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ORIGINAL ARTICLE

Attention Deficit/Hyperactivity Disorder

Paula Faria Souza Mussi de Andrade[1,2], Marcio Moacyr Vasconcelos[2]

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Abstract

Objectives: to review the etiology, diagnosis, comorbidities, differential diagnosis, clinical picture, and treatment of attention deficit/hyperactivity disorder, a neurodevelopmental condition that is characterized by persistent clinical manifestations due to inattention, hyperactivity, and impulsivity. **Methods:** the authors used PubMed to obtain relevant scientific papers that were published over the past five years, through the following keywords: "ADHD", "child", "review", "attention deficit", and "hyperactivity". **Results:** the literature search resulted in hundreds of papers. The authors focused on review papers and analyzed the compiled information. **Conclusions:** attention deficit/hyperactivity disorder is a prevalent condition in childhood and adolescence, and its diagnosis requires a detailed history, a complete physical examination, behavioral scales, and a full consideration of differential diagnosis. Multidisciplinary and multifactorial treatment aims at behavioral modification and personal reorganization, with the ultimate goal to achieve a satisfactory functional performance in every social setting.

[1] Hospital Central da Aeronáutica, Pediatria - Rio de Janeiro - RJ - Brasil.
[2] Hospital Universitário Antônio Pedro, Neurologia Pediátrica - Niterói - RJ - Brasil.

Correspondence to:
Marcio Moacyr Vasconcelos
Hospital Universitário Antônio Pedro. Universidade Federal Fluminense. Av. Marquês do Paraná, 303 - Centro, Niterói - RJ, 24.220-000. Brazil.
E-mail: mmdvascon@gmail.com / marcio.moacyr.vasconcelos@gmail.com

INTRODUCTION

Attention deficit/hyperactivity disorder (ADHD) is a neurobehavioral syndrome characterized by the persistent presence of inattention, hyperactivity, and impulsiveness. The disorder interferes with the development of the individual and may generate motor, perceptual, cognitive, and behavioral disorders. ADHD begins in childhood and can persist into adulthood.[1]

EPIDEMIOLOGY

ADHD is the most common neurodevelopmental disorder in childhood and is one of the main reasons schoolchildren require neuropediatric consultation. A meta-analysis involving 102 studies from different countries found an estimated prevalence of 5.3%,[2] while a Brazilian study on 461 students from disadvantaged social classes showed a rate of 13%.[3] It is likely that the striking differences in prevalences resulted from study methodology,[4] but the possibility that the population samples were heterogeneous should also be considered.

Another striking epidemiological characteristic is the divergent prevalence between sexes, with the prevalence of ADHD being much higher in males than in females at a ratio of 2:1 and reaching 10:1 in some studies.[5,6]

ETIOLOGY

The etiology is multifactorial, involving genetic (endogenous) and environmental (exogenous) factors. Studies have shown that children of parents diagnosed with ADHD are two to eight times more likely to be diagnosed with ADHD than children of parents in the control group.[7] Swanson et al. suggested that two genes may be involved: *DAT* (a dopamine transporter gene) and *DRD4* (a gene that encodes the dopamine receptor).[8] However, none of the investigated genes can be considered essential to the onset of the disorder.[9,10]

Exogenous factors that coexist with the genetic factors can produce lesions or functional changes in the central nervous system. These are divided into prenatal, perinatal, and postnatal factors.[5]

- Prenatal factors: Congenital infections, maternal poisoning (by medications or toxic substances), hemorrhages, radiation, chronic maternal diseases (diabetes, hypertension, for example), trauma, etc.
- Perinatal factors: Maternal causes (pelvic malformations, maternal anemia, excessive sedation, hypotension, and hypertension); fetal causes (fetal macrosomia, prematurity, fetal malformations, newborn respiratory disorders such as hyaline membrane disease, meconial aspiration syndrome, and maternal–fetal blood incompatibility); and childbirth causes (labor dystocia, premature detachment of the placenta, umbilical cord abnormalities, extraction maneuvers, and delivery by cesarean section).
- Postnatal factors: Neonatal infections, hemorrhages, traumatic brain injury, poisoning, and expansive lesions.

In addition, environmental factors include socioeconomic level, family psychological conditions, and education level.

UROBIOLOGY

The neurotransmitters dopamine and norepinephrine play important roles in attention and concentration, in addition to cognitive functions such as motivation, interest, and learning tasks. The prefrontal noradrenergic pathways are known for maintaining attentive focus as well as motivation/interest. The mesocortical dopaminergic projection pathway acts in cognitive functions such as verbal fluency, learning, surveillance during executive functions, and maintaining attention and concentration.[11]

Although dopamine and norepinephrine are the main neurotransmitters studied in the pathophysiology of ADHD, other pathways are involved in the dysfunction inherent to the disorder, such as the serotonin, acetylcholine, opiate, and glutamate pathways, leading to damage in executive function, operating memory, emotional regulation, and reward processing.[12]

Catecholamines are decreased due to lower production, neurotransmitter reuptake by the presynaptic membrane, and/or by the action of the monoamine oxidase enzyme, which destroys norepinephrine and serotonin in the presynaptic neuron, or of the enzyme catechol-O-methyltransferase in the intrasynaptic space.[5]

Study of the pathophysiology of ADHD assists in determining drugs that can alleviate the disorder, which act by increasing the production of the neurotransmitters involved, inhibiting enzymes that degrade them, or acting as agonists in the neurotransmitter receptors involved.[12]

DIAGNOSIS

Diagnosis is clinical and considers the diagnostic criteria established in the 5th edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5).[13]

Diagnosis will be strengthened if the patient meets at least 6 of the 9 criteria relating to inattention and/or at least 6 of the 9 criteria related to hyperactivity (Table 1). Furthermore, diagnosis should only be defined if the symptoms are present for at least 6 months and meet the following requirements:

- Various symptoms manifested before age 12 years.
- Various symptoms occur in at least two environments (home, school, work, in the presence of friends or relatives, and/or in other activities).

- There is social, academic, or professional damage to the individual.
- Symptoms do not occur exclusively during the course of some psychiatric disorder, excluding autistic spectrum disorder.

In individuals aged > 17 years, the minimum number of symptoms in each category required for diagnosis decreases from six to five.

The DSM-5 describes three presentations of ADHD. When only the criteria for inattention are met, there is the *predominantly inattentive* presentation; if only the criteria for hyperactivity are met, the presentation is *predominantly hyperactive/impulsive*; and when both are present, the presentation is combined (or mixed). The combined subtype is the most frequent and responsible for 50%–75% of cases, followed by the inattentive type, which accounts for to 20%–30% of cases.[11,13]

The DSM-5 permits ADHD to be defined as mild, moderate, or severe. Mild cases present few symptoms in addition to those required to confirm the diagnosis and cause little damage to social or professional function; moderate cases present symptoms and damage losses between mild and severe cases, and severe cases present many symptoms in addition to those necessary to confirm the diagnosis and may result in acute damage to social or professional function.[13]

There is also the possibility, according to the DSM-5, of characterizing cases of ADHD as being in *partial remission* when all criteria were met in the past, but not met in the last 6 months, and the symptoms continue to produce some social, academic, or professional damage.[13]

Collection of adequate clinical history is essential in the diagnostic evaluation. The health professional should actively seek exogenous risk factors in the patient's history, which may have contributed to the onset of the disorder, as well as the presence of a positive family history. In many cases, the parents were not diagnosed with ADHD, but during consultation report previous or current symptoms of inattention and/or hyperactivity/impulsiveness. It is also essential to investigate during

Table 1. Diagnostic criteria according to the DSM-5.

Diagnostic Criteria for Attention Deficit/Hyperactivity Disorder-DSM-5	
A	1. Six (or more) of the following symptoms of *inattention* (minimum duration of 6 months):
	a) Often fails to pay attention to details or makes mistakes due to carelessness in school, work, or other activities
	b) Frequently has difficulties keeping attention on tasks or play activities
	c) Frequently seems to not hear when spoken to
	d) Frequently does not follow instructions and does not finish homework, domestic tasks, or professional duties
	e) Frequently has difficulty organizing tasks and activities
	f) Frequently avoids, dislikes, or is reluctant to engage in tasks that require constant mental effort
	g) Frequently loses things needed for tasks or activities
	h) Easily distracted by stimuli extraneous to tasks
	i) Frequently demonstrates forgetfulness in play activities
	2. Six (or more) of the following symptoms of *hyperactivity* (minimum duration of 6 months):
	j) Often fidgets with hands or feet or wiggles in his or her chair
	k) Often leaves his or her chair in the classroom or in other situations when expected to remain seated
	l) Often runs or climbs in school excessively in situations where this is inappropriate
	m) Frequently has difficulty playing or quietly engaging in leisure activities
	n) Is often "100 miles per hour" or often acts at "full steam"
	o) Often talks too much
	p) Impulsiveness (minimum duration of 6 months)
	q) Often gives hasty answers before questions have been completed
	r) Frequently has trouble waiting his or her turn
	s) Often interrupts or gets involved in subjects pertaining to others
B	Some symptoms of hyperactivity–impulsiveness or inattention that cause damage should be present before age 12.
C	Any damage caused by the symptoms is present in two or more contexts (for example: school, work, or at home).
D	There should be clear evidence of clinically significant damage in social, academic, or occupational functioning.
E	The symptoms do not occur exclusively during the course of an invasive development disorder, schizophrenia, or any other psychotic disorder and are not better explained by another mental disorder.

Source: American Academy of Psychiatry (2013).[13]

the consultation the environments in which the symptoms occur because diagnosis requires the manifestation of symptoms in at least two environments.[13]

It is important to emphasize that diagnosis should not be ruled out if the child remains quiet and does not demonstrate symptoms related to the disorder during a medical consultation because some children are capable of controlling their symptoms for a certain period of time. Furthermore, the structured environment during the consultation can facilitate self-control.

Complementary examinations such as electroencephalography, neuroimaging examinations such as computed tomography or magnetic resonance imaging, computed tomography of the skull with single photon emission, laboratory tests, or genetic testing are not necessarily part of the diagnostic investigation in patients suspected to have ADHD.[14]

Some behavior scoring scales can be used in diagnosis. These include the SNAP-IV, Conners Scale, Early Childhood Environment Rating Scale, and Child Behavior Checklist. The Swanson, Nolan, and Pelham questionnaire is best known in the literature as SNAP and was created based on the symptoms listed in the 4th edition of the DSM-4. The SNAP-IV has a Brazilian translation, which was validated by the Attention Deficit Study Group at the Federal University of Rio de Janeiro and the Office of Childhood and Adolescent Research and Psychiatry at the Federal University of Rio Grande do Sul.[15]

The SNAP-IV questionnaire (Table 2) consists of 18 symptoms of ADHD, the first 9 items related to inattention and the other 9 items (10–18) describing hyperactivity/impulsiveness. The questionnaire should be filled out by parents and a member of the school team, e.g., a teacher who spends significant time with the student. Each item covered in the questionnaire should be described on a scale spanning four levels of intensity: "Not at all," "just a little," "quite a bit," or "very much." When the questionnaire is complete, if there are at least six items marked "quite a bit" or "very much" for items 1–9 and/or at least six items marked as "quite a bit" or "very much" for items 10–18, the score is compatible with the diagnosis. The questionnaire can assist in the evaluation of behavior in different environments and is a starting point for investigation, but does not replace the need for a complete patient history obtained by a trained professional.[15]

In short, diagnosis is defined through clinical history, observation of the patient, evaluation of behavior scales, and general physical and neurological examination of the patient.

CLINICAL SIGNS

Clinical signs vary in accordance with the presentation of the disorder, whether it is predominantly inattentive, predominantly hyperactive/impulsive, or combined.[13]

Children with the predominantly inattentive or combined type display difficulty in paying attention to detail, commit frequent errors in daily activities, are unable to follow long instructions, and have difficulty carrying out school and/or domestic tasks. Even in the absence of a specific learning

Table 2. SNAP-IV-adapted behavior scale.

	Not at all	Just a little	Quite a bit	Very much
1. Often fails to pay close attention to details or makes careless mistakes in schoolwork or tasks				
2. Often has difficulty maintaining attention in tasks or play activities				
3. Often does not seem to listen when spoken to directly				
4. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties				
5. Often has difficulty organizing tasks and activities				
6. Often avoids, dislikes, or reluctantly engages in tasks requiring sustained mental effort				
7. Often loses things necessary for activities (e.g., toys, school assignments, pencils, or books)				
8. Is often distracted by extraneous stimuli				
9. Is often forgetful in daily activities				
10. Often fidgets with hands or feet or squirms in seat				
11. Often leaves seat in classroom or in other situations in which remaining seated is expected				
12. Often runs about or climbs excessively in situations in which it is inappropriate				
13. Often has difficulty playing or engaging in leisure activities quietly				
14. Often is "on the go" or often acts as if "driven by a motor"				
15. Often talks excessively				
16. Often blurts out answers before questions have been completed				
17. Often has difficulty awaiting turn				
18. Often interrupts or intrudes on others (e.g., butts into conversations/games)				

Source: Portuguese translation by the Attention Deficit Study Group, Institute of Psychiatry, Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, RJ. Attention Deficit and Hyperactivity Program, Porto Alegre Clinical Hospital (HCPA), Federal University of Rio Grande do Sul (UFRGS), Porto Alegre, RS.

disorder, academic or professional performance tends to be impaired. The patient has difficulty in aspects such as organization, planning activities, and the performance of tasks that require concentration. He or she loses important objects easily and distracts himself/herself with small environmental stimuli.[11,13]

Children with the predominantly hyperactive/impulsive or combined type exhibit hyperkinetic behavior. They are unable to remain in control of their own body for short intervals of time. They may exhibit verbal or ideative hyperactivity. They cannot maintain their focus on a proposed activity, which causes losses in cognitive development and intellectual production. Movements such as fidgeting with their hands and feet, getting up several times, pacing, talking excessively, or running at inappropriate times may be present. Symptoms that suggest impulsiveness include showing impatience in waiting for their turn to perform an activity or to speak. Symptoms such as irritability, apathy, emotional lability, and low threshold for frustration can be associated in these presentations and compromise interpersonal relations.[11,13,16]

Individuals with ADHD may also present with motor instability, gnostic difficulties related to body position, and speech disorders.

The course of the disease is variable; 15% of affected children will be adults with complete symptoms, and up to 65% may exhibit partial remission with some symptoms still present, especially those related to inattention.[5]

COMORBIDITIES

To achieve better therapeutic planning, we should actively look for other associated clinical diseases or psychological comorbidities.

Affected children have learning disorders such as dyslexia, dysgraphia, and dyscalculia in 19%–26% of cases, with dyslexia being the most common comorbidity. Speech disorders, such as speech articulation difficulties, changes in the quality of vocalization, difficulties in syntactic and semantic structuring, and difficulty in processing information.[11]

There is a high prevalence of disruptive behavior disorders such as conduct disorder and oppositional defiant disorder, which are present in 30%–50% of cases. Other psychiatric disorders reported include bipolar behavioral disorder with alternation between depression and mania and anxiety disorders featuring excessive fear. Enuresis is described in some children.[17]

Tic disorder is frequent and may be associated with Tourette's syndrome. Substance abuse is another comorbidity that may be present in affected individuals.[18]

DIFFERENTIAL DIAGNOSIS

Children who come to pediatric or neuropediatric consultations with complaints of inattention or hyperkinetic and/or impulsive behavior should be evaluated through clinical evaluation, history, physical and neurological examination, and auditory and visual screening for the possibility of other disorders that can simulate the cognitive-behavioral framework of ADHD. Table 3 lists the main entities cited in the differential diagnosis.

TREATMENT

ADHD should be understood as a chronic disorder that has no curative therapy. In this way, the goal of treatment is to modify behavior and reorganize the individual to promote satisfactory performance in all environments.

Treatment is multidisciplinary and multifactorial and should encompass:[19]

a) Guidance for parents and patient

Parents/guardians should be informed about the disorder to help their children, providing modifications to the environment, stimulating changes in behavior, and developing different abilities.

(b) Participation of the school

ADHD is not specifically a learning disorder, but its main symptoms have a major impact on academic and professional performance. Academic adjustment is essential.

One meta-analysis[20] evaluated scholastic interventions based on environmental changes and noted positive results for academic performance of students with ADHD. Some strategies for classroom organization include:

- Creating an objective daily routine, with defined periods of rest
- Providing clear, direct, and short instructions and guidelines
- Using audiovisual resources to contribute to teaching
- Checking if the student has all the didactic material essential for the tasks, and if not, helping to obtain it

Table 3. Differential diagnosis.

• Childhood Absence Epilepsy
• Auditory Deficit
• Visual Deficit
• Sequel of Brain Lesions
• Genetic Syndromes: Down syndrome, Fragile X syndrome, Williams syndrome, Fetal alcohol syndrome
• Neurodegenerative Illnesses
• Thyroid Diseases
• Environmental and Teratogenic Toxins
• Sleep Disorders
• Neuropsychiatric Disorders
• Learning Disorders
• Intellectual Disability
• Psychosocial Causes

Fonte: Rotta NT, Ohlweiler L, Riesgo RS (2016)[5].

- Encouraging the use of organizational methods, such as graphs for planning work, tables recording deadlines for activities/evaluations, and notes about the content and use of agenda
- Environmental changes in the classroom, such as rearranging the position of the chairs, placing the student close to the teacher, keeping the student out of areas where elements may lead to distraction (e.g., near windows)
- Reducing the size of tasks and/or dividing them into sections
- Providing positive feedback to the student for good performance in activities and achievements
- Reducing the number of copies of written texts and allowing typing and printing if these are more productive for the student
- Providing a peaceful environment for test-taking
- Producing tests with fewer questions per page
- Asking the child to check test/task responses, verifying what was produced at the end of the activity
- Allowing the student to provide oral answers on tests if writing is difficult
- Respecting the time that each student needs to complete an activity or test
- Setting goals together with the student and asking the student to self-evaluate and reflect on learning and develop strategies to achieve goals.

c) Psychotherapeutic care

Cognitive behavioral therapy is an essential pillar of treatment because it works to modify the individual's behavior, to identify personal difficulties, and to develop social and academic skills.[21]

a) Pharmaceutical therapy

First-line treatment consists of psychostimulant drugs, which may be prescribed starting at 6 years of age. They decrease presynaptic reuptake of catecholamines, raising their levels in the synaptic gap. In this way, they reduce impulsiveness and motor activity, thereby improving short-term memory and academic and social performance, and provide better conditions for therapeutic interventions (Table 4).[5, 17, 22]

In Brazil, there are two categories of psychostimulants available—methylphenidate and amphetamine derivatives.

- Methylphenidate is available in three formulations: Ritalin (at a dose of 10 mg, duration of the effect 3–4 h), Ritalin LA (10-, 20-, 30-, and 40-mg capsules with a longer duration of 6–8 h), and Concerta (18-, 36-, and 54-mg doses and acting time of 10–12 h). Ritalin LA corresponds to methylphenidate-spheroidal oral drug absorption system, and capsules contain two sizes of micrograins, half being the immediately acting methylphenidate and the other half released after 4 h of administration, simulating the administration of two short-duration doses of methylphenidate. Concerta corresponds to methylphenidate-osmotic controlled-release oral delivery system and contains 22% immediately acting methylphenidate and 78% methylphenidate released by an osmotic pump process with an acting time of 12 h.[23,24]
- Lisdexamfetamine (Venvanse), a derivative of amphetamine, has been sold in Brazil since 2011. It has a duration of 10–14 h and comes in 30-, 50-, and 70-mg capsules. It has been recommended for children with body weight exceeding 20 kg.

Psychoactive medication is used by children during school and in most cases is suspended on weekends, except in children with major hyperkinetic and impulsive symptoms, who also benefit from medication during this period.

Side effects of psychostimulants include loss of appetite during the active period of the medication, insomnia (especially if the medication is administered at the end of the day, with the last dose recommended in the early afternoon at the latest), headache, abdominal pain, and onset of tics in predisposed individuals.[25,26]

Familiarity with therapeutic options other than psychostimulants is essential because up to 15% of cases cease treatment due to side effects.[26] In the event of failure with the selected stimulant, switching to another psychoactive is indicated before attempting to change the therapeutic class.[22, 27]

One class of medications that is used as a therapeutic option in cases of psychostimulant failure is tricyclic antidepressants such as imipramine (Tofranil). Before starting these medications, electrocardiographic evaluation should be ordered because tricyclic antidepressants can cause increased heart rate, flattening of the T wave, and prolongation of the PR interval, and are contraindicated in cases of left bundle branch block or total atrioventricular block. The use of imipramine may be advisable when nocturnal enuresis is associated with ADHD.[23, 24]

Non-tricyclic antidepressants such as selective serotonin reuptake inhibitors (fluoxetine) and norepinephrine and dopamine reuptake inhibitors (bupropion) have also been used, especially in the presence of comorbidities such as depression or anxiety disorders. Bupropion presents a risk of decreasing the epileptic threshold and is contraindicated in individuals with epilepsy. In individuals with comorbid chemical dependence, bupropion is indicated.[23, 24]

Clonidine (Atensina), an alpha 2-adrenergic agonist, may be used, especially in the presence of tics or in cases that do not respond to psychostimulants. They are more effective on the symptoms of hyperactivity and impulsiveness[18, 23, 24] and should not be used in children or adolescents with a history of significant depression.[28]

Atomoxetine (Stratera), a norepinephrine reuptake inhibitor, is another therapeutic option in cases that are

Table 4. Drugs used in treatment

Medication	Trade name	Presentations	Average Life (h)	Onset of action
Immediately-acting methylphenidate	Ritalin	10 mg	4	20–30 min
Methylphenidate LA	Ritalin LA	10, 20, 30, and 40 mg	8	30–120 min
Methylphenidate OROS	Concerta	18, 36, and 54 mg	12	30–120 min
Lisdexamfetamine	Venvanse	30, 50, and 70 mg	13	60–120 min
Imipramine	Totranil	10 and 25 mg	6 a 18	2–4 weeks
Bupropion	Wellbutrin	150 mg	3 a 4	1–2 weeks
Clonidine	Atensina	0.100 and 0.200 mg	6	30–60 min
Atomoxetine	Strattera	10, 18, 25, 49, and 60 mg	5	Up to 6 weeks

Fonte: Briars L, Todd T (2016)[22].

refractory to psychostimulants,[28, 29] but it is not yet available in the Brazilian market. Side effects include anorexia, nausea, vomiting, diarrhea, fatigue, mood swings, and dizziness, but tend to subside with continued use over the course of weeks.[28] Atomoxetine has a mild anxiolytic effect, which gives it an advantage in treating patients with comorbid anxiety disorder.[1]

A meta-analysis evaluated the therapeutic efficacy of neurofeedback, which aims to reduce the symptoms of ADHD by lessening aberrant patterns of brain activity that theoretically lead to the disorder.[30] The study concluded that the evidence from well-controlled trials does not favor neurofeedback.

A special issue concerns the treatment of children aged 4–5 years who are diagnosed with ADHD. The guidelines recommend parent training sessions or other behavioral therapy interventions for at least 8 weeks initially, but if this intervention is unsuccessful, in special circumstances, the use of methylphenidate at a low dose can be considered.[31]

PROGNOSIS

Multimodal treatment with drug therapy and appropriate psychological and scholastic support permits approximately 60% of children with ADHD to become functional adults and reasonably adapted to the disorder. The prognosis depends on the early implementation and quality of the multimodal approach. A review of 351 studies concluded that treatment improved the long-term prognosis of children with ADHD in all the explored functional categories, but normal levels of function were not recovered.[32]

One study reported that the stature of young adults treated for long periods with psychostimulants was 1.29 ± 0.55 cm shorter than that of the control group,[8] which reinforces the need for monitoring the effect of loss of appetite associated with psychostimulants and growth parameters throughout treatment.

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