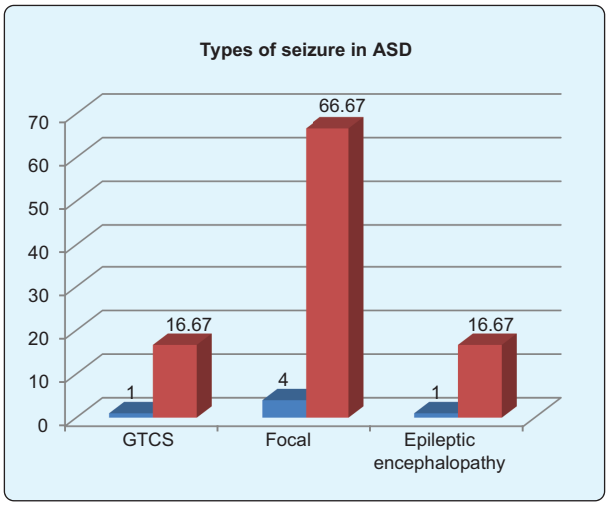

Figure 1: Distribution of seizure in ASD patients. (n=6)

Discussion

Epilepsy is a neurological condition which affects all ages. It affects people of young age more especially in the first two decades of life.[22] In addition to its burden, it is associated with significant psychological consequences.[23] From a meta-analysis authors reported that children with epilepsy are at increased risk for a broad range of emotional and behavioral problems compared with both healthy controls and also children with non-neurological chronic illnesses.[24]This study was designed to assess the extent of ASD in children with epilepsy in Bangladesh.

The co-occurance of epilepsy and ASD had been known since autism was first described by Leo Kanner in 1943.[25] However, the causal relationship between epilepsy and ASD is not clear. But previous studies establish the fact that the prevalence of epilepsy in ASD is well above the general population risk. El Achkar CM 2015 . In our study population, among 68 cases 6 (8.83%) cases had ASD in comparison to none in the control population. A related study done by Clarke DF et al out of 97 children with epilepsy, 9 children were diagnosed as ASD while 31 subjects (32%) found to be at risk of having ASD. Out of them, four children were previously diagnosed as developmental delay and 3 children were diagnosed as tuberous sclerosis complex (TSC).[26]On the other hand, there were several studies on epilepsy in children with ASD. In a large population based study on children with ASD, epilepsy was found in 19% compared to 2% of hospitalized control.[27]

The risk of ASD in children with epilepsy is explained by several factors. It is not clear whether they are caused by common etiology or seizure is the underlying cause of ASD. However, genetic factors play an important role here. For instance, ASD was observed in epilepsy more in syndromic child than the nonsyndromic child.[6] In a study by Pavoneet al epilepsy was seen in 55% of patients with syndromic ASD, compared with only 7.4% of individuals with idiopathic ASD.[28]This studies reflects that one abnormal dysfunction may make the brain more suseptable to other neurological disorders.[29]Moreover, certain genetic mutations are associated with both ASD and epilepsy. Like in one study , it was found that the risk of ASD was much higher in those with TSC associated epilepsy than that of idiopathic epilepsy. Again, in cases with TSC associated epilepsy , cases with low IQ were more associated with ASD. The authors identified drug resistance, early onset seizure and severe seizure type as the predictor of ASD symptoms in this cases.[30]

On the other hand, one population based study reported that rate of ASD was higher in epilepsy patients whom etiology was unknown compared to structural or metabolic etiology.[31]Thus the relationship of ASD and epilepsy is very complex and yet undetermined, thus more randomized controlled study are needed.

In this study population, the commonest seizure type in children with ASD were focal epilepsy obsereved in 66.67% of the cases. In related studies focal seizue was the commonest form of seizure which coincides with our finding.[31–34]In their study, Matsuo M et al found that focal seizure had 8.9 times greater risk to develop ASD than that to generalized seizure. This may be explained by the fact that focal seizure is commonest type of seizure in less than 10 year age.[33]Again some studies showed different result where epilepsy syndromes like west syndrome and Dravet syndrome were more associated with ASD in comparison to generalized epilepsy.[35,36]Other type of seizure in this study were epileptic encephalopathy (west syndrome) and generalized epilepsy.

Regarding the other comorbid conditions, in this study, ADHD/Hyperkinesiswas the most frequent psychiatric disorder (case-20.6%vs control-1.5%, p= <0.001). Similar higher proportion of ADHD was found in other related studies in children with epilepsy.[37,38]

In the present study, the average age of the children was 9.49±3.03 years and the majority belonged to the age group 8 – 10 years (39.7%). The age range is higher than that noted in an earlier study done in Dhaka Shishu (Children's) Hospital . The median age in that study was 3 years [39]. Another study conducted by Ferdous et al. noted that majority children belonged to the age group 5 – 10 years (80.77%).[40]Most of the respondents were male in this study (64.7% and 35.3% were male and female respectively). This corroborates the findings of the previous studies conducted in the country.[39–41] Prevalence studies from other countries also showed a male preponderance.[42–44] Gender differences in some epilepsy syndrome are well documented but the neurobiology behind this difference is still unclear.[45]

Education and occupation of parents did not influence epilepsy in children in this study. But the monthly family income of the parents was significantly lower than that of controls. Ferdous et al. found that the majority of children with epilepsy came from lower socioeconomic conditions.[40] A family history of psychiatric illness was significantly more common among cases (p-value=0,007). This indicates a possible bidirectional relationship between psychiatric illness and epilepsy which was contemplated in several previous studies.[46,47]Most of the children was on monotherapy during the initial assessment (63.2%) and the most commonly used drug was sodium valproate (42.6%) in the current study. This is concordant with the findings of a previous study done on children with epilepsy.[41]

Conclusion

The result of the present study obsereved a significant association of autism spectrum disorder with epilepsy among children. Besides, majority of the children with epilepsy had neurodevelopmental, emotional and behavioural disorders. Moreover, focal seizure was commonest form of seizure among ASD children with epilepsy. However, further larger multicentre study is recommended to strengthen the finding of this study and to explore the nature of this association.

Limitations

The data was a one point source and so could not evaluate the trends observed over time.

Acknowledgement

We acknowledged Ministry of Science and Technology, Government of the People's Republic of Bangladesh for funding this study.

Conflict of Interest: There was no conflict of interest.

Funding: Ministry of Science and Technology, Dhaka, Bangladesh.

Ethical approval: Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka, Bangladesh.

Submitted: 28.04.2021

Final revision received: 17.07.2022

Accepted: 14.08.2022

Published: 01 August 2022

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