Subclinical Epileptiform Dysfunction in Children with Idiopthic Autism

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Abstract: Background: Many studies reported high incidence of epileptiform discharges in children with autism, but with different rates and different patterns, few studies done for children with idiopathic autism. Aime of work: is to study the pattern of subclinical epileptiform discharge, and its clinical correlations for childern with idiopathic autism. Patients and methods: 47 children with idiopathic autism,with their ages range from 3-12 years (mean 6.96± 2.19), compared to 24 healthy age and sex matched contols. All children were assessed by electroencephalography (EEG) and brain imaging as a part of routine care, Childhood Autism Rating Scale (CARS) was done for assessing the severity of autism in patients group. Results: We found that,there were higher incidence of epileptiform discharges at children with idiopathic autism (51.1%) compared to 8.3% at the control group,(*P value* 0.002). The pattern of epileptiform abnormalities is highly correlated to the severity of autism (*P value* 0.000). Focal EEG changes (focal frontal ,occipital or temporal) predominate in severe cases of idiopathic autism (72.7%). In conclusion: subclinical epileptiform dysfunction were detected at higher rate in children with idiopathic autism, different EEG patterns were identified according to severity of autism. we recommend EEG study as a dignostic tool for children with idiopathic autism specially moderate and severe cases.
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1. Introduction

Autism is a complex neurodevelopmental disorder that is behaviorally defined. The behavioral manifestations that define autism include qualitative deficits in social interaction and communication and restricted repetitive and stereotyped patterns of behavior, activities, and interests **[1].** Prevalence figures range from 4 to 10 per 10,000 up to 2 to 5 per 1000 [**2**]. Epilepsy is common in autism, but the rates of seizures vary, with the highest risk in those with the greatest degree of cognitive and motor impairment and the most significant deficits in receptive language deficit.There has been significant controversy regarding the causal role of seizures in autism. The relationship of children who have autism, regression of language,and an epileptiform EEG to those children with Landau-Kleffner syndrome(LKS) is not presently understood. Specific age, behavioral, and EEG profile differences between children with autistic regression and seizures or an epileptiform EEG and those children with LKS do exist, and this may have important etiologic and therapeutic implications. The complex and controversial relationship between autism and epilepsy (clinical and subclinical) has been reviewed by **Tuchman and Rapin [3].**

The developing brain is well known to be more susceptible to seizures than the mature brain**.[4,5]** Some studies suggest that epileptiform discharges on electroencephalography (EEG) without clinical seizures can cause behavioural and cognitive impairment. [**6,7]** Some children who have benign partial epilepsy of childhood with rare seizures but very active centrotemporal epileptic EEG foci have shown cognitive impairment, although long-term data are still limited**.[8]** The same may be true of electrical status epilepticus during slow-wave sleep (ESES). **[9]** Recent research suggests that even in the absence of clinical seizures, epileptiform activity (subclinical epilepsy) seen in partial epilepsies or in EEG-diagnosed syndromes such as ESES may not be entirely benign and can cause specific cognitive, language, and behavioural dysfunction. **[10-13]**

Epileptiform discharges are common among patients with active epilepsy, but are reportedly rare (1-4%) in healthy children **[14,15].** One intriguing finding in autism spectrum disorders (ASD) is the high rates of these abnormalities, even in the absence of epilepsy. This raises questions about whether these discharges could be considered a biomarker of cortical dysfunction in this population, and whether these discharges have a causal association with any of the autism phenotypes. **[16]**

Our hypothesis:

Subclinical epileptiform discharges in children with idiopathic autism ,may have diagnostic ,prognostic and therapeutic importance in these children.

Aim of work: is to study the pattern of subclinical epileptiform discharge, and its clinical correlations for children with idiopathic autism.

2. Patients and methods

Patients:

This study was done on 47 children with idiopathic autism,with their ages range from 3-12 years (mean 6.96± 2.19), compared to 24 healthy age and sex matched contols. Our patients are recriuted from the out patient clinics of psychiatry and pediatric neurology at Mouwasat Hospital,Dammam city, Saudi Arbia. The patients were coming from most of the eastern region at the period from October 2009 to October 2011. To be included in the study, patients were required to meet diagnostic criteria for autism according to Diagnostic and Statistical Manual of Mental Disorders 4th ed. (DSM-IV).[1] Excluded from the study children with specific genetic syndroms and children with known secondry cause of autism.

Methods:

Electroencephalography (EEG)

The qualitative referential 20-channel EEG data were collected using international 10-20 system for electrode placement including the central locations. Electrode placements were made using an electrode cap (Electro Cap Co.: Eaton, OH) and Electrogel conductive gel (Weaver and Co.: Aurora, CO). An electrode was placed at Oz using a discrete electrode to provide an additional recording site. Linked ear electrodes were used as the reference. EEGs were looked out by two reviewers independently and when there were differences, EEGs revised by both reviewers . EEG was done at the morning for all patient and control under standard condition.

Childhood Autism Rating Scale (CARS)

One of the most widely used assessment tools in the United.

States is the Childhood Autism Rating Scale (CARS) **[17].** Evidence suggests that factor analysis–based scores using the CARS is helpful in identifying subgroups of children with autism. Total CARS scores range from a fifteen to 60, with a minimum score of thirty serving as the cutoff for a diagnosis of autism on the mild end of the autism spectrum. CARS is a diagnostic assessment method that rates children on a scale from one to four for various criteria, ranging from normal to severe, and yields a composite score ranging from non-autistic to mildly autistic, moderately autistic, or severely autistic. The scale is used to observe and subjectively rate fifteen items. These items are: relationship to people, imitation, emotional response, body & object use, adaptation to change, visual response, listening response, taste-smell-touch response and use, fear and nervousness, verbal communication, non-verbal communication, activity level, level and consistency of intellectual response and general impressions**.[17]**

Brain imaging was done as apart from routine care .Informed consent was given by parents of our Patients and controls.

Data collection

The study was a case control study .Where all children meeting our inclusion criteria, during routine out patients' visits were enrolled in the study. Assessment of EEG was done by pediatric neurologist. Autism rating scale was done by clinical psychologist.

Statistical methods

IBM SPSS statistics (V. 19.0, IBM Corp., USA, 2010) was used for data analysis. Data were expressed as both number and percentage for categorized data. Chi-square test was done to study the association between each 2 variables or comparison between 2 independent groups as regards the categorized data. The probability of error at 0.05 was considered significant.

2. Results

Demographic data of children with idiopathic autism versus controls:

There were 47 patients diagnosed with idiopathic autism without epilepsy,with there ages ranging from 3 to 12 years and mean age was 6.96± 2.19, 70.2% (male).They were compared to 24 normal children with matched age (*P value* 0.823) and sex*(P value* 0.317). We found that,there were higher incidence of epileptiform discharges at children with idiopathic autism (51.1%) compared to 8.3% at the control group,(p value 0.002). We didn´t found statistical difference regarding the brain imaging abnormalities between patiens and control groups (*P value* 0.250). Also, no difference between patients and controls regarding the family history of epilepsy (*P value* 0.124) (Table 1).

Pattern of epileptiform abnormalities and severity of autsim

In the conducted study ,we found that the pattern of epileptiform abnormalities is highly correlated to the severity of autism (*P value* 0.000). There were high incidence of normal EEG in children with mild autism (78.3%), high incidence of generalized EEG changes in children with moderate autism(53.5%),while focal EEG changes (focal frontal ,occipital or temporal) predominate in severe cases of idiopathic autism (72.7%), using CARS for assessment and scoring (Table 2).

Table (1): Descriptive characteristics of children with idiopathic autism versus control.

Parameter	idiopathic autism N=47	Control N=24	P value
age	6.96±2.196	6.83±2.297	0.823
sex	70.2%(male)	58.3%(male)	0.317
Epileptiform discharge	(26) 51.1%	(2) 8.3%	0.002*
Abnormal brain imaging	12.8%	4.2%	0.250
Family history of epilepsy	17.0%	4.2%	0.124

*p value <0.05 considered significant ,Abnormal brain imaging means any significant abnormalities noticed at brain CT or MRI .

Table 2: EEG patern in correlation with severity of auitism in children with idiopathic autism.

Severity of autism	EEG pattern			P value
	Focal	Generalized	Normal	
Mild	0(0%)	4(30.8%)	18 (78.3%)	0.000*
Moderate	3(27.3%)	7 (53.8%)	4 (17.4%)	
Severe	8 (72.7%)	2 (15.4%)	1 (4.3%)	

*p value <0.05 considered significant,severity of autism was assessed by Childhood Autism Rating Scale (CARS).

4. Discussion

There are many studies that reported interictal EEG changes in individuals with autism. It is important to note that these abnormalities may occur in individuals without seizures, and their presence should not be considered evidence of epilepsy. Rather, these EEG changes are considered to be signs of cerebral dysfunction.[**16]** Epileptiform discharges are common among patients with active epilepsy, but are reportedly rare (1-4%) in healthy children**.[18,19]** In this study ,we found high rate of subclinical epileptiform abnormalities at children with idiopathic autism (51.1%) compared to 8.3% at the control group,(p value 0.002). In the study of **Yasuhara 2010,**abnormal EEG discharges occurred in 85.8% (870/1014) of the patients with autism spectrum disorders (ASD)[19]. In the study of **Hara 2007**,he reported that 18% of non-epileptic children with autism exhibit epileptic discharges on EEG [20]. Many other studies found that, approximately one third of children with pervasive developmental disorders have associated epilepsy, and a significant minority without clinical epilepsy present epileptiform discharges [21-25]. In this study ,we found that the pattern of epileptiform abnormalities is highly correlated to the severity of autism(*P value* 0.000). EEG was abnormal in 21.7% children with mild autism but there were higher incidence of generalized EEG changes in children with moderate autism(53.5%),while focal EEG changes (focal frontal ,occipital or temporal) predominate in severe cases of idiopathic autism (72.7%). Nordin and Gillberg in 1998 concluded that, epilepsy is considered a negative prognostic factor for the outcome of autism.[26] Different studies reported that epileptiform EEGs appear to be more common than non-epileptiform abnormalities[27-30]. However, no consistent pattern of epileptiform discharges across investigations with most studies reporting a variety. These include diffuse or generalized, multi-focal, and focal discharges, unilateral or bilateral and localized to many different brain areas [21,31-33]. Some studies suggest that temporal abnormalities may be more common [31,34], but others do not support this view[27]. **Chez et al 2006** did a retrospective review of 24-hour ambulatory digital EEG data collected from 889 ASD patients presenting between 1996 and 2005 (with no known genetic conditions, brain malformations, prior medications, or clinical seizures) shows that 540 of 889 (60.7%) subjects had abnormal EEG epileptiform activity in sleep with no difference based on clinical regression. The most frequent sites of epileptiform abnormalities were localized over the right temporal region.[31] **Gabis et al 2005** found that, abnormal EEGs and epilepsy occurred at significantly higher rates in children in the more impaired range of the autism spectrum (P<0.05).[33] **Baird etal 2006** studied 64 children with autism and without epilepsy, using sleep EEG. They found that, there was no significant difference in epileptiform activities in those who showed regression compared children without.[34] In the conducted study, we studied other factors like brain image abnormalities and family history of epilepsy ,we did not found significant differences regarding both factors between children with idiopathic autism and controls. These findings suggest that the use of neurological investigative techniques such as EEG should be a consequence of careful clinical evaluation and should be considered routinely during evaluation of more impaired individuals.

Conclusion:

Subclinical epileptiform dysfunction were detected at higher rate in children with idiopathic

autism ,different EEG patterns were identified according to severity of autism .Mild cases EEG commonly will be normal while generalized and focal EEGs pattern were common at moderate and severe cases. Lastly, we recommend EEG study for all children with autism specially moderate and severe cases. With respect that both autism and epilepsy are considered neurodevelopmental disorder of the brain. EEG epileptiform abnormalities being highly correlated to severity of autism could serve as a prognostic tool for those children. Further research on large scale to detect whether use of antiepileptic drugs could help those children.

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