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Review

Headache and attention deficit and hyperactivity disorder in children: Common condition with complex relation and disabling consequences

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ABSTRACT

The aim of this review was to analyze literature data on the complex association between headache and attention deficit and hyperactivity disorder (ADHD) in children, in order to explore its possible consequences on child neurological development.

Headache and ADHD are two common conditions in the pediatric population. They both are disabling diseases that impact the child's quality of life and are associated with severe cognitive, emotional, and behavioral impairments. To assess and analyze literature data about the association of ADHD and headache in children and possible physiopathogenesis relationships, we searched for the following terms: headache, migraine, tension-type headache, ADHD, and children (MESH or text words).

We found different studies that assess the clinical, epidemiological, and physiopathogenetic overlap between these two diseases, with contrasting results and unresolved questions. Structural and functional abnormalities in brain networks have been found to be central in both headache and ADHD pathophysiology. It will be crucial to gain a better understanding of how subcortical–cortical and corticocortical network development is altered during the onset of the disorders.

1. Introduction

Headache is a common disease in the pediatric population [1]; it may become a disabling condition for both children and families, impacting the child's quality of life and leading to worry in parents and caregivers [2,3]. Recurrent, episodic, and paroxysmal attacks are suggestive of primary headache disorders, subdivided into migraine, tension-type headaches (TTHs), cluster headaches, and other (uncommon) types in children. Migraine is among the most common chronic conditions with an estimated prevalence of 10–28% among children and adolescents [2]. It is a painful and disabling condition, particularly in childhood, often accompanied by severe impairments, including low quality of life, low emotional functioning [4,5], absenteeism from school, and poor academic performance [6,7], as well as poor cognitive functioning [8,9], motor coordination, sleep habits [10,11], and high maternal stress. Several studies have focused on the impact of headaches on school performance and on the association between primary headaches and attention deficit, hyperactivity, and emotional and behavioral problems, raising a number of controversial points.

Attention deficit and hyperactivity disorder (ADHD) is also common among the pediatric population, with a worldwide prevalence of 5.3% [12], and is considered to be an important factor leading to poor academic performance. It is one of the most common childhood-onset neuropsychiatric conditions characterized by developmentally inappropriate behavioral symptoms categorized into three subtypes: inattentive, impulsive and hyperactive, and combined type. It has been associated with epilepsy [13], learning disability [14], and behavioral problems [15,16].

The prevalence of ADHD among children with headaches as well as its association with headache duration and frequency are still contradictory. The two diseases may influence each other simultaneously; concentration difficulties, hyperactivity, inappropriate behavioral symptoms, as well as stress among the family or at school are psychological predictors of headaches [17]. On the other hand, frequent headaches may increase distractibility and further impair learning.

Literature data suggest that pediatric migraine is associated with impaired attention span [18] and hyperactivity–impulsivity [19] but not with fully developed ADHD [19]. However, it is interesting to

Abbreviations: ADHD, attention deficit and hyperactivity disorder; TTHs, tension-type headaches; PAG, periaqueductal gray matter; SDB, sleep-disordered breathing; RLS, restless leg syndrome; PLMs, periodic limb movements; ID, iron deficiency.

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observe that both ADHD and migraine have well-established comorbid connections with mood and anxiety disorders. This has been shown both in clinical [20,21] and epidemiological [22] studies. There is also evidence for the involvement of dopaminergic systems in the pathophysiology of all three categories of disorders [23], which is one of the possible attractive pathophysiological ways to explain linkage between headaches and ADHD. Other possible explanations have focused on dysfunctional brain iron metabolism, possible genetic linkage, and an underlining common sleep disturbance [24].

2. Epidemiological data

Arruda et al. in a cross-sectional study on 1856 participants aged 5 to 11 years demonstrated that migraine and TTH are not comorbid to ADHD overall but are comorbid to hyperactive–impulsive behavior [19]. Leviton reported in a study on 150 elementary school children with recurrent headaches that about 40% had academic difficulties. These results are also in accordance with other recent studies that found a significantly high incidence of hyperactivity and impulsivity symptoms in children with headaches compared with healthy controls [25]. Strine et al. [26] demonstrated in a population of 4- to 17-year-old children that the ones who were referred for neurological assessment for frequent headaches were 2.6 times more likely to have inattention and hyperactivity. Genizi et al. in a recent retrospective study on 243 children and adolescents aged 6–18 years showed that learning disabilities and ADHD are more common in children and adolescents who are referred for neurological assessment for primary headaches compared with the general pediatric population [6].

However, the association between attention deficit and hyperactivity disorder and headache type remains controversial. Villa described impaired visual attention in children with migraine and suggested that impaired attention depends on neurotransmitters such as dopamine and noradrenalin. These same neurochemical aspects involved in the pathophysiology of migraine, therefore, may dispose those children to attention deficit and hyperactivity disorder [27].

In a recent study, Riva et al. compared 62 children with headaches (14 patients with migraine headaches with aura, 29 patients without aura, and 19 patients with tension-type headaches) with 52 controls using Conners' Continuous Performance Test. They found that patients with headaches had mean scores in hit reaction time significantly different from those of controls and also had a higher percentage of atypical scores in 2 indices of Conners' Continuous Performance Test (faster mean reaction time and more commissions) [28]. They found no differences between migraine and tension-type headache. Therefore, they suggested that these two conditions form a continuum that may share the same pathophysiological mechanisms [29] and that the same cerebral circuits underlining headache, personality profile, and attention overlap.

3. Pathophysiology

Several studies tried to identify alterations of neuronal circuits and cerebral regions which could explain the comorbidity between migraine and ADHD and clarify the association between the two conditions and between them and the different diseases often associated with them.

The pathophysiology of primary headaches involves the neurovascular system with cortical spreading depression and trigeminovascular activation, followed by transmission through the thalamus to higher cortical structures [30,31].

Despite extensive research, the pathophysiological mechanisms underlying ADHD are not completely understood [32]. Neuronal deficits in attention and executive function processing networks have been frequently reported in ADHD using structural and functional neuroimaging approaches [33,34]. Neuroimaging studies have demonstrated global cortical maturation delay based on reduced cortical thickness and reduced GM and WM volumes, specifically in the frontal lobe [35], regional WM microstructural abnormalities in the frontal, temporal, and parietal lobes [36–38], and aberrant neuronal activations in the interregional functional connectivity of these cortical areas [39,40].

All these structural and functional abnormalities in the brain have been associated with impaired cognitive, affective, and motor behaviors seen in ADHD.

3.1. Sleep disorders and dopaminergic dysfunction

The analysis of the associations between sleep disorders and both migraine and ADHD could help to better understand the complex relationship between headaches and ADHD. It is known that sleep is related to the occurrence of some headache syndromes while headache may cause sleep disruption and several sleep disturbances either in adults or children. Headache episodes are known to occur in relationship with various sleep stages. On the other hand, an excess or lack of sleep or bad quality or inadequate duration of sleep can trigger headache [10,11].

The trigeminal nucleus caudalis in the pons and midbrain is considered to be the migraine generator, and the hypothalamus is involved in the prodromal symptoms of migraine, such as hunger, fatigue, mood changes, and sensory and visual distortions, that are commonly considered as dopaminergic premonitory symptoms [41,42]. The hypothalamus is connected with anatomical structures involved in the control of the sleep–wake cycle as well as in the modulation of pain [43] (limbic system, pineal gland, noradrenergic locus coeruleus, and serotonergic dorsal raphe), with the serotonergic system playing an important role in the relationship between headache and sleep.

The role of dopamine in the pathogenesis of migraine has been evaluated by different studies: individuals susceptible to migraine appear to have genetic polymorphisms in the dopamine D2 gene, which increase responsiveness to dopamine, or defects in tyrosine hydroxylase, which inhibit dopamine metabolism, and an imbalance of the dopaminergic system is responsible for some premonitory symptoms of migraine, such as nausea, yawning, and dizziness [44,45]. Finally, melatonin is a chronobiotic substance that has demonstrated therapeutic efficacy in some forms of migraine and headache [46,47].

An imbalance between neurotransmitters, with damaged serotonergic and dopaminergic pathways, which characterizes both migraine and sleep disorders, could begin in the early period of life and tend to persist during childhood and adolescence, leading to disorders of the sleep–wake rhythm in infancy and determining the comorbidity between altered neurodevelopment and headache disorder [48]. An altered modulation of synaptic potentiation and pruning by dopamine during development, which results in altered patterns of corticocortical connectivity, has been linked to the structural and functional connectivity deficits of the ADHD [49].

One important anatomical region for the connectivity of headache and sleep is the ventrolateral part of the periaqueductal gray matter (PAG), which is responsible for “rapid-eye-movement sleep-off” when activated by orexin. On the other hand, orexin can stimulate neurons in the ventrolateral part of the PAG, inhibiting antinociceptive activity in the trigeminal nucleus caudalis, thus facilitating trigeminal nociception and triggering a migraine attack. Dysfunctional hypothalamic activity might contribute to both altered sleep–wake function and altered pain processing via its orexinergic neurons [50].

It is, therefore, very likely that pain processing can be modulated via these circuits by vegetative/autonomic symptoms and reflex mechanisms: sleep can trigger a migraine attack, and on the other hand, through changes of the autonomic homoeostasis, it can facilitate or suppress pain processing.

Subcortical regions may also significantly contribute to the pathophysiology of ADHD [51]. Neuroimaging studies have demonstrated regional structural and functional deficits of the basal ganglia, especially in the striatum; as mentioned, disturbed WM structural connectivity and atypical functional connectivity have been shown in the frontal–