Subclinical Epileptiform Abnormalities in ADHD Children: Effect of Stimulant Medications.

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Abstract: Background: Attention–deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder in children. The relationship between ADHD and subclinical epileptiform abnormalities still vague. In addition, there are controversies about the use of stimulant medications in such case. **Aim of the study:** To assess the effects of stimulant medications on subclinical epileptiform abnormalities in children with ADHD. **Patients and methods:** We recruited 50 newly diagnosed children with ADHD without clinical seizures; they were assessed by EEG before and after 6 months of stimulant medications. Patients were aged from 6 to 12years, including 33males (66%) and 17 females (34%). Patients were categorized according to the subtype of ADHD into hyperactive subtype (n=19, 38%), inattentive subtype (n=10, 20%), and combined type (n=21, 42%).We used 20 channels EEG under standard condition for assessing children before and 6 months after treatment with stimulant medications. **Results:** Epileptiform abnormalities were detected in 16 (32%) of ADHD children before start of stimulant medication (methylphenidate), in comparison with 7 (14%) after stimulant therapy (p= 0.349) .We didn't find any correlation between ADHD subtypes and pattern of epileptiform discharge before and after therapy. Therefore stimulant treatment has nothing to do with epileptiform activity, moreover there is increased percent of normal EEG after treatment to be 86%, which was 68% before stimulant treatment. **Conclusion**: Stimulant medication can be used safely in ADHD children even in the presence of EEG changes without increased seizure risk.
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Key words: subclinical, EEG abnormalities, Children, ADHD, stimulant medication

Abbreviations: ADHD, attention-deficit–hyperactivity disorder, EEG, electroencephalogram, DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th ed.

1. Introduction

Attention –deficit/hyperactivity disorder is the most common neurobehavioral disorder in childhood with an estimated prevalence of 7.4-16%[(1)]. Many hypothesis have been put forward in an attempt to explain the association between ADHD and epilepsy[(2)].The EEG results revealed a temporal relation between subclinical epileptiform discharges and cognitive dysfunction [(3)].Some children present with transient behavioral and learning difficulties correlated with epileptiform discharges without clinical epilepsy[(4)]. Stimulant medication are the most commonly used treatment for ADHD , although it is still not entirely known how these medication work [(5)]. Stimulants are believed to lower the threshold for seizures. Although several studies have revealed that stimulants do not exacerbate well-controlled epilepsy, there is a paucity of data about seizure risk in non-epileptic children treated with stimulants [(6)].

Finally ,although children with subclinical EEG abnormalities are assumed to have increased risk of development of seizures ,there are insufficient data to support this hypothesis. [(7)]

Aim of the study: To assess the effect of stimulant medication on subclinical epileptiform activity on children with ADHD**.**

2. Patients and Methods

This study was done at Mouwasat hospital , Dammam city, Saudi Arabia where patients and control were recruited from most of eastern region of Kingdom of Saudi Arabia (KSA), during the period from December 2010 to December 2011.The study is approved by research ethics board of this hospital.

This study is prospective follow up study , conducted on 75 patients who were diagnosed with ADHD without epilepsy were recruited from outpatient clinic of Child Psychiatry and Neurology, of those only 50 patients completed follow up EEG. .

Those 50 patients were assessed by EEG before and after 6 months of stimulant medications, Aged from 6 to 12years, including 33males (66%) and 17 females (34%). Patients were categorized according to the subtype of ADHD into hyperactive subtype (n=19, 38%), inattentive subtype (n=10, 20%), and combined type (n=21, 42%).

Included patients should meet diagnostic criteria for ADHD according to DSM-IV (primarily inattentive, primarily hyperactive/ impulsive, or combined subtypes) [8], excluded children known to had epileptic changes before the study, children with malformation, known syndromes with epilepsy, known systemic diseases with impact on EEG, and children who received drugs that can affect the result of EEG. Informed consent was given by all parents of our patients.

Methods

Electroencephalogram

The qualitative referential 20-channels 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 single reviewer. EEG was done at the beginning and 6 months after treatment with stimulant medications .

Conners parent rating scale-revised

The 93-item original version of the Conners Rating Scale (CRS) and its revised and abbreviated version is the one currently in common use [9]. Those items of the revised CPRS that are rated by parents and school teachers, are very useful for assessing ('0' to '3' rated) the behavioral symptoms of ADHD, viz. inattentiveness, hyperactivity and impulsivity.

Brain imaging: was done as apart from routine care .

Statistical analysis:

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; while at 0.01 and 0.001 is highly significant.

3. Results

We prospectively evaluated the EEGs of all outpatients aged between 6 and 12 years meeting diagnostic criteria for ADHD according to Diagnostic and Statistical Manual of Mental Disorders 4th ed. (DSM-IV). All patients were newly referred to pediatric neurology or psychiatry clinic between December 2010 to December 2011. The 75 patients diagnosed with ADHD without epilepsy, only 50 patients completed follow up and were assessed by EEG before and after 6 months of stimulant medications**.**

EEG changes and clinical subtypes of ADHD

There was no statistically significant relation between presence of any epileptiform abnormality in EEG and any ADHD subtype before treatment (*p* value 0.215) (Table 1).

There was no statistically significant relation between presence of any epileptiform abnormality in EEG and any ADHD subtype after 6m of stimulant treatment (*p* value 0.117) (Table 2).

Effect of stimulant medication on EEG

There was no significant correlation between stimulant medications use in ADHD patients and presence of EEG abnormalities(*p* value 0.349). EEG changes even normalize after 6 m of stimulant as there is increased percent of normal EEG after treatment to be 86%, which was 68% before stimulant treatment (*p* value 0.215).

Risk of clinical seizures after medication

There is highly significant correlation between presence of epileptiform abnormality in EEG, (specially focal abnormalities) and occurrence of clinical seizures after 6 m of stimulant treatment (*p* value 0.000). There was no significant correlation between ADHD subtype and occurrence of clinical seizures (*p*=0.836). There was no statistically significant relation between presence of positive family history of epilepsy in ADHD children and development of clinical seizures (*p* value 0.241).There is highly significant statistical correlation between brain image abnormalities and occurrence of clinical seizures (*p* value 0.000) as 2 of total 3 patients who had clinical seizures were having abnormal brain MRI (Table 4).

Table (1): relation between EEG changes and different ADHD subtypes before treatment

	Hyperactive Subtype (n=19)	Inattentive Subtype (n=10)	Combined Subtype (n=21)	Total	*P* value
Focal frontal	0	3	1	4 (8%)	0.215
Focal occipital	1	0	0	1 (2%)	
Focal temporal	1	1	1	3 (6%)	
Generalized activity	3	1	4	8 (16%)	
Normal EEG	14	5	15	34 (68%)	

P >0.05 insignificant

Table (2): relation between EEG changes and different ADHD subtypes after 6m of stimulant treatment .

	Hyperactive Subtype (n=19)	Inattentive Subtype (n=10)	Combined Subtype (n=21)	Total	*P* value
Focal frontal	0	1	1	2 (4%)	0.177
Focal occipital	0	0	0	0	
Focal temporal	0	1	0	1 (2%)	
Generalized activity	1	2	1	4 (8%)	
Normal EEG	18	6	19	43 (86%)	

P >0.05 insignificant

Table (3): comparison between ADHD children before and after 6m of stimulant treatment regarding EEG changes.

EEG pattern	EEG before treatment	EEG after treatment	*P* value
Focal frontal	4 (8%)	2 (4%)	0.349
Focal occipital	1(2%)	0 (0%)	
Focal temporal	3 (6%)	1(2%)	
Generalized activity	8 (16%)	4 (8%)	
Normal EEG	34 (68%)	43 (86%)	

P >0.05 insignificant

Table (4): Factors affecting development of clinical seizures after 6months stimulant therapy in ADHD children .

Factor	Number of children with seizures (n=4)		Number of children without seizures (n=46)		P value
ADHD subtypes	Number	%	Number	%	
Hyperactive	1	(33.3%)	18	(38.3%)	0.836
Inattentive	1	(33.3%)	9	(19.1%)	
Combined	1	(33.3%)	20	(42.6%)	
EEG pattern after					
Focal frontal	0	(.0%)	4	(8.5%)	0.021*
Focal occipital	0	(.0%)	1	(2.1%)	
Focal temporal	1	(33.3%)	2	(4.3%)	
Generalized	2	(66.6%)	6	(12.8%)	
Normal	0	(.0%)	34	(72.3%)	
EEG pattern after					
Focal frontal	0	(.0%)	2	(4.3%)	0.000**
Focal occipital	0	(.0%)	0	(.0%)	
Focal temporal	1	(33.3%)	0	(.0%)	
Generalized	1	(33.3%)	2	(4.3%)	
Normal	0	(.0%)	43	(91.5%)	
Brain image					
Simple arachnoid cyst	0	(.0%)	1	(2.1%)	0.000**
Temporal lobe sclerosis	1	(33.3%)	0	(.0%)	
Tuberous sclerosis	1	(33.3%)	0	(.0%)	
Wide cistern magna	1	(33.3%)	1	(2.1%)	
Normal	0	(.0%)	45	(95.7%)	
Family history of epilepsy					
Positive	1	(33.3%)	5	(10.6%)	0.241
Negative	2	(66.6%)	42	(89.4%)	

* *P* value < 0.05 is significant ,** *P* value < 0.001 is highly significant

4. Discussion

Stimulants are an effective treatment frequently prescribed for ADHD, but they commonly are believed to lower the threshold for seizures . Although several studies have revealed that stimulants do not exacerbate well-controlled epilepsy, there is a paucity of data about seizure risk in non-epileptic children treated with stimulants. [6] Apart from an increase in risk of seizures

and need for caution in use of stimulants, studies show that epileptiform discharges in the EEG are linked to a better response of attention deficit to methylphenidate and a higher cognitive performance. [10]

In our study, we found that there was no statistically significant relation between presence of any epileptiform abnormality and ADHD subtypes. This finding is in concordance with Hemmer *et al.,* 2001 addressed the question of seizure risk in ADHD without co-morbid epilepsy by reviewing 234 stimulant-naive patients who were diagnosed with ADHD. Epileptiform EEGs were found in 15% of patients prior to treatment.[6] In another study of Hughes *et al.;* EEG has also been reported to be abnormal in 18-30% children with ADHD. In this study, EEG recordings showed predominantly focal rather than generalized spike and wave complexes[11]. Similarly, Holtman *et al.,* reported that the frequency of centro-temporal (rolandic) spikes in children with ADHD was significantly higher than expected from normal children, based on epidemiological studies (5.6% versus 2.4% respectively), [12] and have therefore suggested that all children being evaluated for a possible diagnosis of ADHD should undergo EEG, irrespective of whether have they have experienced any epileptic seizures[13] .

In our study there was no statistically significant relation between presence of any epileptiform abnormality in EEG and any ADHD subtype after 6m of stimulant treatment. Therefore stimulant treatment has nothing to do with epileptiform activity, moreover there is increased percent of normal EEG after treatment to be 86%, compared to 68% before stimulant treatment. In concordance with our finding study done by Gucuyener *et al.,* 2003 where 119 children with ADHD with epilepsy were studied, they suggested that EEG abnormalities were improved by medication[14].

In the conducted study, we found highly significant correlation between presence of subclinical EEG changes and occurrence of clinical seizures after 6 m of stimulant treatment (*p* value 0.000), even that these specific changes can have predictive value before starting treatment. In the study of Hemmer *et al.,* normal EEG can be used to assign children with ADHD to a category of minimal risk for seizure[6].

In contrast, an epileptiform EEG in neurologically normal children with ADHD predicts considerable risk for the eventual occurrence of seizure. The risk, however, is not necessarily attributable to stimulant use [6]. Dunn and Kronenberger reported that stimulant drugs are safe and effective in children with epilepsy and currently are first-line agents for treatment of attention problems in this population [18]. In our study, we didn't found significant correlation between ADHD subtype and occurrence of clinical seizures. While we found highly significant statistical correlation between brain image abnormalities and occurrence of clinical seizures as 2 of total 3 patients who had clinical seizures were having abnormal brain MRI.

Finally, the definition of ‘‘epileptiform’’ activity on EEG varies between studies. These practical and experiential difficulties may in part explain the reported different EEG findings in children with ADHD.[6,15-17] Tan and Appleton reviewed the association between methylphenidate treatment in ADHD and epilepsy, they reported that there is no reason to believe that methylphenidate should be pro-convulsant and therefore lower seizure threshold. The drug primarily acts on the pre-synaptic reuptake of the neurotransmitters noradrenaline and dopamine rather than the neurotransmitters commonly associated with the pathophysiology of seizures (gamma aminobutyric acid (GABA), glutamic and aspartic acids). It is not known to affect calcium or sodium channels, which are also implicated in the pathophysiology of many of the epilepsies [2].

Limitation of the study:

Small sample size due to some of patients missed follow up .This makes deficiency of data available for statistical analysis.

Conclusion:

We appreciate the use of EEG as one of diagnostic tools for assessing children with ADHD, because of the higher incidence of subclinical epileptiform changes reported in this study and others. Stimulant medication can be used safely in ADHD children even in the presence of EEG changes without increased seizure risk. Children who will develop clinical seizures, should be evaluated for possible underling brain pathology.

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5. References

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