ABSTRACT
The attention deficit hyperactivity disorder (ADHD), considered a common cause of disorders in children and adolescents, is a neurobiological condition characterized by inattention and disorganization, hyperactivity and impulsivity. The first reports emerged in the sixteenth century and since then a process that extends to the present time to establish the best nomenclature, process diagnosis, etiology and its clinical characteristics has started. As this is a long and fragmented process, it becomes necessary to conduct a review of the main topics related to the subject, including its historical context. The aim of this study is to present, through the literature review, an overview of the main historical aspects, diagnosis and clinical of ADHD. To do so, we conducted a search of the databases with the following keywords: “ADHD”, “prevalence”, “etiology”, “diagnosis”, “clinical manifestations” and “comorbidities”, combined or not, in native and not native languages (English). The articles were selected according to the objectives of the study. As it is considered a complex and heterogeneous disorder, as well as for not having a well-defined etiological process, and for suffering diagnostic tendencies, more studies are needed.

Keywords: attention deficit hyperactivity disorder, ADHD, history, diagnosis.

RESUMO
O transtorno de déficit de atenção e hiperatividade (TDAH), considerado uma causa comum de doenças em crianças e adolescentes, é uma condição neurobiológica caracterizada pela desatenção e desorganização, hiperatividade e impulsividade. Os primeiros relatos surgiram no século XVI, e desde então um processo que se estende até o presente momento para estabelecer a melhor nomenclatura, diagnóstico e etiologia e suas características clínicas teve início. Como esse é um processo longo e fragmentado, torna-se necessário proceder com revisão dos principais temas relacionados ao assunto, incluindo seu contexto histórico. O objetivo deste estudo é apresentar, por meio de revisão de literatura, uma visão geral dos principais aspectos histórico, diagnóstico e clínico de TDAH. Para isso, foi realizada uma pesquisa dos bancos de dados com as seguintes palavras-chave: “TDAH”, “prevalência”, “etiologia”, “diagnóstico”, “manifestações clínicas” e “comorbidades”, combinadas ou não, em línguas naturais e não (inglês). Os artigos foram selecionados de acordo com os objetivos do estudo. Como ele é considerado um distúrbio complexo e heterogêneo, bem como por não ter um processo etiológico bem definido, e por sofrer tendências de diagnóstico, são necessários mais estudos.

Palavras-chave: transtorno de déficit de atenção com hiperatividade, TDAH, história, diagnóstico.
INTRODUCTION

The attention deficit hyperactivity disorder (ADHD), considered a common cause of disorders in children and adolescents, is understood as a neurodevelopmental disorder that begins in childhood and often persists in adult life. The ADHD is characterized by an inappropriate development in the levels of attention, organization and/or hyperactivity – impulsivity, resulting in academic, family and social functional impairment. In over 50% of cases, it is associated with comorbidities such as: learning disorders, mood and anxiety disorders, disruptive behavior disorders and substance and alcohol abuse disorders. It does not have a well understood etiologic process and its diagnosis, despite having well-established criteria by the Diagnostic and Statistical Manual of Mental Disorders (DSM) or by the International Classification of Diseases (ICD-10), may suffer influence of the subjects around the child and his examiner.

ADHD is considered a common disorder among children, affecting one in every twenty children in the U.S., with a worldwide prevalence of 5% in children and 2.5% in adults. The prevailing data differ mainly when compared to studies with different methodologies. The literature devoted to describing topics about ADHD generally does not address in the same manuscript, historical issues, epidemiological, etiological, diagnostic process and major comorbidities. This can compromise the process of understanding the subject, being necessary to have a work review of the literature that addresses the historical context, describing the process of discovery, characterization and contextualization of ADHD in order to provide the reader with an overview of this disorder. The aim of this study is to present, through the literature review, an overview of the main historical aspects, diagnosis and clinical of ADHD.

METHODS

This literature review has used two books of extreme importance for the discussion of the topic presented, one in English that discusses in detail the historical context of ADHD, and the other in Portuguese, which has a comprehensive review of the clinical context of ADHD. Besides the books, articles indexed in the following databases were selected: Index Medicus, Biological Abstracts; PubMed; Bireme; PEDro and Lilacs, using the following keywords: ADHD, prevalence, etiology, diagnosis, clinical presentation and comorbidities, together or not, in native and not native language (English). The articles were selected according to the objectives of the present study, being excluded the articles that addressed with priority treatment, and included systematic review studies, original articles and some studies that showed relevance described in the initial sources, such as the DSM-IV, 1994. The search period was from 1994-2013, with 75% (28 references) coming from the last 10 years, 62% (23 references) of the last 8 years and 48% (18 references) of the last five years.

RESULTS AND DISCUSSION

The literature related to the study of ADHD often discusses the diagnostic and therapeutic process, the clinical presentation, comorbidities associated to various etiological possibilities, and its new research horizons, without reporting the historical trajectory that allows a view of the effort that has been made over the years to understand ADHD.

Historical context

The earliest literary references of individuals with disorders of attention, hyperactivity and impulsivity started with Shakespeare, who made reference to a disease of attention allegedly acquired by King Henry VII. In children, hyperactivity was first described in 1970 in a Russian poem called “The restless Phil”, written by the physician Heinrich Hoffman (in Stewart, 1970 cited in Mash & Barkley, 2003). In 1902, the English physician George Still, in three conferences, initiated a discussion more focused on clinical issues and argued that: (1) this disorder was more prevalent in males, (2) it was accompanied by comorbidities, antisocial behavior and depression, (3) it was associated with alcohol dependence, criminal behavior and depression among family members, (4) there was a familial predisposition and likely heredity, (5) there was the possibility of this disorder have occurred after the acquisition of an injury to the nervous system. Their correlations corroborated to the findings of the next century when many were proven with further studies.

Throughout the nineteenth century, when the first references about the hyperkinetic disorders emerged,
ADHD received a wide nomenclature, in an attempt to build one that corresponded to the clinical presentation. Table 1 presents a temporal perspective of the main nomenclatures and characteristics associated with the disorder over the years. The current nomenclature was established by DSM-IV and maintained in DSM-5: “Attention Deficit Hyperactivity Disorder” (ADHD). DSM-IV established five diagnostic criteria for ADHD bringing greater consistency to the diagnostic process and allowing the beginning of the classification into 3 subtypes of ADHD: (1) inattentive, (2) hyperactive/impulsive, and (3) combined. But the latest DSM, in its fifth edition, proposed changes to two previously established diagnostic criteria for DSM-IV replacing the term “subtype” with “presentation”, in order to denote that the profile of symptoms that may change with the time, and allowed the classification of ADHD in Mild, Moderate and Severe, according to the severity of functional impairment of the individual.

Table 1. Nomenclature adopted over the time and its historical context

<table>
<thead>
<tr>
<th>Year</th>
<th>Nomenclature</th>
<th>Historical context</th>
</tr>
</thead>
<tbody>
<tr>
<td>1940</td>
<td>&quot;Minimal Brain Injury&quot;</td>
<td>It was not accepted by the difficulty in confirming an injury and its impact</td>
</tr>
<tr>
<td>Beginning of 1960</td>
<td>&quot;Minimal Brain Dysfunction&quot;</td>
<td>Proposed by DSM. Transferred the idea of altering the structure to the function, Understand signs of restlessness, impulsivity and difficulty in learning</td>
</tr>
<tr>
<td>1968</td>
<td>&quot;Hyperkinetic Reaction of Childhood and Adolescence&quot;</td>
<td>Proposed by DSM-II that did not define diagnostic criteria</td>
</tr>
<tr>
<td>1980</td>
<td>&quot;Attention Deficit Disorder&quot;</td>
<td>Proposed by DSM-III. Included the condition of inattentiveness and impulsivity associated or not to hyperactivt</td>
</tr>
<tr>
<td>1980</td>
<td>&quot;Hyperactivity Disorder with Attention Deficit&quot;</td>
<td>Statement adopted during the revision of DSM-III</td>
</tr>
<tr>
<td>1994</td>
<td>&quot;Hyperactivity and Attention Deficit Disorder&quot;</td>
<td>Proposed by DSM-IV. Including well-established diagnostic criteria</td>
</tr>
</tbody>
</table>

Epidemiology

The worldwide prevalence of ADHD is estimated at 3%-6%. Evidence points higher prevalence among boys, with a ratio of up to 4:1 in children. For a long time, ADHD was considered a disease “created in the United States”, and therefore, several studies have focused on discussing the prevalence of ADHD around the world. The feasibility of comparing prevalence studies was given initially by the use of the DSM-IV, which standardized diagnostic criteria, allowing a cultural adaptation of the studies. When studies that adopt their own diagnostic criteria or various methodologies are analyzed, it is observed that there are large discrepancies between the prevalence worldwide.

In order to evaluate the distribution of the worldwide prevalence of ADHD, we performed two meta-analysis. The first examined files of January 1978 to December 2005, comprising 102 articles that were grouped by regions, among which stood out Europe and North America for the amount of publication. Other regions such as Asia, South America, Oceania, Middle East and Africa had a smaller volume of studies. These were carried out mostly with male children. After observing the prevalence per group, an analysis was made that showed a significant difference between the prevalence rates of ADHD in the Middle East and Africa compared with rates in North America and Europe. When comparing the model of the study, it was found that this difference would be more related to the diagnostic criteria and methodology used, than with geographical location. Thus, for the authors of the study, the factors that influence on the differences in prevalence around the world are the different diagnostic criteria used and the different sources of information (parents, teachers) at the time of data collection. In their study, the worldwide prevalence of ADHD could be set at 5.29%.

The second meta-analysis compared the prevalence of ADHD determined by the criteria of the DSM-IV in 86 studies of children and adolescents. It was found that when all the diagnostic criteria of DSM-IV are applied, the prevalence of ADHD in children and adolescents is similar (5.9%-7.1%), with no significant differences between world regions, weakening cultural theory. When it comes to a smaller sample and more regional, several factors are presented as prevalence influencers of ADHD and not only the adoption of the diagnostic criteria. Among these factors are included: the type of sample extracted (schools versus community), the tools and the source of information obtained in the process of diagnostic evaluation (parents, children, adolescents and/or teachers) and the socioeconomic and historical conditions of population.
Etiology

ADHD is considered to be a complex and heterogeneous disorder and its etiology is not well understood, allowing the establishment of several causal hypotheses. Evidence suggests that two main factors are associated with the increased susceptibility of the individual to ADHD. These are environmental and genetic factors, understood on a neurobiological hypothesis that addresses behavioral and biological factors (structural and genetic).9,18,20

Environmental factors are usually related to the family and socioeconomic context (Table 2).9,21 These have a strong positive association with ADHD. Other factors affect specific brain processes, such as fetal exposure to alcohol, maternal smoking, low birth weight of the newborn, contamination by lead and even perinatal brain damage in the frontal lobe, affecting processes of attention, motivation and planning.9,22 Studies indicate an influence parental/family in ADHD with an increased risk 2-8 times in parents of children with the disorder.9,18 In addition to a significant familiar recurrence, there is also a high heritability for this disorder (76%).9,22,23

Molecular studies have investigated the genes which encode not only the component of the dopaminergic and noradrenergic, but also the serotonergic system.22 Furthermore, studies with enzymes related to metabolism of these neurotransmitters were also subject to investigation.9,18,23

Genetic influence on the development of the condition of ADHD is supported by studies that do not point to a specific gene, but to many genes of small effect that, when they interact, they confer a higher genetic susceptibility to the disorder. When added to environmental factors, these genes promote greater predisposition to the development of the disorder.9,23 Several genes correlated with the dopaminergic system have been studied to date, being DAT1 (dopamine transporter gene) and DRD4 (dopamine D4 receptor gene), the most discussed. The DAT1 has a proven effect, even if small, in ADHD. DRD4 has association with the personality dimension “new search” probably related to ADHD, and its product that focuses on areas of the brain whose functions are implicated in disease symptoms.9,18,23,26,27

Recent studies on the noradrenergic system address the genes that encode receptors and the dopamine beta-hydroxylase enzyme (DHβ). The receptors which had their genes investigated were: α2 (ADRA2A) and α2C (ADRA2C). But the gene that encodes the enzyme was DHβ. Finally, the genes related to the serotonergic system which are the serotonin transporter gene, the 5HTT and the serotonin receptor genes 5HTR2A 5HTR1B, are also implicated. Thus, due to its high clinical complexity, the studies suggest that ADHD has no gene considered necessary or sufficient for the development of this disorder.23 The case study of Genro et al.18 that analyzed main works related to the genetics of ADHD, points to the need to conduct further studies to fully explain the genetic component of the disorder, since according to them, overall results suggest that each gene could explain only a small part of the ADHD phenotype, making it inconclusive. At the end of their work, it is also reported that other systems and processes begin to be suggested in the literature as promising possibilities for studies in ADHD, including cell division, adhesion and polarity, neuronal migration and plasticity, regulation of extracellular matrix and remodeling cytoskeleton processes.

<table>
<thead>
<tr>
<th>Table 2. Environmental factors related to the etiology of ADHD9,21</th>
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<tbody>
<tr>
<td>Psychosocial adversities, as family problems and low social class</td>
</tr>
<tr>
<td>Big family</td>
</tr>
<tr>
<td>Parents criminality</td>
</tr>
<tr>
<td>Psychopathology or mental change in the parents</td>
</tr>
<tr>
<td>Adoption</td>
</tr>
</tbody>
</table>

Studies of structural and functional magnetic resonance imaging (MRI) show structural differences in the brains of individuals with ADHD. These show that the control circuits of attention are smaller and less active in individuals with ADHD when compared to the control group,19,24,25 suggesting a change in the fronto-striatal-cerebellar axis.18 Studies suggest that variations in size and volume influence on neuronal communication of the cerebral hemispheres, which could explain some of the cognitive and behavioral symptoms of ADHD, as well as some neuropsychological aspects related to the frontal lobe and subcortical areas.18 The frontal-striatal-cerebellar axis comprises areas rich in catecholamine receptors.19,20 Several studies have argued that dopamine26 and noradrenaline are involved in the etiology of ADHD.9,18,20 Different neurotransmitters have been strongly correlated with the pathophysiology of ADHD. Molecular studies have investigated the genes which encode not only the component of the dopaminergic and noradrenergic, but also the serotonergic system.22 Furthermore, studies with enzymes related to metabolism of these neurotransmitters were also subject to investigation.9,18,23
In addition to the neurobiological hypotheses outlined above, there are other lines of research that seek to associate other variables with the construction process of the clinical condition of ADHD. One is the theory of influence of circadian rhythms and sleep onset chronic insomnia on the inattention condition and motor restlessness, present in patients with ADHD. Studies conducted in adults and children with ADHD indicate the existence of reduction of rapid eye movements during sleep, increased nocturnal activity, and excessive daytime sleepiness in children, as well as delay in melatonin production at night when compared with normal children. Another source of research has been the sensorial question, increasingly addressed in children with ADHD, mostly for its direct correlation with the learning process. Studies correlate sensorial issues with body posture, and both with learning difficulties. This correlation points to the need for an interdisciplinary approach to the patient with ADHD in order to reduce overlapping comorbidities and improve their quality of life.

**Diagnosis**

The diagnosis of ADHD is fundamentally clinical, based on clear and well-defined operational criteria, initially established by DSM-IV and presently by ICD-10 or DSM-5. Authors agree in stating that the first question to be examined is the frequency of symptoms, also agreeing with the DSM-5 and ICD-10 classification systems that emphasize the necessity that each symptom must occur frequently and should not be related to any stressful or initiator event to be considered positive, defining more accurately the cutoff time of diagnosis.

DSM-IV was the first to establish clear and objective diagnostic criteria for the diagnosis of ADHD, dividing them into five criteria: (1) presence of six symptoms presented in specific questionnaire, which persist for at least 6 months, in proportion inconsistent with the level of development; (2) presence of some symptoms of hyperactivity/impulsivity or inattention, that cause impairment before 7 years of age; (3) presence of any of the impairments caused by the symptoms in two or more settings (e.g., school/work and at home); (4) the existence of clear evidence of clinically significant impairment in social, academic, or occupational functioning, and (5) lack of association with another disorder that may present the same symptoms, not allowing the symptoms to be uniquely assigned to ADHD. According to the responses obtained in each diagnostic criteria, the presence of ADHD and its subtypes would be characterized or not, with the possibility of having inattentive, hyperactive/impulsive or combined predominance. DSM-IV also established that individuals who at the time of reassessment did not fulfill all the criteria to be classified as “In Partial Remission”. Rohde et al. stated that the threshold for the presence of six or more symptoms of hyperactivity/impulsivity can be lowered to five or fewer symptoms when there is a significant overall impairment in the individual evaluated.

However, in the latest version of the DSM, the DSM-5 two alterations in diagnostic criteria were made, being the first alteration in age, extending it to 12 years of age, and the second in allowing diagnosis of ADHD in the presence of autism. Another alteration was the change of the term “subtype” for presentation in order to demonstrate possible changes over the time. This latest version also allows a classification of ADHD in Mild, Moderate and Severe, according to the degree of commitment that cause symptoms in people’s lives. The collected data based on the criteria proposed by the DSM-IV allowed the diagnosis, prevalence and classification in three presentations of ADHD: (1) with a predominance of inattention (prevalence 20%); (2) with a predominance of hyperactivity/impulsiveness (15%) and (3) combined (most common, 50 to 75%). However, the combined form has less functional disability rates when compared to the other presentations. Currently, the diagnosis of ADHD is a challenge because several disorders may exhibit common warning signs and symptoms, such as Pervasive Developmental Disorders (PDD), Mental Retardation (still controversial); Dyslexia (learning disorder), Oppositional Defiant Disorder (ODD), Conduct Disorder (CD), Depression, Bipolar Disorder, Anxiety Disorders and Tic Disorders (TD). In an attempt to promote an integrated diagnosis, some authors suggest four other evaluation methods: (1) the referral objective scales for evaluation of ADHD that can be easily filled by teachers at the school (MTA-SNP-IV); (2) neurological examination; (3) and neuropsychological evaluation.
(4) psycho-educational or pedagogical evaluation. The visual and auditory evaluation has been considered necessary, since there is evidence supporting the idea that sensory deficits may generate a condition of attention difficulties. Other authors suggest that within the visual assessment, the analysis of eye movement should be included, as the clinical signs of ocular motility disorders may worsen a condition of ADHD or tend to another diagnosis. Studies demonstrate that children with learning disorders have changes in some oculomotoricity tests compared with children without complaints.

Clinical presentation

Although ADHD presents classic signs as inattention, disorganization and/or hyperactivity and impulsivity, clinical signs may be influenced by the current stage of child development. In each of these phases independent errors/classic signs can be observed. For instance, inattention can be shown in the difficulty of sticking to details, careless mistakes in simple activities, in the constant dispersion, in the act of not seeming to listen when spoken to directly, and in fact of not completing their tasks several times. Hyperactivity can be seen in frequent uneasiness, either of the hands or legs, in the difficulty sustaining a posture for a certain time, in the maintenance of a state of full agitation most of the time, in proportions greater than expected for the activities performed. The symptoms of impulsivity, however, are demonstrated by the difficulty for waiting for the turn, answering the question before it is completed, and often interrupting the conversation of others. The early onset of ADHD symptoms is related to a worse cognitive function in evaluations of language, high rates of comorbidity and family maladjustment. While the late installation establishes relationships with high levels of inattention and reading disorders that may lead to academic performance below expected.

Comorbidities

The combination of comorbidities with ADHD is a common situation, with a rate of 20%-50%. In general terms, the main complaints associated with ADHD are language disorders, psychomotor changes, social isolation, mood swings, anxiety, substance and alcohol abuse, impaired academic performance and social interaction. Studies suggest that individuals with ADHD have a risk two times higher of having accidental injuries compared with their siblings who do not have ADHD. Moreover, patients with ADHD also possess greater predisposition to engage with problems in traffic or with school violence, either in the role of aggressors or as victims. In the same study, a significant association between ADHD and severity of addition to internet, binge eating and suicide were found. The existence of any of these disturbances influence on the treatment, and the prognosis worsens progressively in each association. Numerically, the main clinical conditions and their rates of combination with ADHD are disruptive behavior disorders (30%-50%), depression (15%-20%), anxiety disorders (25%), learning disabilities (10%-25%), substance abuse or dependence (9%-40%) and developmental coordination disorder with motor coordination difficulties, changes in academic performance and difficulty in socializing (50%).

CONCLUSION

Historically, ADHD seems to have been misunderstood, even during analysis of prevalence that tried to establish its existence and expressiveness. Currently, ADHD is considered a common childhood disorder that persists into adulthood and is usually associated with comorbidities that affect primarily executive functions. This, has a complex, heterogeneous clinical presentation, as well as an etiologic process that is not well understood. Its diagnosis, despite having well-established criteria, is still questioned because it can be influenced by individuals around the child (parents, teachers) and the examiner. New studies that investigate and elucidate its clinical presentation and etiology are needed to clarify ADHD and guide its therapeutic process.

REFERENCES