Epilepsy & Behavior xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Targeted Review

Key issues in addressing the comorbidity of Attention Deficit Hyperactivity and disorder and pediatric epilepsy

Jay A. Salpekar *, Gaurav Mishra

Center for Neuroscience and Behavioral Medicine, Children's National Medical Center, George Washington University School of Medicine, Washington, DC, USA

ARTICLE INFO

Article history:
Received 7 March 2014
Revised 22 April 2014
Accepted 23 April 2014
Available online xxxx

Keywords:
Pediatrics
ADHD
Epilepsy
Treatment
Diagnosis

ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is a common comorbidity of epilepsy encountered by clinicians. However, relatively little information is available to guide optimal diagnostic and treatment strategies. Differentiating ADHD from effects of epilepsy requires careful history taking and emphasis upon characteristic symptoms and course of illness. Rating scales for ADHD are well validated and may aid clinical management. Use of antiepileptic drugs may cause cognitive or behavioral side effects yet may improve behavior in some cases. Historically, clinicians have been hesitant to treat ADHD comorbidity for fear of lowering the seizure threshold. However, an aggregate of recent evidence now suggests that stimulants may be well tolerated and effective for ADHD comorbid with epilepsy. Studies that further clarify pathophysiology and treatment outcomes are needed in order to enhance clinical efficacy and quality of life for this population.

Key questions

1. How common is attention deficit hyperactivity disorder (ADHD) in children and adolescents with epilepsy?
2. How can seizures and related inattention be distinguished from ADHD?
3. Do antiepileptic drugs cause problems with attention and concentration?
4. Is stimulant medicine safe in patients with epilepsy and comorbid ADHD?
5. What research is needed to advance care and treatment of ADHD in pediatric epilepsy?

1. How common is ADHD in children and adolescents with epilepsy?

Attention deficit hyperactivity disorder (ADHD) is a common illness in pediatrics and also represents the most common psychiatric comorbidity associated with pediatric epilepsy [1,2]. Attention deficit hyperactivity disorder is usually identified in a school-aged population aged 6–12 years and is characterized by a constellation of symptoms that encompass inattention, hyperactivity, and impulsivity. Despite the heterogeneity of clinical presentations, ADHD may represent one of the most reliably applied diagnoses in all of psychiatry. The interrater reliability for ADHD among psychiatry clinicians and researchers is excellent and favorably compares with diagnostic agreement for mood disorders or psychosis in the pediatric population [3].

A key point to emphasize for clinicians and caregivers is that ADHD is common, and very likely to be encountered in epilepsy clinical care centers. Even conservatively designed epidemiology studies report a worldwide prevalence of ADHD in 3–6% of the pediatric population [4,5]. However, ADHD is overrepresented in epilepsy, with several studies reporting prevalence ranging from 30 to 40% [6]. A diagnosis of epilepsy has been associated with a 2.5–5.5 times higher chance of having co-occurring ADHD. The predominantly inattentive subtype of ADHD may be especially common. In a clinical sample of chronic pediatric epilepsy, one group found inattentive subtype at 24%, combined subtype at 11%, and hyperactive/impulsive subtype at 2% [7]. However, a prospective research study noted the combined type of ADHD to be prevalent in 58% of a sample of pediatric epilepsy [8]. Another unique phenomenon in this population is the disappearance of usual gender differences in the prevalence of ADHD. Without epilepsy, ADHD is seen in school-aged children with a male to female ratio of 2–3:1; however, the ratio is 1:1 when comorbid with epilepsy [9].

The cooccurrence of both illnesses is so frequent that some investigators have posited a pathophysiologic overlap between the two conditions. A recent study compared 76 children and adolescents with recent-onset epilepsy with 62 healthy controls and found that 31% of the children with epilepsy had ADHD versus only 6% in the control group [10]. The intriguing aspect of this study is that, in most cases,

* Corresponding author at: Department of Psychiatry and Behavioral Sciences, Children's National Medical Center, 111 Michigan Ave., NW, Washington, DC 20010, USA. Tel.: +1 202 476 3932; fax: +1 202 476 5039.
E-mail address: doctorjay911@gmail.com (J.A. Salpekar).

http://dx.doi.org/10.1016/j.yebeh.2014.04.021
1525-5050/

ADHD preceded the first seizure. Along with other studies of populations with new-onset epilepsy, these findings suggest that ADHD may represent an intrinsic pathologic process. The ADHD in these cases cannot be attributed to medication side effect because, in most cases, antiepileptic drugs (AEDs) had not yet been initiated. Furthermore, inattention potentially resulting from the cumulative deleterious effects of chronic seizures would also be unlikely in a new-onset population.

Recent studies have reinforced the possible transactional nature of epilepsy and ADHD. Children with ADHD not only have a higher chance of developing epilepsy in the future but also have increased severity of epilepsy [11]. Some hypotheses point to ADHD being a "successive comorbidity" to epilepsy, developing due to a lowered seizure threshold. In that manner, early onset of epileptiform discharges may interfere with the typical development of brain regions or networks associated with attention and impulsivity [12]. Ongoing epileptic seizures and subclinical epileptiform discharges may have lasting effects on attention and cognitive function. The impaired brain development would then yield ongoing impairment even when seizures are well controlled. A recent study supports the premise that the presence of ADHD symptoms at the time of epilepsy onset is a risk factor for atypical cognitive development in the future [13].

Recent advances in genetics and in neuroimaging studies have also suggested important overlaps between epilepsy and ADHD [14]. Attention deficit hyperactivity disorder is a highly heritable condition, and children with both ADHD and epilepsy are more likely to have mothers with ADHD [15]. Additionally, activation patterns in brain regions impacted in ADHD may be similar for children with or without epilepsy [16]. Impaired connectivity in attention networks may also be present in childhood absence epilepsy and be identified by neuropsychological tasks geared toward ADHD assessment [17].

Electroencephalographic (EEG) studies have furthered speculation regarding a physiologic overlap between the two conditions [18]. Several studies have shown a higher frequency of EEG abnormalities in patients with ADHD when compared with the general population [19,20]. Although sampling issues may confound generalizability, a handful of studies have found epileptiform complexes in 6–30% of the patients with ADHD and without epilepsy as compared with the rate of 3.5% in the general population [21–23]. One study reported a sample where 53% of children with ADHD had epileptiform abnormalities in overnight EEG readings [24]. The increase of resting theta waves in frontal regions seems to be a particularly consistent EEG abnormality found in patients with ADHD [25]. Abnormal alpha asymmetry [26] and a higher theta-to-beta ratio [27] have also been reported. It should be noted that implications of these abnormalities in terms of seizure occurrence or propagation in children with epilepsy are largely unknown.

Although the implications are largely unknown, the presence of subclinical "nonconvulsive" epileptiform complexes, possibly occurring during seizure-free periods, may have significant effects on vigilance, memory, and processing speed. This phenomenon was described in the 1980s and referred to as transient cognitive impairment and was seen in nearly 50% of patients with epilepsy who also had frequent subclinical epileptiform discharges in the alert state [28]. Transient cognitive impairment can be detected by testing short-term memory and language and is detected during approximately one-third of epileptiform discharges in two-thirds of patients [29]. In this study, the resolution of these interictal discharges with AED treatment had a positive effect on attention and cognitive functioning, though the extent of interference by these discharges is still difficult to quantify [29].

Although a clear consensus is lacking, attempts have been made to correlate seizure types or localization with the incidence of ADHD. Epilepsy associated with frontal lobe seizure foci has been frequently associated with inattention and impulsivity—constituent symptoms of ADHD. Impulsivity, hyperactivity, irritability, and executive function deficiencies are also key features of ADHD and have been associated with prefrontal cortex dysfunction. Thus, it may be intuitive to suggest that ADHD may be more likely to occur in patients with frontal lobe seizure foci.

Overall, ADHD commonly cooccurs with pediatric epilepsy in up to one-third of cases or more. The overlap is significant to such a degree that common pathophysiology may be imputed. Frontal lobe seizure foci appear to present a significant risk, but overall network effects may similarly be awry and lead to ADHD symptoms. The differential diagnosis may be challenging, and factors such as sleep disruption and seizure severity may play important roles in the prevalence and impact of ADHD symptoms [30–32]. For clinicians, identification of potential ADHD is an important practicality that challenges optimal management of epilepsy.

2. How can seizures and related inattention be distinguished from ADHD?

Symptoms of inattention and distractibility present challenges to clinicians attempting to differentiate ADHD from seizures. Subsyndromal problems with attention perhaps even associated with subclinical EEG abnormalities or nonconvulsive seizures may be difficult to differentiate from ADHD. Other attention issues that complicate diagnosis may be side effects of antiepileptic drugs (AEDs), preictal auras, or confusion associated with the postictal periods. Finally, specific seizure types, namely, absence seizures, may be very difficult to distinguish from state abnormalities of ADHD.

The clearest course for clinicians attempting to characterize inattention is thorough history taking. Attention deficit hyperactivity disorder itself is a diagnosis based upon history and, in many cases, represents a diagnosis of exclusion. Epilepsy may similarly be a diagnosis based upon history as seizures may be uncommonly witnessed by clinicians, and physical exam findings are typically absent. Typical ADHD symptoms occur in multiple settings at home or at school and are usually only mitigated by high degrees of structure. Epilepsy may be less predictable, and symptoms may be more prominent in periictal time periods, especially if prodromes and postictal periods are liberally extended on the order of many hours or days. Key differences are found in Table 1.

Some investigators have attempted to find unique symptoms or task performance that may more reliably identify either condition. A prospective study distinguished epilepsy and ADHD based upon performance on timed cognitive decision-making tasks and reaction times. Attention deficit hyperactivity disorder was characterized by impulsive errors and disinhibition on simple reaction time tasks, whereas patients with epilepsy had a generalized slower performance on complex decision-making tasks [33]. This suggests that ADHD may have inconsistent cognitive processing, while epilepsy may have more global slowed function. The authors also note that many performances on psychological tasks did not differ between epilepsy and ADHD.

Absence seizures can account for nearly 10–15% of all childhood-onset epilepsies and represent a particularly challenging differential diagnosis. Absence seizures may, on the surface, appear very similar to lapses of attention that characterize ADHD. Even beyond the discrete seizure episodes, children with absence epilepsy demonstrate higher rates of distractibility and more problems with homework and require more educational resources compared with controls [34]. A cumulative effect of cognitive dysfunction makes it harder to differentiate the inattention that may result from chronic absence epilepsy from the inattentive phases of ADHD. Some studies have implicated similar cortical–subcortical networks in the pathophysiology of absence seizures and attentional disorders [35].

A clever study done by Williams and colleagues attempted to identify behavioral symptoms that suggest specific associations with either absence seizures or ADHD. A list of 40 behavioral symptoms was assessed from observers. The strongest specific predictor of seizures was the occurrence of "change of breathing" and "glassy eyes". The strongest predictor of ADHD included "fidgeting", which was not commonly seen in patients with epilepsy [36].

For ADHD, multiple rating scales have been developed that very effectively measure the presence and severity of ADHD. Rating scales may be nonspecific, especially with diagnostic confounds potentially

Please cite this article as: Salpekar JA, Mishra G, Key issues in addressing the comorbidity of Attention Deficit Hyperactivity and disorder and pediatric epilepsy, Epilepsy Behav (2014), http://dx.doi.org/10.1016/j.yebeh.2014.04.021