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Signs and symptoms of Attention Deficit Hyperactivity Disorder and its main comorbidities: A systematic review

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ABSTRACT
Objective: The aim of this study is to survey the latest scientific evidence on the symptoms of attention deficit hyperactivity disorder associated or not with comorbidities. The knowledge and use of clinical criteria reverberate in the benefit of early diagnosis, optimizing positive results in the phase of greater brain plasticity. Methodology: Systematic literature review, using the Pubmed and VHL databases, with the descriptors: Attention Deficit Hyperactivity Disorder, Signs and Symptoms and Differential diagnosis, from 2018 to 2023. A total of 299 articles were identified and, after applying the inclusion and exclusion criteria, 20 studies were selected for analysis. Results: Attention deficit hyperactivity disorder (ADHD) is a heterogeneous disorder with different clinical presentations, namely predominantly inattentive, predominantly hyperactive-impulsive, and combined. Among these presentations, inattentiveness is considered the most prevalent and symptoms include difficulty maintaining attention on tasks, difficulty finishing imposed tasks, not paying attention to details, and not following instructions. Diagnosis is made using DSM-5 criteria. ADHD is reported to be associated with several comorbidities and other co-occurring and overlapping disorders, such as anxiety disorder, mood disorder, substance use disorders, reading disorders, sleep disorder, and dyscalculia. However, anxiety disorder is the most prevalent comorbidity in patients with ADHD. Conclusion: Scientific studies have contributed to demonstrate the main signs and symptoms of ADHD, in addition to listing the main comorbidities that can affect children with this pathology.

Keywords: Attention deficit hyperactivity disorder, Signs and symptoms, Comorbidities.

1 INTRODUCTION

The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-V) defines attention deficit disorder with or without hyperactivity disorder (ADHD) as a syndrome that occurs during childhood and consists of three symptoms: hyperactivity, inattention, and impulsivity. In the absence of a specific biomarker, this triad is the only element for diagnosing ADHD. (PIERRE M. et al., 2020) This disorder begins during early childhood, affecting the patient's functional status in academic and social life, and leads to inappropriate behaviors in social settings. Recent studies have established that ADHD persists into adulthood. (KOYUNCU A. et al., 2019)

The variable combinations of symptoms and their educational and social repercussions are the cause of the different clinical presentations: a predominantly attentional subcategory, a predominantly hyperactive subcategory and, finally, a mixed subcategory that associates symptoms of inattention and hyperactivity. (PIERRE M. et al., 2020) ADHD manifests a

heterogeneity of presentations, which may take opposite forms due to the presence of frequent comorbidities and/or overlap with other disorders that may or may not become apparent during clinical examination. (DRECHSLER. et al; 2020)

The estimated prevalence of ADHD is 5 to 7%, with a predominance of males (3:1) and within the clinical forms there is a greater representation of the hyperactive subtype by males, while affected women tend to have lower rates of hyperactivity and aggression and are more likely to be diagnosed with ADHD of the inattentive type. (Rodrigues Silva et al., 2022, p. 2887-2890) (LANDAU, Z.; PINHAS H.O., 2019) ADHD is the most common neurodevelopmental disorder in childhood. It has been shown that the prevalence of ADHD increased by 33% during 1997-1999 and 2006-2008. (LANDAU, Z.; PINE CONES H.O., 2019)

The etiology of ADHD is complex and still poorly understood, although there appears to be a high level of heritability of the condition, indicating a significant genetic component. (LANDAU, Z; PINHAS H.O., 2019) Thus, the etiology of the disorder is multifactorial, encompassing polygenic, neurological, and environmental factors that are associated with socioeconomic variables, psychodynamic factors, and personality itself. (Rodrigues Silva et al., 2022, p. 2887-2890) Non-inherited neurological factors that affect brain development or result in brain injury are implicated in the pathogenesis of ADHD. The contribution of pregnancy and childbirth complications is mixed, but strong evidence supports a higher risk of ADHD after in utero exposure to alcohol or tobacco and low birth weight (<2,500 g). Hypoxic and chemoymic brain injury, epileptic disorders, and traumatic brain injury also contribute to the risk. (BÉLANGER. et al; 2018; LANDAU, Z.; PINHAS H.O., 2019) A growing body of evidence supports a model in which various genetic and environmental factors interact with each other during the prenatal and early postnatal periods, increasing the neurobiological predisposition of the disorder, which in turn leads to subtle changes in various brain systems, resulting in different deficits in multiple neuropsychological domains. This model recognizes a high degree of pathogenetic heterogeneity in the ADHD population, with significant individual differences. (CARUCCI S. et al., 2023)

To be diagnosed with ADHD, the symptoms of the disorder are observed in two or more settings and have negative effects on fundamental aspects of the child's daily activities. (ATHANASIADOU A. et al., 2020) ADHD, according to the DSM-5, remains a diagnosis of exclusion if behavioral symptoms are better explained by other mental disorders (e.g., psychotic disorder, mood or anxiety disorder, personality disorder, substance intoxication, or withdrawal). (DRECHSLER. et al; 2020)

Contrary to what might be expected after years of intense research, the ADHD criteria defined by nosological systems, such as the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) and the International Classification of Diseases, editions 10 and 11 (ICD-10/11) have not become more restrictive and specific. Instead, they have become broader, for example, encompassing larger age groups, thus placing more emphasis on the importance of the specialization and experience of the pediatric medical professional. (DRECHSLER. et al; 2020)

The general objective of the present study is to analyze the scientific literature on attention deficit hyperactivity disorder, seeking to relate the benefit of good description and recognition by health professionals, of the signs and symptoms that permeate ADHD, as well as of the comorbidities that may be associated with the condition.

2 METHODS

This is a systematic review that seeks to understand the clinical aspects of Attention Deficit Hyperactivity Disorder, aiming to ensure greater knowledge about the clinical picture and diagnosis of this disorder, as well as to demonstrate the main comorbidities associated with the condition. For the development of this research, a guiding question was elaborated through the PVO strategy (population, variable and objective): "What are the clinical repercussions of ADHD for pediatric patients and their main associated comorbidities?"

The searches were carried out through searches in the PubMed Central (PMC) and Virtual Health Library (VHL) databases. Three descriptors were used in combination with the Boolean term "AND": Attention, Deficit, Hyperactivity, Disorder, Signs and Symptoms, and Differential diagnosis. The search strategy used in the PMC database was: Attention Deficit Hyperactivity Disorder (AND) Signs and symptoms and Attention Deficit Hyperactivity Disorder (AND) Differential diagnosis, and in the VHL it was Attention Deficit Hyperactivity Disorder (AND) Differential diagnosis. From this search, 299 articles were found, which were subsequently submitted to the selection criteria. The inclusion criteria were: articles in English, Portuguese, and Spanish published in the period from 2018 to 2023, which addressed the themes proposed for this research, in addition to the review, observational, and experimental studies made available in full. The exclusion criteria were: duplicate articles, those made available in the form of abstracts, those that did not directly address the proposal studied, and those that did not meet the other inclusion criteria.

After the association of the descriptors used in the researched databases, a total of 299 articles were found. Of these, 292 articles belonged to the PubMed database and 7 articles to the

Virtual Health Library. After applying the inclusion and exclusion criteria, 20 articles were selected from the PubMed database and 0 articles from the Virtual Health Library, and a total of 20 studies were used to compose the collection.

3 DISCUSSION

Attention deficit hyperactivity disorder (ADHD) is considered a childhood-onset neurodevelopmental disorder that includes symptoms of inattention, motor hyperactivity, and impulsivity, and is extremely detrimental to the child's proper development. It is considered a heterogeneous disorder in terms of clinical manifestations, etiology, and comorbidities. As a result, ADHD has different clinical presentations, namely: predominantly inattentive, predominantly hyperactive-impulsive, and combined (DE LA PEÑA. et al; 2020).

Regarding the predominantly inattentive presentation, it is considered the most prevalent subtype, corresponding to 23% of cases in preschool children, 45% of cases in elementary school children, and 75% of cases in adolescents. Symptoms related to the inattentive subtype include difficulty maintaining attention on tasks, difficulty finishing imposed tasks, not paying attention to details, and not following instructions. Patients who have this subtype usually avoid situations in which they require effort and sustained attention. (DE LA PEÑA. et al; 2020) On the other hand, clinically relevant hyperactive and impulsive behaviors are present only in individuals with predominantly hyperactive-impulsive and combined subtypes. (DE LA PEÑA. et al; 2020)

According to the study conducted by CARUCCI S. et al. (2023), it is possible to evidence a significant difference in the clinical presentation of the disorder based on the individual's gender, with girls diagnosed with ADHD being more likely to present the predominantly inattentive form. Generally, they are less hyperactive and are more likely to develop comorbidities such as anxiety, mood, and eating disorders. In addition, they are more likely to start smoking or become pregnant while they are still in middle or high school. (CARUCCI S. et al., 2023; ANTONIOU et al., 2021) Men diagnosed with ADHD are more prone to hyperactive, aggressive, and disruptive behaviors, in addition to having higher rates of alcohol abuse. (CARUCCI S. et al., 2023)

Neuropsychological processes such as working memory and processing speed are important for the presentation of ADHD. Working memory is considered a primary executive function and encompasses the cognitive ability to sustain information for short periods of time. Deficits in working memory have been evidenced in children with ADHD, regardless of subtype. (DE LA PEÑA. et al; 2020) It was found that a worse performance in working memory is related

to a worse outcome in the literacy process, involving reading comprehension, writing, and spelling. (MCDOUGAL. et al., 2022)

Children with ADHD are highly impaired in their social relationships, contributing to passive and withdrawn behaviors, resulting in situations of neglect and social isolation, in addition to increasing the significant risk of generating failures in behavioral, family, and academic situations. (DE LA PEÑA. et al; 2020; CARUCCI S. et al., 2023).

Early identification of ADHD is essential to ensure a better prognosis for the patient and optimize their quality of life, based on this, it can be highlighted that there is scientific evidence that children with ADHD have worse gross and fine motor skills compared to children who do not have the disorder. Thus, this spectrum of motor impairments may be potential early indicators of ADHD development, with a delay in gross motor function observed in infants aged 3 to 9 months who were later diagnosed with ADHD. (ATHANASIADOU A. et al., 2020)

It is noteworthy that the diagnosis of ADHD is considered difficult to perform due to the presence of heterogeneous symptoms, the lack of specific biomarkers and the correlation with several clinical comorbidities, however, with the update of the DSM-5, criteria that describe essential behaviors in a broader and broader age group were incorporated, contributing to better diagnostic elucidation. (BÉLANGER. et al; 2018)

According to the DSM-5, the disorder is a diagnosis of exclusion and should not be made if the symptoms are explained by another clinical condition such as mood disorder, anxiety, psychotic, personality, or substance abuse. For the DSM-5, the symptoms that define ADHD are divided into presentations based on inattention and hyperactivity/impulsivity. Presentations of ADHD can be defined using DSM-5 criteria, with ADHD being predominantly inattentive when 6 of the 11 symptoms are scored, predominantly hyperactive/impulsive when there are 6 of the 9 symptoms, and combined presentation when both criteria are met. Symptoms must be present in two or more settings before the patient reaches 12 years of age for a minimum of 6 months and must reduce or impair social, academic, or occupational functioning. (DRECHSLER. et al; 2020)

It is possible to stratify the severity of ADHD into mild, moderate and severe, with the mild form being defined by the presence of few symptoms and minor functional impairments. On the other hand, the moderate form has symptoms and functional impairment ranging from mild to severe, and in the severe form, many clinical symptoms or symptoms are observed that result in marked functional or occupational impairment. (DE LA PEÑA. et al; 2020)

ADHD has been observed to be significantly associated with several comorbidities and other concomitant disorders. Among them: eating disorders, such as anorexia nervosa, bulimia

nervosa, binge eating disorder, and addictive eating behavior, even when no eating disorder is diagnosed. One hypothesis for this phenomenon is that the impulsivity associated with ADHD may increase the overall risk of sensation seeking, as well as justifying substance use disorders and behavioral addictions. It is reported that 23.1% of individuals with substance use disorder meet the DSM criteria for ADHD. (EL ARCHI. et al; 2020)

Specifically, individuals with ADHD have consistent patterns of reduced gray matter volume in the frontal-striated circuit. Hypoactivation of this circuit was observed during inhibition tasks in individuals with ADHD relative to controls, validating its regulatory role in abnormal inhibitory function. In addition, they manifest brain abnormalities in structures related to reward and activation. The ventral striatum, the most prominent component of the reward system, exhibits lower volume as well as lower activation during reward anticipation in people with ADHD. Consequently, these individuals are at high risk of developing substance use disorders, as they have shown greater activation in the reward processing network during impulsivity-related tasks, suggesting an overactive reward system as the potential cause of this comorbidity. (LONG. et al; 2022)

Patients affected by ADHD have a high incidence of associated comorbidities, in which the specific learning disorder of reading (dyslexia) stands out. Learning to read is essentially based on the maturity of a series of skills. Among them, the phonological process that includes the ability to perceive, segment and manipulate the sounds of conversation. The consolidation of reading is essential in the efficient management of grapheme-phoneme conversion rules. It was possible to observe that children with a higher ADHD symptomatology show lower decoding speed. There is also a relationship between reading difficulties and symptoms of lack of attention, in which one of the two disorders mentioned causes associated symptoms in a secondary way (SÁNCHEZ-CARMONA. et al; 2021)

In addition to educational and behavioral symptoms, children with ADHD may face a number of challenges in cognitive aspects. Differences in attention change and actualization, inhibition, short-term memory delay, and working memory are included. Together, these researches point to broad, not isolated, cognitive difficulties in ADHD. We know that children with broad cognitive disabilities also have poorer reading skills than children without these difficulties or those with isolated deficits. (MCDOUGAL. et al; 2022)

ADHD is characterized by having comorbidities and overlapping with other neurodevelopmental and mental disorders, such as anxiety disorder (34%), mood disorder (22%), behavioral disorder (15%), substance use disorders (11%), reading disorders (15–50%),

dyscalculia (5–30%), autism spectrum disorder, which since the DSM-5 is no longer seen as an exclusion criterion for ADHD diagnosis (70–85%), Tourette's disorder (20%), obsessive compulsive disorder (5%), and developmental coordination disorder (30–50%). (EL ARCHI. et al.; 2020; DRECHSLER. et al; 2020)

Adolescents with ADHD are at higher risk of experiencing psychopathology such as anxiety and depression. In addition, emotion regulation deficiencies in children with ADHD are associated with a more severe ADHD phenotype and prospectively predict greater functional impairment in adulthood. If reduced sleep contributes to poorer affective and emotional functioning in adolescents with ADHD, then sleep may be an important, though often not addressed, treatment target for this population. Insufficient sleep duration worsens mood and emotion regulation in adolescents with ADHD, particularly as observed by parents. (BECKER S.P. et al., 2020)

In the past, ADHD and anxiety disorders were mostly studied separately. However, this viewpoint has changed with recent studies. Many epidemiological studies have found high rates of comorbidity between anxiety and ADHD in children and adolescents. (LANDAU, Z.; PINE CONES H.O., 2019; KOYUNCU A. et al., 2019) Studies suggest that anxiety may decrease the response to psychostimulants in ADHD, while ADHD medications may improve concomitant anxiety symptoms, so the close relationship between ADHD and anxiety is evident. In addition, ADHD can be considered a risk factor for the development of anxiety disorder, just as the age of onset of anxiety disorders in childhood has been shown to be more frequent the younger the ADHD patient. (KOYUNCU A. et al., 2019)

Along with this, it has been seen that attention deficiency can be anxiogenic and, on the contrary, anxiety can also worsen the symptoms of inattention. As children with ADHD age, symptoms of hyperactivity tend to decrease, while symptoms of inattention often persist, and consequently, anxiety may become more dominant in clinical presentation over time. (KOYUNCU A. et al., 2019)

ADHD increases the risk of substance misuse disorders by 1.5 times and problematic media use by 9.3 times during adolescence. There was also a 1.2-fold increase in the risk of becoming obese for adolescent girls, which was associated with different forms of unregulated eating. Frequent neurological comorbidities of ADHD include migraine, which is three times more frequent in ADHD than in typically developing children, and epilepsy is three times more frequent in children with ADHD. (DRECHSLER. et al; 2020)

The presence of sleep-related problems has been evidenced in up to 70% of children diagnosed with ADHD. (DIMAKOS J. et al., 2021) Children with this disorder may have delayed circadian rhythm due to a delay in the onset of melatonin production and abnormalities/genetic dysregulation in the clock genes, associated with this, we can report that excessive use of screens at night may contribute to the presence of sleep-related disorders in children with ADHD. (DIMAKOS J. et al., 2021) (MARTIN. et al; 2019) Scientific studies have shown that, compared to typically developing children, children and adolescents with ADHD have higher sleep latency and a moderate decrease in sleep efficiency as measured by actigraphy. (LIANG. et al; 2023) As a consequence of sleep-related problems in children with ADHD, a high prevalence of daytime sleepiness is observed, directly affecting the social and academic performance of individuals with the disorder. (BACKER et al; 2019)

Children with ADHD may present irritability, low tolerance to frustration and emotional lability, these situations may favor the formation of internalizing behavioral problems (anxiety, depressed mood) and/or externalizing (opposition/defiance, misconduct, irritability). These behaviors contribute to the formation of social, occupational, and educational problems. Sleep problems are common in children with ADHD, contributing significantly to the manifestation of behavioral problems. (DIMAKOS J. et al., 2021)

In addition to psychological and psychiatric comorbidities, there are still significant correlations between ADHD and metabolic alterations. Metabolic syndrome describes a constellation of metabolic abnormalities that are associated with visceral adiposity. These disorders include insulin resistance, hypertension, hypertriglyceridemia, low levels of high-density lipoprotein cholesterol, and central obesity. As far as hypertension is concerned, it is known that methylphenidate and amphetamines are commonly used in the treatment of ADHD in both children and adults. By increasing noradrenergic and dopaminergic transmission, these agents can increase blood pressure, a well-known adverse effect of stimulants. (LANDAU, Z.; PINE CONES H.O., 2019)

5 CONCLUSION

It is concluded that attention deficit hyperactivity disorder (ADHD) is a heterogeneous disorder with different clinical presentations, called predominantly inattentive, predominantly hyperactive-impulsive and combined. The diagnosis is made through criteria established by the DSM-5, and the symptoms must be present in two or more environments before the patient is 12 years of age with a duration of at least 6 months and must impair social, academic or occupational functioning.

ADHD is reported to be associated with several comorbidities and other concomitant and overlapping disorders, such as anxiety disorder, mood disorder, behavioral disorder, substance use disorders, reading disorders, sleep disorder, dyscalculia, and obesity. Scientific studies have contributed to demonstrating the main signs and symptoms of ADHD, listing the main comorbidities as well as the incessant search for markers of early neuropsychomotor development to optimize the diagnosis. Thus, effective early actions in the child's first thousand days, a period of greater brain plasticity, will allow an adequate quality of life in the long term.

The state of the art in the diagnosis of ADHD is an inexhaustible source of interest in view of the increasing incidence today. The reason for this increase still has its causes not understood and is the basis for new studies, as well as the clinical observation of new predictive signs and symptoms in the face of changes in psychosocial and nutritional habits in recent decades and studies of the influence of genetic range-rationality.

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