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Attention Deficit Hyperactivity Disorder and Associated Cognitive Dysfunction in Pediatric Epilepsy

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Attention deficit hyperactivity disorder (ADHD) is the most common neuropsychiatric comorbidity associated with childhood epilepsy, affecting about a third of children with epilepsy. In contrast, ADHD in the general population occurs in 4%-12% of school-aged children. The cause of this association remains unclear. It is likely that common mechanisms underlie the vulnerability for both executive deficits and epileptogenesis. There are characteristics unique to children with ADHD and epilepsy. The inattentive type of ADHD is more prevalent than the combined presentation in children with epilepsy, while the combined type is more common in the general population. Interestingly, there is an equal sex distribution of ADHD in patients with epilepsy, while in the general population, ADHD is 3-7 times more prevalent in boys. Specific features of ADHD seen in different epilepsy syndromes are frequently associated with executive deficits. Early screening of ADHD symptoms in children with epilepsy is essential, as timely interventions can improve academic and social function and outcomes. The mainstays of therapy include behavioral interventions and pharmacotherapy, with evidence demonstrating that stimulants are both safe and effective in children with ADHD and epilepsy.

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Introduction

The Diagnostic and Statistical Manual of Mental Disorders—5th edition (DSM-5) includes attention deficit hyperactivity disorder (ADHD) in the section of neurodevelopmental disorders and divides it in 3 categories:

1. Predominantly inattentive
2. Predominantly hyperactive, impulsive
3. Combined

To fulfill the diagnosis, patients younger than 17 years must display at least 6 of 9 inattentive or hyperactive impulsive symptoms; however, for individuals older than 17, only 5 symptoms per category are needed. They should interfere with, or reduce the quality of social academic, or occupational functioning.

ADHD is the most common neuropsychiatric comorbidity associated with childhood epilepsy, affecting about a third of children with epilepsy.[1] ADHD and epilepsy are 2 of the most common neurologic disorders of childhood.

Epilepsy has a prevalence of 0.5%-1%,[2] being more frequent in the young and elderly. In general, children with epilepsy are at increased risk for developmental and mental health problems.[2] Population-based studies have shown a rate of psychiatric disorders of 26%-38% in children with uncomplicated epilepsy, with a significantly higher prevalence (56%-58%) in patients with complicated epilepsy.[3,4]

The prevalence of ADHD from community—population-based studies of childhood epilepsy varies from 23%-33%.[2,5,6] In contrast, ADHD in the general population occurs in about 4%-12% of school-aged children.[7]

The cause of this association remains unclear. It is likely that common mechanisms underlie the vulnerability for both executive deficits and epileptogenesis. Significant behavior problems and attention deficits can predate the onset of seizures or be present at the time of epilepsy diagnosis.[8-12]

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Hesdorffer et al[11] demonstrated that children presenting with their first unprovoked seizure were 2.5-fold more likely than controls to meet DSM IV criteria for ADHD before seizure onset. Hermann et al[12] found impairments in executive functions in children with new-onset epilepsy. The neuropsychological deficits were independent of syndrome type and occurred early in the course of the disorder.

Conversely, population-based studies also showed higher incidence of epilepsy among children with ADHD.[6,13] An association between the inattentive type of ADHD and increased risk for seizures has been reported,[12] suggesting the possibility of a dysfunction in the norepinephrine system as a common etiology for both disorders.

Are There Specific Characteristics to ADHD in Children With Epilepsy?

1 Multiple studies have shown specific differences between ADHD in patients with epilepsy and ADHD in children without epilepsy.

   The inattentive type of ADHD is more prevalent than the combined presentation in children with epilepsy, while the combined type is the most prevalent in the general population.[11,14–16]

   In a study of children with severe epilepsy, patients with the combined type of ADHD had earlier onset of seizures and more refractory epilepsy, compared to children with the inattentive presentation. These children also had a tendency to present with generalized epilepsy, lower adaptive levels, and poor quality of life scores.[17]

2 There is an equal gender distribution of ADHD in patients with epilepsy,[11,15] while ADHD in the general population is 3-7 times more prevalent in boys than girls.[16]

Similar to children with ADHD without epilepsy, children with epilepsy and ADHD are predisposed to other neuropsychiatric comorbidities such as anxiety and oppositional defiant disorder

ADHD Associated to Specific Epilepsy Syndromes

Childhood Absence Epilepsy

Childhood absence epilepsy (CAE) is one of the most common syndromes observed in childhood, affecting 10%-17% of children with epilepsy.[18,19] The peak incidence is between 6 and 7 years of age, and is more frequent in girls than in boys. The typical EEG shows bisynchronous 3 Hz spike and wave discharges with normal background activity.[20]

The large multicenter "Childhood Absence Epilepsy Treatment Study" conducted by Glauser et al[21] showed clinically significant baseline attention problems in 35% of children with absence seizures, demonstrated by elevations in the confidence index on the Conners' Continuous Performance Test (≥0.60). These deficits persisted despite successful seizure control, suggesting that attention problems and seizures may be the manifestation of a common dysfunction in cortical networks important for both executive function and absence seizure generation.

Results from one study using functional imaging and EEG provided some evidence for this hypothesis. Activation of the thalamus and extensive inhibition of neuronal networks involved in attention was observed during generalized spike-wave discharges.[22] Despite these observations, seizure frequency does not appear to be directly linked to executive dysfunction. However, seizures lasting longer than 20 seconds may place children at greater risk for attention deficits.[23,24]

Children with absence seizures usually exhibit the inattentive presentation of ADHD rather than the hyperactive type, and parents may underreport symptoms. Deficits in attention may negatively affect the academic performance of children with otherwise normal cognition, due to a direct effect on memory and learning.[25] Population-based studies in patients with absence epilepsy, particularly children without remission, also showed poor psychosocial outcomes.[26] It is then essential to screen children with absence epilepsy for the presence of attention deficits and institute early interventions.

Benign Rolandic Epilepsy

Benign Rolandic epilepsy (BRE) is the most common focal epilepsy syndrome with a peak incidence between 7 and 8 years of age. It represents up to 24 % of all pediatric epilepsies, and there is a male predominance.[27] The syndrome is considered "benign" due to the previous notion of absence of intellectual disability and resolution of seizures by age 16.[27,28]

Further studies have shown that despite the favorable seizure prognosis, there is a strong association between BRE and cognitive deficits.[29] Specific learning disabilities, mainly in verbal domain, are well recognized.[30] There are multiple publications demonstrating a high rate of neurobehavioral disorders with symptoms of ADHD reported in up to 31% of children.[31] These include problems with impulse control and inhibition.[32] A comprehensive review of this association was recently presented by Besag et al.[33] These findings support the recommendation to substitute the term "self-limited"for "benign" issued by the International League against Epilepsy commission for classification and terminology of the epilepsies.

Holtmann et al[34] evaluated the EEG of 483 children aged 2-16, meeting diagnostic criteria for ADHD, and discovered rolandic spikes in 5.6% of them. This is significantly higher than the rate of focal epileptiform discharges observed in normal children.[35] In this study, children with rolandic spikes demonstrated more hyperactive impulsive symptoms. The majority were boys, presented with clinical manifestations at an earlier age, and had a right hemispheric spike predominance. Other studies also noted increased impulsivity and distractibility in children with ADHD and rolandic spikes, compared to those without spikes.[36] The behavioral and intellectual