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Review article

Attention deficit hyperactivity disorder in children with epilepsy

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Abstract

Attention deficit hyperactivity disorder (ADHD) is more frequent in children with epilepsy than in general pediatric population. Several factors may contribute to this comorbidity, including the underlying brain pathology, the chronic effects of seizures and of the epileptiform EEG discharges, and the effects of antiepileptic drugs. Symptoms of ADHD are more common in some specific types of epilepsies, such as frontal lobe epilepsy, childhood absence epilepsy and Rolandic epilepsy, and may antedate seizure onset in a significant proportion of cases. In epileptic children with symptoms of ADHD, treatment might become a challenge for child neurologists, who are forced to prescribe drugs combinations, to improve the long-term cognitive and behavioral prognosis. Treatment with psychotropic drugs can be initiated safely in most children with epilepsy and ADHD symptoms.

Keywords: ADHD; Frontal lobe epilepsy; Childhood absence epilepsy; Rolandic epilepsy; Methylphenidate; Antiepileptic drugs

1. Introduction

Attention deficit/hyperactivity disorder (ADHD) is a common brain disorder with onset in early childhood, due to structural and functional abnormalities in widespread, but specific areas of the brain [1]. ADHD is a frequent comorbidity experienced by children with epilepsy, has a negative impact on their quality of life, and represents a significant risk factor for academic underachievement [2].

ADHD has been reported in epilepsy since the Fifties of the 20th century [3]. More recently a high association between the two disorders, with an increasing evidence of a bidirectional relationship, has been postulated [4–7]. The mechanisms underlying attention deficits are still unknown and appear to be different between focal and generalized epilepsies. In the clinical practice, this association may represent a challenge for child neurologists since antiepileptic therapy and drugs used to treat ADHD may aggravate the clinical picture of each other [8,9].

The purpose of this article is to discuss the current understanding of the pathogenesis and the neurobiological links among ADHD and epilepsy, and provide a practical review of the major considerations that guide child neurologists to tailor treatments according to clinical needs.

2. Literature search strategy

A scoping search on PubMed was undertaken to identify pertinent articles using "epilepsy and ADHD" as key words. Trials recruiting only patients with single seizure or febrile convulsions, people over 18 years old and mixed age groups were not considered.

3. Epidemiology

An increased risk for seizures is a symptom that is often associated with ADHD [10]. In ADHD children

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the prevalence for epileptiform EEG discharges range from 5% to 60% [11]. The predictive value of epileptiform EEG abnormalities for developing subsequent seizures in ADHD children is 14% [11].

Children with epilepsy have a significant risk for ADHD, with clinical studies suggesting a prevalence of 30–40% [12,13], that is much higher than in the general pediatric population [14,15]. ADHD was reported to be the most common disorder in preschoolers and school-aged children with epilepsy [12], with equal representation of boys and girls [10,14].

In an epilepsy sample observed in a Tertiary Centre characterized by early age of onset, significant duration of epilepsy, high seizure frequency, and intractability, the proportion of children meeting DSM-IV criteria for either ADHD-C or ADHD-I was over 60% [16]. However, ADHD is also significantly more prevalent in new onset epilepsy than healthy controls (31% versus 6%) [17,18]. The interpretation of these studies is difficult, as they differ widely in the number of patients studied, and the severity and type of epilepsy, as well as in the methods used to make the ADHD diagnosis.

4. Pathophysiology

Attention is subserved by many brain structures, and neuroimaging studies showed evidence of at least three anatomic networks that function separately and together to support various aspects of attention [19,20]. These interacting networks are (1) a vigilance network comprising the right frontal and right parietal lobes; (2) an executive attention network including the left lateral frontal areas and the anterior cingulated; (3) an orienting network consisting of parietal, midbrain and thalamic circuits [19,21,22]. Different impairment of these systems may cause inattention, hyperactivity/impulsivity, or both. Several hypotheses have been proposed regarding the possible pathophysiology of the comorbidity between ADHD and epilepsy in the context of brain development, including the effects of chronic seizures and of EEG epileptiform discharges, as well as the AEDs [23,24]. However, ADHD with epilepsy and ADHD without epilepsy seem to have common pathogenetic mechanisms, suggesting that inattention and hyperactive/impulsive behavior commonly observed in children with epilepsy truly constitute ADHD [25]. Increasing evidence suggests that ADHD may sometimes antedate the onset of epilepsy, indicating that both these conditions may represent epiphenomena of underlying neurobiological abnormalities that remain to be identified [10]. Quantitative MRI demonstrated that ADHD in epilepsy is associated with significantly increased grey matter in distributed regions of the frontal lobe and significant smaller brainstem volume [18]. It is known that lesions to the prefrontal cortex produce a profile of inattention, impulsivity, poor planning and hyperactivity [26]. Neuroimaging studies have reported several abnormalities in brain structure in ADHD, including decreased overall cerebral tissue volume with preferential involvement of the prefrontal areas, cerebellum, and caudate, also giving convincing evidence of fronto-striatal dysregulation in ADHD [19]. Although there are suggestions of predominance of frontal cortex abnormalities [27], more recent data showed a significant reduction in all lobes bilaterally [28]; ADHD children also showed a significant decrease in surface area in cortical folding bilaterally. These findings could be consistent with onset early in neural development, during gestation through infancy when folding is increasing.

fMRI findings suggest that children with ADHD have anomalous development of cortical systems and atypical motor and sensory cortex activation [29]. Furthermore, striatal glutamate concentration is higher in ADHD children than in the controls [30]. Animal models of ADHD suggest that synaptic abnormality in excitatory glutamatergic transmission may contribute to vulnerability for epilepsy and ADHD, and could help to identify common pathophysiological events between these two conditions [31–33].

5. Epilepsies usually associated with ADHD

Attention problems are frequently reported in children with intractable symptomatic epilepsy, as well as in idiopathic epilepsies [13,34,35]. Patients who have generalized epilepsies are more frequently reported to have attentional difficulties than patients suffering from partial seizures. Furthermore, certain epilepsy syndromes may predispose to ADHD-like behavior [14,15,36]. ADHD is a prevalent comorbidity of new onset idiopathic epilepsy, associated with a series of cognitive and behavioral complications that antedate epilepsy onset in a significant proportion of cases, and appear related to neurodevelopmental abnormalities in brain structures [18]. The presence of ADHD symptoms at the time of epilepsy onset is a major marker of abnormal cognitive development [37].

5.1. Frontal lobe epilepsy (FLE)

Frontal lobe epilepsy shares behavioral features with ADHD, presenting in some patients with impulsivity, disinhibition, and excitement/irritability [38,39]. The prefrontal cortex plays a key role in the neuronal networks responsible for executive functions, including inhibition control and set shifting [40,41]. Therefore, the pattern of behavioral and cognitive impairment observed in some patients with FLE might be related to an epilepsy-induced impairment of these networks [42,43]. There is a critical early stage of brain maturation during which frontal lobes epileptiform EEG discharges perturb the development of brain system that underpin