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Chapter

Attention Deficit Hyperactivity Disorder

Sophia Bakhtadze, Tinatin Tkemeladze and Tinatin Kutubidze

Abstract

Attention deficit hyperactivity disorder (ADHD) is a mental disorder of the neurodevelopmental type. The disorder represents one of the common causes of referral for behavioral problems in children to medical and mental health doctors all around the world. The diagnosis can be done by DSM-V criteria. According to DSM-V, there are three main subtypes of ADHD: ADHD-inattentive type, ADHD-hyperactive-impulsive type, and ADHD-combined type. The etiology of ADHD is not definitively known. A genetic imbalance of catecholamine metabolism in the cerebral cortex appears to play a primary role. Various environmental factors may play a secondary role. Cognitive impairments in a variety of domains have been found in ADHD as well as impairment in overall intellectual function. A meta-analysis of children and adolescents with ADHD showed impairments in several aspects of executive functioning. The most important part of any intervention plan for a child with ADHD is the physical, behavioral and neuromotor/neuropsychological examination. Medication should be started with one of the stimulants. Both d-amphetamine and methylphenidate have been shown to be effective for improvement of hyperactivity, concentration problems, learning disorders, and other comorbidities.

Keywords: ADHD, inattention, hyperactivity, impulsivity, behavioral therapy

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a mental disorder of the neurodevelopmental type. It is characterized by difficulty paying attention, excessive activity and acting without regards to consequences, which are otherwise not appropriate for a person's age. The disorder represents one of the common causes of referral for behavioral problems in children to medical and mental health doctors all around the world. It is one of the most prevalent psychiatric conditions in children affecting 5% of children and adolescents worldwide. Symptoms which are specific for ADHD could decrease with age as almost 65% of children with ADHD have partial resolution of signs but 15% of ADHD children exhibit complete disappearance of clinical picture in adulthood [1].

A meta-analysis of 175 research studies worldwide on ADHD prevalence in children aged 18 and under found an overall pooled estimate of 7.2% [2].

The number of children with ADHD can reach millions. According to data received in 2016 from USA almost 6.1 million of children have ADHD (9.4%). About

388,000 children are 2–5 years of age; 4 million children are 6–11 years; and 3 million children aged 12–17 years. Boys are more likely to be diagnosed with ADHD than girls [3]. The prevalence age for diagnosis is 2–17 years.

Centers for Disease Control and prevention (CDC) uses datasets from parent surveys and healthcare claims to understand diagnosis and treatment patterns for ADHD. Estimates for diagnosis and treatment can vary depending on the source [4]. The methods used for ADHD assessment are also different.

Coexisting disorders are common in children with ADHD. According to a national 2016 parent survey every 6 in 10 children with ADHD could have at least one other mental, emotional or behavioral disorder; almost half of the children with ADHD have coexisting behavioral and conduct disorders. One third of ADHD children could exhibit anxiety disorders as well. Depression, autism spectrum disorder and Tourette syndrome are also common disorders accompanying ADHD [2].

The first information about ADHD appeared in 1865 while German doctor Heinrich Hoffman described hyperactive child ("Fidgety Phil"). The enormous scientific contribution was done by George Still and Alfred Tregold who were the first authors to emphasize those clinical clues which still persist [5]. In 1922, the condition was called as "postencephalic behavior disorder", later in 1947, it was changed with "brain-injured child," then in 1963 it was renamed as "perceptually handicapped child" and ending with "minimal brain dysfunction" in 1966 [6]. Two years after in 1968 Diagnostic and Statistical Manual (DSM) recognized it as a syndrome under the term "hyperkinetic reaction of childhood or adolescence." In late 80s DSM-III recognized two subtypes of attention deficit disorder (*ADD) with hyperactivity and ADD without hyperactivity.* DSM-III revised the term ADD and changed it with "attention-deficit hyperactivity disorder (ADHD)." Finally DSM-IV identified three subtypes of the syndrome: ADHD-inattentive type, ADHD-hyperactive-impulsive type, and ADHD-combined type [7]. The DSM-V shared the same clinical forms of ADHD and identified strict diagnostic criteria for each [8].

2. DSM-5 diagnostic criteria

A. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development as characterized by (1) and/or (2):

1. **Inattention:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impact directly on social and academic/occupational activities.

Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older) at least five symptoms are required.

a. Often fails to give close attention to details or make careless mistakes in schoolwork, at work or during other activities (e.g., overlooks or misses details, work is inaccurate).

b. Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations or lengthy reading).

c. Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction).

d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked).

e. Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order, messy, disorganized work; has poor time management; fails to meet deadlines).

f. Often avoids, dislikes or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adult, preparing reports, completing forms, reviewing lengthy papers).

g. Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).

h. Is often easily distracted by extraneous stimuli (for older adolescents and adults may include unrelated thoughts).

i. Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults returning calls, paying bills, keeping appointments).

2. **Hyperactivity and impulsivity:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility or a failure to understand tasks or instructions. For older adolescents and adults (age 17 and older) at least five symptoms are required.

a. Often fidgets with or taps hands or feet or squirms in a seat.

b. Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace or in other situations that require remaining in place).

c. Often runs about or climbs in situations where it is inappropriate (Note: In adolescents or adults may be limited to feeling restless).

d. Often unable to play or engage in leisure activities quietly.

e. Is often "on the go" acting as if "driven by a motor" (e.g., is unable to be or uncomfortable being still for extended time as in restaurants, meeting; may be experienced by others as being restless or difficult to keep up with).

f. Often talks excessively

g. Often blurts out an answer before a question has been completed (e.g., complete people's sentences; cannot wait for turn in conversation).

h. Often has difficulty waiting his or her turn (e.g., while waiting in line).

i. Often interrupts or intrudes on others (e.g., butts into conversations, games or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).

B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.

C. Several inattentive or hyperactive-impulsive symptoms are present in two or more setting (e.g., at home, school or work; with friends or relatives; in other activities).

D. There is clear evidence that the symptoms interfere with or reduce the quality of social, academic or occupational functioning.

E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

Specify whether

314.01 (F90.2) Combined presentation: If both criterion A1 (inattention) and criterion A2 (hyperactivity-impulsivity) are met for the past 6 months.

314.00 (F90.0) Predominantly inattentive presentation: If criterion A1 (inattention) is met but criterion A2 (hyperactivity-impulsivity) is not met for the past 6 months.

314.01 (F90.1) Predominantly hyperactive/impulsive presentation: If criterion A2 (hyperactivity-impulsivity) is met but criterion A1 (inattention) is not mere over the past 6 months.

Specify if:

In partial remission: When full criteria were previously met, fewer than the full criteria have been met for the past 6 months and the symptoms still result in impairment in social, academic or occupational functioning.

Specify current severity:

Mild: Few if any symptoms in excess of those required to make the diagnosis are present and symptoms result it only minor functional impairments.

Moderate: Symptoms or functional impairment between "mild" and "severe" are present and symptoms result in only minor functional impairments.

Severe: Many symptoms in excess of those required to make the diagnosis or several symptoms that are particularly severe, are present or the symptoms result in marked impairment is social or occupational functioning.

2.1 Etiology

The etiology of ADHD is not definitely known. A genetic imbalance of catecholamines in the cerebral cortex appears to play a primary role. A genetic contribution to the pathogenesis of ADHD is supported by the increased risk of ADHD in the first-degree relatives of patients with ADHD and twin studies from different countries that consistently provide heritability estimates of approximately 75% [1].

Various environmental factors may play a secondary role; the significance of environmental factors is controversial. Dietary influences, sleep deficiency, prenatal medications, prematurity, iron deficiency, iodine deficiency and etc.

2.1.1 Dietary influences

The influence of diet on attention, hyperactivity, and behavior is controversial. Some children may demonstrate mild adverse behavioral effects of diets containing food additives, artificial colors, excess sugar, or reduced intake of essential fatty acids and minerals.

2.1.2 Food additives

Food additives were first suggested as potential cause of hyperactive behavior in the 1970. Systematic reviews and the meta-analyses of randomized trials with methodological limitations suggest that some children with ADHD respond favorably to elimination diets [9, 10]. However, this conclusion is not universally accepted, and the issue remains controversial.

2.1.3 Refined sugar

Adverse behavior effects including hyperactivity are commonly attributed to excess sugar intake by parents and teachers. Parent of children with ADHD frequently note a worsening of hyperactivity after consuming high carbohydrate meal. There are proposed mechanisms: sensitivity to refined sugar and functional reactive hypoglycemia (which triggers release of stress hormones such as adrenaline) after ingesting sugar [11].

There is no evidence that sugar effects the behavior and/or cognitive performance [11]. Future studies are necessary to confirm the effect on even a small subset of children.

2.1.4 Food sensitivity

Food allergy is proposed as a possible factor in the cause of ADHD. There are few well-designed trials evaluating the potential association between food sensitivity (allergy or intolerance) and behavior. Demonstration of such association requires removal of the suspect food(s) from child's diet (elimination diet). Followed by challenge with suspected food(s) versus placebo. The role of food sensitivity as a cause of ADHD is difficult to document, cooperation on neurologist, allergist and dietician being essential. The hypoallergic diet deserves further study [4].

2.1.5 Iron deficiency

The role of iron deficiency in the ADHD has not clearly defined. A comparison of clinical characteristics of children with the lowest serum ferritin

levels (20ng/ml) and those with highest serum ferritin levels (60ng/ml) show no significant difference in severity or frequency of ADHD and comorbid symptoms [4]. In addition, there appears to be an overlap between restless leg syndrome (which is associated with iron deficiency) and ADHD symptom in children [12].

2.1.6 Zinc deficiency

The role of zinc in ADHD is also controversial. Several studies have been conducted to find out the role of zinc in the etiology of ADHD. Study by Arnold and colleagues [13] did not show that the zinc alone could improve the ADHD symptoms. In another study zinc was a part of the treatment [14]. In conclusion, zinc is tolerated well in children with ADHD. However, further evidences are required to indicate whether zinc is effective for treating children with ADHD. It is recommended to replicate the randomized well-controlled trials [15].

2.1.7 Prenatal exposure to tobacco smoke

Prenatal exposure to tobacco smoke is consistently associated with development of ADHD in case-control and cohort studies [16]. Smoking during pregnancy increased the risk of offspring ADHD. The risk of ADHD was greater for children whose mothers were heavy smokers than for those mothers were light smokers. The authors suppose that there can be relationship between maternal smoking and ADHD in children but could not clarify if other confounding risk factors can affect on this causality. Thus it is necessary to perform more studies in order to detect association between maternal smoking and ADHD in offsprings.

2.1.8 Iodine deficiency and children with ADHD

Correlation of the Iodine deficiency and ADHD in children is of high interest. Thyroid hormones are necessary for the normal metabolic function and the Iodine is important element in the synthesis and regulation of thyroid hormones. It is well known that Iodine deficiency (ID) can lead to mental retardation although preventable and the most critical period for this is fetal development. Maternal thyroid function and Iodine concentration of infant are strongly correlated and the group of disorders due to disturbances in this correlation are called ID disorders. According to Hope Abel and colleagues [17] maternal ID during pregnancy has direct association with severe ADHD symptoms in offsprings at eight years of age. Although it is not recommended maternal iodine intake in order to avoid ADHD risk in child especially as it is known iodine supplementation in the first trimester is associated with an increased health risks

2.1.9 Lead exposure and ADHD

Lead (Pb) has as a neurotoxic effect leading to abnormal behavior in children. There are plenty of studies attempting to detect correlation between exposure to heavy metals and other harmful environmental factors in the pathogenesis of behavioral disorders. In 1991 recommended level of lead in children's blood (BLL) by CDC is set to 10 micrograms of lead per deciliter of blood (μg/dL) and it has not been changed since then. Donzelli et al. [18] performed systematic review of 17 studies assessing the correlation of lead level and ADHD. According to their results there is a direct correlation between low lead level of lead in ADHD children's blood

and severity of ADHD symptoms. However, we need more high quality clinical studies to prove this relationship.

Although evidence shows that ADHD is a worth recognizing disorder many environmental risk factors such as exposure to heavy metals, dietary factors, environmental exposure to different substances could intensify or accelerate the progression of this disease. The efforts for early diagnosis of the disease is crucial, and identifying the contributing factors is of prime importance to prevent ADHD.

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2.2 Genetic factors

It has been implicated that genetic factors play a critical role in the etiology of ADHD as well as its comorbidities. Based on multiple familial, twin, adoption and single epidemiological studies ADHD is considered as one of the psychiatric disorders which shows the strongest genetic basis. Several twin studies have revealed that concordance in monozygotic (MZ) twins is higher than in dizygotic (DZ) twins with heritability estimates of approximately 75–80%. Large numbers of linkage studies, genome wide association studies (GWAS) and meta-analyses have been conducted and numbers of susceptibility variants, genes and chromosomal regions have been reported to be associated with ADHD. Moreover, number of studies also shows that about one third of ADHD's heritability is due to a polygenic component encompassing many common variants, where each variant individually has small effect but their cumulative effect contributes to the development of the condition. Investigation of copy number variants (CNVs) has also shown that rare insertions or deletions contribute to the part of ADHD's heritability. Recent progress in identifying ADHD susceptibility genes underlines new biological pathways that may have implication for prevention and treatment development.

According to the literature the mean heritability across multiple twin studies of ADHD is 74–80% [19, 20] and it is similar in ADHD males and females [21]. According to one study, where 894 probands with ADHD and their 1135 siblings were studied, there was nine-fold increased risk of ADHD in siblings of ADHD probands compared with siblings of controls. Several adoption studies also indicate that ADHD is greater among the biological relatives of non-adopted ADHD children than adoptive relatives of adopted ADHD children and the risk for ADHD in adoptive relatives is similar to the risk in relatives of control children. Additionally, adoption studies suggest that the familial aggregation of ADHD is defined more by genetic factors rather than common environmental factors. Based on the largest longitudinal study to date on familial aggregation of ADHD, the closer was the relatedness of probands and their relatives the higher was the familial aggregation [20]. Consistently, among full siblings, the familial aggregation did not differ significantly by index person's sex. Moreover, it is expected that genetic factors play more important role in explaining familial aggregation than shared environmental factors [22], given that the familial aggregation is remarkably higher in MZ twins than in DZ twins and similar between DZ twins and nontwin full siblings.

Genetic linkage was the first genome-wide method applied to ADHD. This method looks through the genome to find evidence that a segment of DNA is transmitted with a disorder within families. According to the literature there is no

clear-cut evidence about which chromosomal regions are linked to ADHD and so far none of the findings met genome-wide significance, suggesting that common DNA variants having a large effect on ADHD may not exist [23].

Genome-wide association studies (GWAS) scan the entire genome to detect common (frequency more than 1%) DNA variants that have very small etiologic effects. The early GWAS of ADHD did not discover any DNA variants that achieved genome-wide significance. However, recent studies have implicated contribution of some genes with relevant biological roles in ADHD. For example *USP6* is involved in regulation of dopamine levels in the synapses and regulates neurotransmitter homeostasis. Certain variants in *LINC00461* are associated with educational attainment and *ST3GAL3* and *MEF2C* are associated with ID and psychiatric disorders [24]. The GWAS analyses also showed that polygenic effects may also contribute to ADHD's heritability, where multiple common risk variants each with very small effects contribute to the development of the disease as a cumulative effect. The polygenic nature of ADHD was confirmed by evaluating polygenic risk scores and revealing that it predicted ADHD, in a dose-dependent manner. The discovery of a polygenic susceptibility to ADHD does not show which DNA variants comprise the susceptibility, however significant findings implicate that genes involved in biological processes such as synaptic plasticity, catecholamine metabolic processes, G-protein signaling pathways, cell adhesion, neuronal morphogenesis and neuron migration were over-represented in ADHD. Moreover, many of these genes show considerable interactions with genes identified as trending towards significance in GWAS [25].

It has been known for a long time that rare DNA variants can lead to ADHD. Because chromosomal deletions and duplications often delete or duplicate a large segment of DNA which may include part of a gene or even several genes, they often have clear implications for gene functioning. Several studies indicate that there is a greater burden of large, rare CNVs among ADHD patients compared with controls [26]. Despite the fact that deletions and duplications are equivalently over-represented in ADHD individuals, statistical significance for ADHD is observed only for duplications, as well as in schizophrenia and ASDs [27] Several well-known syndromes and chromosomal abnormalities may be associated with multiple medical and psychiatric problems along with ADHD. Among these are Klinefelter syndrome, Turner syndrome, 22q11 deletion syndrome, fragile-X syndrome, tuberous sclerosis, neurofibromatosis, Williams syndrome, as well as translocations involving *SLC9A9*, duplication of 7p15.2-15.3 and deletion of 15q13. It is noteworthy to mention that such larger chromosomal rearrangements show increased incidence of ADHD along with global developmental delay (GDD), intellectual disability (ID) and ASD [28]. Beside chromosomal abnormalities there is increasing evidence of single-gene contribution to ADHD, including inactivating mutation in *TPH2*, duplication of *CHRNA7* and pathogenic changes in *PARK2*, *FBXO33* and *RNF122* [29]. New technologies like next generation sequencing (NGS) and whole exome sequencing (WES) revealed several novel rare variants in candidate genes, among them *TBC1D9*, *DAGLA*, *QARS*, *CSMD2*, *TRPM2*, and *WDR83*, *NT5DC1*, *SEC23IP*, *PSD*, *ZCCHC4*, and *BDNF* [30].

It is clear that certain DNA variants increase the risk for ADHD. It is not common that only a single genetic alteration may cause ADHD in the absence of other DNA variants. At the same time it is clear that there are no common DNA variants that are necessary and sufficient causes of ADHD. GWAS show that a genetic susceptibility to ADHD encompasses of many common DNA variants, but yet we do not know exactly which variants or how many of them contribute to the polygenic nature. The heritability that cannot be explained by main effects of rare or common variants is likely due to gene-gene and gene-environment interactions. The

accumulating evidence for ADHD risk factors genes does not exclude the environmental etiological factors which likely work through epigenetic mechanisms, but these yet have barely been studied in ADHD. In the coming years, we can expect breakthroughs in the genetics of ADHD. Unraveling the genetics of ADHD will not be easy, but with rapid development of technologies and with wider application and better interpretation of whole exome and whole genome sequencing (WGS) data the knowledge and significance of various rare and common variants will increase dramatically. Such advances will enable us to understand the etiology of ADHD and set forth opportunities to diagnose and treat the disorder.

2.3 Biological basis

Attention problems manifested in ADHD are due to dysfunction of ventral catecholaminergic pathways projecting to prefrontal and frontal cortex. More than thirty structural and functional neuroimaging studies in ADHD brain have been reported. The main area in the brain implicating in ADHD is prefrontal cortex and its innervations of subcotrical regions such as caudate-putamen, nucleus accumbens, and amygdala. Reduced size of corpus callosum has been detected in some children with ADHD and typically larger corpus callosum in the human female brain may be protective against ADHD. Cerebellum has been implicated in cognition and emotion besides the well-known role in coordination and maintaining body posture, suggesting a possible role contributing to ADHD that is consistent with reports of disorders of fine motor movements in ADHD children. Hippocampus as an important site for memory is also can be considered as possible participant in pathogenesis of ADHD. Structural brain imaging could not confirm the structural abnormalities of hippocampus but functional imaging found reduced cerebral glucose metabolism in hippocampus in adolescents with ADHD [31].

2.4 Neurobiology

The neurotransmitter dopamine has been recognized to play a role in attention and cognition especially executive functioning and reward processing [32]. It is a key contributor to behavioral adaptation.

Dopamine transporter is the most important molecule in the regulation of dopamine signaling in most areas of the brain-is the main target of stimulants like Methylphenidate and also dexamphetamine-drugs for ADHD treatment. These drugs block the dopamine transporter and lead to an increase in dopamine concentration particularly in the parts of the basal ganglia that are highest in the expression of the transporter, the striatum [33]. Positron emission tomography (PET) shows that people with ADHD have more dopamine transporter activity compared with healthy controls [34]. Besides genetic studies reveal that disorders in dopamine signaling could occur due to alteration in dopamine receptors which also has to be seen by PET**.** Meta analyses have shown significant involvement of dopamine transporter protein (DAT) and its gene- *DAT1* gene 3'-regulatory region in a larger group of patients with ADHD suggested association of this set of genes with severity of symptoms in children with this disorder [35].

Norepinephrine signaling is related with dopamine system as norepinephrine is a downstream product of metabolism of dopamine. Innervation of the prefrontal cortex by norepinephrine pathways is very important to understand ADHD. Norepinephrine and dopamine signaling are linked in prefrontal cortex thus influencing each other in organizing prefrontal cortex performance in cognitive tasks [36]. The role of norepinephrine can be explained by the fact that

Methylphenidate and dexamphetamine inhibit the norepinephrine transporter together with DAT [36]. It is proved that altering norepinephrine signaling can improve ADHD symptoms but there is lack of evidence to link it with ADHD neurobiology [37].

Serotonin has been studied closely in animal models of ADHD. It was found that serotonin-potentiating agents can inhibit effects on motor hyperactivity [38]. Serotonin neurotransmission may modulate the severity of ADHD symptoms rather than being related to ADHD onset [39]. Other position means that it may be the comorbidity especially with conduct disorder, obsessive compulsive disorder and aggression and mood disorders rather than the core symptoms of ADHD which is influenced by serotonin [40]. Although serotonin receptor gene HTR1B and gene encoding the serotonin transporter (SLC6A4, 5-HTT, SERT) have been implicated in ADHD the effect of environment on ADHD symptoms may explain some of the observed inconsistency across studies especially the effect of stress on ADHD seems to be influences by genetic variation in the serotonin transporter gene [37]. In experimental models serotonin may be critically involved in mediating the behavior inhibiting effects of stimulants [41]. All these suggest that serotonin may play a role in pathogenesis in some circumstances but do not establish serotonin-enhancing drugs as useful treatment.

2.5 Main cognitive finding associated with ADHD

Cognitive impairments in a variety of domains have been found in ADHD as well as impairment in overall intellectual function. Deficit in executive function are common in children with ADHD. Executive functioning are the group of cognitive processes which are responsible for purposeful, goal-directed and problem solving behavior. A meta-analysis of children and adolescents with ADHD showed impairments in several aspects of executive functioning.

2.5.1 Intellectual function

Visuospatial abilities (block-design subtest) and general knowledge (vocabulary subtest) on the Wechsler Intelligence Scale for Children-III (WISC-III) have to be changed in children with ADHD compared with healthy controls. Children with predominantly inattention without hyperactivity have disorders of visuospatial abilities. In contrast, the ADHD group predominantly with hyperactivity have the same evidence in visuospatial abilities or vocabulary as their healthy teens [1].

2.5.2 Language

Language can be impaired in ADHD children. A meta-analysis of children with ADHD found impairments in verbal fluency especially in phenomic fluency compared with semantic fluency [42]. Sometimes in adolescents with ADHD the disorders with object naming also can be revealed [43].

2.5.3 Learning and memory

Working memory is considered to be the most central executive function. Working memory disorders are quite variable in ADHD children. Mainly working memory is impaired and becomes the core feature of ADHD with the strongest impairments reported for the spatial domain of working memory as opposed to the verbal or phonological domain [44]. Visuospatial working memory is provided

predominantly by inferior and superior parietal areas together with dorsolateral prefrontal regions [45–48, 49], Cerebellum also can be activated during visuospatial working memory tasks [50, 51]. Learning disorders also can be seen in ADHD children. Children with learning disorders and ADHD have more severe learning problems than children who have only ADHD. Learning disorder and attention problems are on continuum, are interrelated and usually coexist [52]. Comorbidity with learning disorders is a modifying factor in the health related quality of life of children with ADHD [4]**.** It was found that 5% of children have ADHD without learning disorder, 5% have learning disorder without ADHD and 4% have both conditions. Boys are more likely those girls to have each diagnosis. In 2006 approximately 4.5 million school aged children have ever been diagnosed with ADHD and 4.6 million children with learning disorders [53, 54]. Thus ADHD associated learning and language disabilities are important comorbidities. Neurological assessment is recommended in children with learning disorder who fail to make academic progress despite appropriate educational intervention. The adolescents with ADHD experienced written expression impairment (17.2–22.4%) at a similar rate to reading impairment (17.0–24.3%) and at a slightly lower rate than mathematics impairment (24.7–36.3%) [4]. Dyslexia occurs in 5–10% of school children; it overlaps with ADHD and shows similar genetic characteristics but different brain localizations [4].

Another part of executive disorder is **impairment of response inhibition**. Response inhibition specifically is the ability to control oneself by suppressing or altering intended actions that are no longer required or appropriate. Thus normal response inhibition enables people to adapt properly to changes in the environment. Impaired response inhibition is central to theoretical models of ADHD [55]. According to Barkley [56] response inhibition is a central deficit of ADHD affecting top-down multiple executive functions including working memory, self-regulation, internalization of speech and reconstitution. A large community study showed that ADHD symptoms in children and adolescents are associated with worse response inhibition and slower response latency [57]. Response inhibition deficit in ADHD is proved by magnetic resonance imaging (MRI). Healthy children activate core network of brain regions involved in response inhibition including a frontal-striatal and frontal-parietal network. Children and adolescents with ADHD show decreased activation in frontal, medial and parietal regions during inhibition compared with healthy teens [58].

Willcut et al [59] found impairments in other domains of executive functioning like planning and vigilance in addition to response inhibition and working memory. They noted that while impairment in executive functioning are closely associated with ADHD such deficits do not explain all of the cognitive impairments observed in ADHD suggesting that executive dysfunction is only one part of the cognitive impairments associated with ADHD [1].

Another frequently described comorbidity is disorder of **cognitive flexibility**. It is clear that ADHD children are more likely to respond with overlearned and automatic responses when faced with problem-solving situations or context that demand the thoughtful formation of strategies and the flexible shifting of thought [60]. Barkley et al [60] suggested that **behavioral or verbal creativity** can be impaired in children with ADHD as a consequence of their poor verbal inhibition.

Decision making can be considered as important part of executive functioning. ADHD children and adolescents have specific decision making deficits. ADHD people have no impaired learning rate per se as it was suggested before [61]. ADHD individuals exhibit less comprehensive decision process and more frequent exploration activity compared with controls. This feature could occur due to impaired reward prediction processing in the medial prefrontal cortex which is considered as an integrative hub in the brain responsible for decision making and learning. The deficit

in decision making in adolescents and adults was similar in severity to the deficits in attention in individuals with ADHD [62].

Reward sensitivity is an evolutionary important part of executive functioning. Rewards are accompanied by positive feeling and they reinforce reward linked behavior [37]. This process of reinforcing behavior forms the basic principle of learning [63]. Individuals with highly sensitive to rewards shows maladaptive behavior like risky behavior and addictions [37]. Theoretical model of ADHD consider altered reward sensitivity as a main cognitive mechanism [64], Children and adolescents with ADHD are performing risky and suboptimal decisions. ADHD population with impaired reward processing and impulsivity show increased activations in the anterior cingulated and anterior frontal cortex as well as in orbitofrontal cortex and nucleus accumbens [65]. Other studies in ADHD adolescents have reported less triatal activation during reward compared with healthy teens [66].

Specific motor deficits may be found in children with ADHD but like other measures of neuropsychological functioning, such difficulties are not specific predictors of the presence of ADHD [67]. Commonly difficulties can be seen in coordination. When both attention and coordination deficits co occur in conjunction with perceptual problems the term "deficit in attention, motor control and perception (DAMP)" can be applied [68]. The concept of DAMP is fairly controversial and the label is more widely used in Scandinavian countries than in UK or USA.

2.5.4 Treatment

The most important part of any intervention plan for a child with ADHD is the physical, behavioral and neuromotor/neuropsychological examination followed by oral and written information of parents, child, teacher about the type of problems the child exhibits and their possible etiology.

Special education- many children with ADHD need special educational measures. In order to acquire some academic skill some children will need individualized education lasting for several hours every day [69].

The two most commonly used behavioral interventions are:

1. Creating and maintaining a well structured environment to compensate for poor stimulus control

2. Parent training

It is very important to organize the school environment with minimal distractions and with seating that is somewhat isolated and close to the front of the classroom in front of the teacher. Common triggers that can easily distract child are instructional demand, withholding of a desired object or activity and withdrawal of parental attention.

Behavior therapy can be considered as the best method for treatment of ADHD children and youths regarding the improvement of behavior, self-control and self-esteem. It is recommended for parents of children younger than 12 years of age to start training in behavior therapy. For children less than 6 years of age it is better to start behavior therapy before prescribing ADHD medicine. Behavior therapy helps parents to learn skills and strategies to improve their children academic achievement at school, behavior at home and improve their social interaction. Although studying and practicing of behavioral therapy needs time and effort from parents the sequence benefit for the child and family could last for a long period of time.

Parent training in behavior management is also known as parent behavior therapy, behavioral parent training or just parent training. If possible, families should look for a therapist who focuses on training parents. Some therapists will have training or certification in a parent training program that has been proven to work in young children with ADHD.

The following are the main goals for therapist while working with parents:

- Parents need to know how to make positive reinforcement, how to construct and control child's behavior. Thus they need to acquire these skills and strategies.
- Parents need to be aware how to interact and communicate with their ADHD children
- Therapists needs to teach parents practical skill how to work with their child
- Therapist needs to meet with family members to observe the progress in their activity and to provide support
- Therapist needs to re-evaluate treatment strategy and method and in case if it is needed to change strategy plans.

3. What can parents expect?

It is recommended for parents to attend eight or more session with a therapist who can work with groups of parents or only with one family. It is necessary to work on a regular basis in order to monitor progress of parents and to change the working strategy in case if it needed. Parents' role in treatment planning and implementing is extremely crucial as they can have greatest influence on their child's behavior. There are many treatment options for therapist for working with ADHD children. Play therapy and talk therapy could be considered as one of the best treatment option. Talk therapy uses verbal communication between ADHD child and therapist in order to improve child's emotional state. Although behavioral therapy needs time and effort its effect could last for long period of time [70].

Successful treatment for ADHD means both behavior therapy and medication. For children 6 years of age and older, the American Academy of Pediatrics (AAP) recommends both behavior therapy and medication. For children under 6 years of age behavior therapy is recommended as the first line of treatment [71].

Medication should be start with one of the stimulants. Both d-amphetamine (10–40 mg/day given in 2–5 dosed with 3-hour intervals in order to last through the school day) and methylphenidate (20–80 mg/day given in the same fashion) have been shown to be effective for improvement of hyperactivity, concentration problems, learning disorders and other comorbidities. Both drugs have minimal side effects. "Long-acting," "slow-release" preparations of methylphenidate have also been shown to have good effects and they can sometimes be dosed (18–54 mg/day or 10–60 mg/day depending on preparation) only once daily. Relatively common side effects are loss of appetite, a tendency to increase the likelihood of tics and stereotypies, reduced mimicry and hallucinations. They can easily stop with drug discontinuation. There are some evidence that long-term methylphenidate treatment should be as effective as the combination of methylphenidate and behavioral therapy and considerably more effective than behavioral therapy alone [72]. Combination of methylphenidate and behavioral therapy is the best choice for improving both ADHD

and ADHD plus depression and anxiety. Doctor should be careful for monitoring the child's height, drug dependency while treating the child with stimulants for long term period although they appear rare compared with tricyclic antidepressants.

The noradrenergic reuptake inhibitor atomoxetine has also been shown to have beneficial effects on ADHD as a second line treatment in children with ADHD. Although clinical effects appear to be less effective than with methylphenidate but the advantage if this medication is that it can be used only once daily and it is not stimulant [69].

Author details

Sophia Bakhtadze[1*], Tinatin Tkemeladze[2] and Tinatin Kutubidze[3]

1 Department of Paediatric Neurology, Tbilisi State Medical University, Tbilisi, Georgia

2 Department of Molecular and Medical Genetics, Tbilisi State Medical University, Tbilisi, Georgia

3 Department of Child and Adolescent Medicine, Tbilisi State Medical University, Tbilisi, Georgia

*Address all correspondence to: sophiabakhtadze@yahoo.com

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