International Journal of Medical and Health Research
ISSN: 2454-9142, Impact Factor: RJIF 5.54
www.medicalsciencejournal.com
Volume 2; Issue 9; September 2016; Page No. 57-60

Attention deficit hyperactivity disorder in childhood epilepsy: An overview

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Abstract
Epilepsy and Attention-deficit/hyperactivity disorder are both common childhood neurodevelopmental disorders. The relationship between Epilepsy and Attention deficit hyperactivity disorder (ADHD) is complex and is not clearly understood. It has been found out that ADHD is more common in pediatric epilepsy than in general pediatric population. There may be several factors contributing to the comorbidity which can include the underlying brain pathology, the chronic effects of seizures and EEG changes and the effects of antiepileptic pharmacotherapy. In epileptic children with symptoms of ADHD, treatment becomes a challenge for pediatrics neurologists. But unfortunately there is a lack of management guidelines regarding mental health disorders in children with epilepsy on anti-epileptic medications. The following review article has been planned accordingly to look into the various aspects of childhood epilepsy which will help the pediatricians and the psychiatrists to treat the child accordingly.

Keywords: ADHD, epilepsy, anti-epileptic drugs, pediatrics

Introduction
Attention-deficit/hyperactivity disorder (ADHD) is a common disorder of childhood onset has its impact on the development of the child [1] Epilepsy can be defined as two or more unprovoked, non-febrile seizures. It affects up to 1% of children and adolescents [2, 3]. Epilepsy and Attention-deficit/hyperactivity disorder are both common childhood neurodevelopmental disorders. The relationship between Epilepsy and Attention deficit hyperactivity disorder (ADHD) is complex and is not clearly understood. It has been found out that ADHD is more common in pediatric epilepsy than in general pediatric population. There may be several factors contributing to the comorbidity which can include the underlying brain pathology, the chronic effects of seizures and EEG changes and the effects of antiepileptic pharmacotherapy [4].

It has been seen that the symptoms of ADHD are more common in some specific types of epilepsies, such as frontal lobe epilepsy and childhood absence epilepsy and may anticipate seizure onset in a significant proportion of cases [5]. In epileptic children with symptoms of ADHD, treatment becomes a challenge for pediatrics neurologists. The treatment depends upon the drugs combinations in order to improve the long-term cognitive and behavioral prognosis of the epileptic child [6] Both ADHD and Epilepsy have important implications on for a child's learning, social and behavioral development [7]. Attention Deficit Hyperactivity Disorder (ADHD) is a common comorbidity in childhood epilepsy, but unfortunately little is known regarding the nature, frequency and timing of associated neurological and cognitive complications or the underlying aetiology of ADHD in epilepsy [8] The association has been attributed to the epilepsy or its treatment, although it is impossible to determine in previous studies which condition occurs first [9].

The present review article will summarise the incidence of ADHD in children diagnosed with epilepsy on anti-epileptic medications. Inspite of strong association of ADHD with childhood epilepsy, the area has been less researched and calls for more studies to understand the link better. This will be essential for the pediatricians and the psychiatrists to manage the epileptic child better [10] Pediatricians and psychiatrists should be able to collaborate for a better outcome. But unfortunately there is a lack of management guidelines regarding mental health disorders in children with epilepsy on anti-epileptic medications. The following review article has been planned accordingly to look into the various aspects of childhood epilepsy which will help the pediatricians and the psychiatrists to treat the child accordingly.

Risk factors and causes for developing ADHD in epileptic children
According to a study published in Pediatrics, children with epilepsy or febrile seizures have a greater risk of developing attention-deficit/hyperactivity disorder (ADHD). The study done in Denmark from 1990 through 2007, and follow up until 2012 stated that children with epilepsy have nearly 3 times the risk of developing ADHD compared to children without epilepsy. Children who had febrile seizures appeared to have an almost 30% increased risk of ADHD [11].

Many studies have reported that the symptoms of ADHD often start before the appearance of first seizures, and in spite of good seizure control, patients still struggle with ADHD. Studies have reported that ADHD with epilepsy can affects the quality of life of children even more than the epilepsy alone. Some studies found out that newly diagnosed epilepsy (most often within 3 months) have more chances of developing ADHD [12]. There are several factors which contribute to the comorbidity of epilepsy with ADHD. They include the underlying brain

pathology, genetic predisposition, noradrenergic system dysregulation, chronic effects of seizures, effects of antiepileptic drugs, effects of stimulants, and psychosocial factors [13].

ADHD is a behavioral disorder that results from damage to the frontal-striatal brain networks. Most often structural brain abnormalities can cause seizures or the same brain networks may be disrupted by seizures itself. With such disruption and abnormalities, the child may also struggle with the same type of behaviour problems seen in ADHD. As stated above already, children with new onset epilepsy or earlier age of developing seizure at a greater risk of developing ADHD as compared to those children with development of seizure at a later age or having old seizure. The frequency and severity of seizures also influence the development of ADHD symptoms, with higher amounts of ADHD symptoms seen in people with more frequent and/or more severe seizures. Also, studies have stated that the use of some anti-epileptic drugs and their side-effects have an effect on the behavior pattern of the child and can provoke ADHD in such children [14].

Incidence of ADHD in children with epilepsy.

In a study done in Italy, out of 300 pediatric patients on anti-epileptic drugs, 172 of them developed ADHD [15]. The prevalence of ADHD in children in the general population is 5%–7%, whereas in children with epilepsy is around 20%–40%. [16, 17] A study done in Vancouver, Canada stated that there are 25-30% of children diagnosed with epilepsy who exhibit symptoms of ADHD [14].

Another study done in Israel stated that 27.7% epileptic children developed ADHD (sample size 284) [19]. Recent studies suggest that ADHD is a common co-morbid condition in childhood epilepsy. ADHD has been found to be more prevalent in new onset epilepsy than healthy controls (31% VS 6%) [20].

A research done on 107 children between the ages of 6-13 years, 27% of them were found to have both epilepsy and ADHD. Population studies also support the common occurrence of ADHD and epilepsy co-morbidity. A review of literature between 1990−2010 reported 20−40% to have developed ADHD with epilepsy [21].

Analyzing ADHD and Childhood Epilepsy

Researches on ADHD in epilepsy have suggested that epileptic children exhibit inattentive type of ADHD more commonly than other subtypes [14]. It has been seen that the new onset epileptic seizures lead to cognitive deterioration specially Complex partial seizures in children tend to cause more inattention problems with ADHD [22, 23].

Inattention subtype of ADHD has been seen to be more common than hyperactivity and impulsivity in children with epilepsy [17]. Children with benign childhood epilepsy with centrotemporal spikes, commonly referred to as BCECTS, complex partial seizures, frontal lobe epilepsy, rolandic epilepsy, and absence type of epileptic seizure may be more likely to show symptoms of ADHD [24, 25]. Researches have also studied and concluded that the combined type of ADHD is more common in the general pediatric population, whereas the inattentive type of ADHD seems to be more common in children with epilepsy [26, 27]. Another study confirmed that the symptoms of ADHD tend to occur more with complex partial seizures than with generalized seizures in children [28]. Another study by Sherman *et al.* also reported the incidence of inattentive type of ADHD more as compared to hyperactivity and impulsivity in epileptic children [29].

Cognitive Dysfunction and Pharmacotherapy of the epileptic children.

Antiepileptic drugs (AED) function by decreasing the membrane excitability, increasing the postsynaptic inhibition and altering the synchronization of neural networks in order to decrease excessive neuronal excitability associated with seizure development. Slowed motor and psychomotor speed, poorer attention and mild memory impairment can occur due to decrease in the neuronal excitability [30].

There have been plethora of studies on adult epilepsy explaining the pattern of AED but we lack sufficient studies in pediatric epilepsy to formulate AED guidelines in children. An attempt on that has been made by the American Academy of Neurology [31].

It has been seen that Phenobarbital and traditional benzodiazepines are associated with the greatest risk of cognitive side effects in epileptic children. In some researches, children on phenobarbital displayed IQ declines whereas the IQ improved following discontinuation of phenobarbital. On testing for 3-5 years, long-term achievement effects were seen in those children [32].

Treatment Modalities

Keeping in mind the side-effects of the anti-epileptic drugs and comorbidities of epilepsy in childhood, current guidelines recommend starting with a trial of a stimulant, methylphenidate [MPH] or amphetamine [AMP] [33]. Both the drugs are equally effective with a combined response rate of 85% when tried sequentially [34]. Children should be started on a long-acting formulation to promote greater adherence to treatment [35]. However, short-acting stimulants and lower doses are often used in children at the age of 5 years or younger due to higher rates of emotional adverse events and slower metabolism of MPH in this age range [36].

On the other hand, tricyclic antidepressants used in children with ADHD have been found to lower the seizure threshold and should be avoided in children with epilepsy. There are no studies with reports of interaction between atomoxetine or alpha adrenergics and AEDs in children [37]. There are not sufficient studies to review the alpha-2 adrenergic agonists, both in their impact on ADHD treatment in children with epilepsy and on their effect on seizures [38, 39].

Non-medical treatment plays a major role in treating an epileptic child with ADHD. Behaviour interventions should be implemented at home as well as school and both the parents and the teachers should work in collaboration. Research studies have shown that greater success is achieved when both medication and behaviour management techniques are applied and are effective in treating the symptoms of ADHD [40].

Health Related Quality of Life

In a study done by Sherman *et al*. inattention type of ADHD was found to be more (40% vs. 18% for hyperactivity-impulsivity). Parameters like the age of onset, epilepsy duration, and seizure frequency were not related to severity of inattention or hyperactivity-impulsivity. Over 60% of children met screening criteria for ADHD-Inattentive subtype or ADHD-Combined Inattentive/Hyperactive-Impulsive subtype.

Compared to inattentive type of ADHD, combined ADHD was associated with earlier onset of seizures, generalized epilepsy, lower adaptive level, and in normally developing children, a higher degree of intractability. Localization-related epilepsy was more related to inattentive type of ADHD. Also a trend for a higher use of AEDs with cognitive side effects in this group was noted.

ADHD is a significant predictor of poor HRQOL in epilepsy, particularly in the case of ADHD combined type. ADHD has been associated with poor Health related Quality of Life (HRQOL). Two- and four-fold likelihood of low HRQOL has been reported in inattentive type and combined type of ADHD respectively [41].

Conclusion

ADHD in epileptic children might not differ much in children with well-controlled seizures and minimum or no intellectual disability may not occur too. When diagnosing children with ADHD in epileptic children, clinicians should first evaluate the children's intelligence before determining whether their behaviors are consistent with their developmental level, and they should also consider frequent seizures as a confounding factor to be controlled prior to ADHD diagnosis, especially in children having absence seizures.

Future studies are needed to understand the occurrence of both ADHD and epilepsy in a child which influences a child's development. It has been seen that the psychosocial factors do not contribute significantly to the etiology of ADHD, but they influence the severity and persistence of symptoms.

Children with uncontrolled epilepsy are more likely to have problems with attention, behavior and poor academic achievement. Studies have shown that these children can have benefit from the use of psychostimulants. Regarding the medical treatment, there is a lack of double blinded and randomized trials in children with epilepsy and ADHD. This has resulted in improper evaluation of the safety of MPH. But the open-label studies and the experts' opinions allow us to consider the use of this stimulant as effective and safe in children with controlled epilepsy.

Most importantly, in order to prevent the development of ADHD, epilepsy in children should be diagnosed and treated as early as possible. The AED side effects should be conveyed to the parents and the teachers for the development of any behavioral problems in future. Non-medical treatment should be given as much importance as the medical treatment. More studies are required especially in India to evaluate and understand the relationship between epilepsy and ADHD and the management modalities.

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