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ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD): A RECENT REVIEW

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ABSTRACT
Attention Deficit Hyperactivity Disorder (ADHD) is the most commonly diagnosed behavioral disorder of childhood associated with inattentiveness, over-activity, impulsivity, or a combination. It affects about 3 - 5% of school aged children. The prevalence of ADHD is alarmingly increased in last few years. Many of the neurotransmitters are metabolically derived from amino acids. Analyses of plasma amino acid levels determined that phenylalanine, tyrosine, tryptophan, and isoleucine were lower in ADHD patients than in controls.The treatment of ADHD requires a multimodal approach. Conventional treatment most often includes medications like methylphenidate or amphetamine, which are stimulant drugs. Pyridoxine, folic acid, thiamin, niacin, and vitamin C are the nutrients most commonly found to be low in children who responded to supplementation with measurable improvement.Reports indicates that alternative medicine treatments can reduce ADHD symptoms. Yoga and meditation help children relax and learn discipline, which may help them manage their symptoms of ADHD.

KEYWORDS: ADHD, Attention Deficit Hyperactivity Disorder, dopamine, COMT, nutrients.

1. INTRODUCTION
Attention deficit hyperactivity disorder (ADHD) is one of the neurobiological deficits most commonly diagnosed in children and teens.[1] It is a chronic condition that affects millions of children and often persists into adulthood. Symptoms include difficulty staying focused and paying attention, difficulty controlling behavior, and hyperactivity. Recent epidemiological studies have indicated that ADHD is often a "hidden disorder" in girls because the symptoms are less overt in females.[1,2] Children with ADHD also may struggle with low self-esteem, troubled relationships and poor performance in school. Symptoms sometimes lessen with age. However, some people never completely outgrow their ADHD symptoms. But they can learn strategies to be successful. Underlying neurobiological causes have been proposed on the basis of strong heritability, anatomical and genetic associations, and the effectiveness of treatment with psycho stimulant drugs. However, causative pathophysiological mechanisms for ADHD have not yet been identified, and at present, there is no biomedical laboratory test that is diagnostic for ADHD. The diagnosis is based on the observation of a number of behavioural symptoms of inattention, impulsivity and hyperactivity in different settings and over a certain period of time. The lack of a demonstrable physical cause for ADHD is problematic for the development of an animal model to guide clinical drug development. The symptoms used in the diagnosis of ADHD are not unique to this disorder. Inattention, impulsivity and hyperactivity exist in the normal population and may be normal at earlier developmental stages. While treatments not cure ADHD, it can help a great deal with symptoms. Treatment typically involves medications and behavioral interventions. Early diagnosis and treatment can make a big difference in outcome.[3]

2. Causes and complicationsof ADHD
A typical ADHD child may be predominantly hyperactive-impulsive or predominantly inattentive or combined hyperactive-impulsive and inattentive. Inattention, hyperactivity, and impulsivity are the key behaviors of ADHD. It is normal for all children to be inattentive, hyperactive, or impulsive sometimes, but for children with ADHD, these behaviors are more severe and occur more often. To be diagnosed with the disorder, a child must have symptoms for 6 or more months and to a degree that is greater than other children of the same age.[4]

Results from several international studies of twins show that ADHD often runs in families. Researchers are looking at several genes that may make people more likely to develop the disorder.[5,6] Studies also suggest a potential link between cigarette smoking and alcohol use during pregnancy and ADHD in children.[7,8] In addition, preschoolers who are exposed to high levels of lead, which can sometimes be found in plumbing fixtures or paint in old buildings, may have a higher risk of developing ADHD.[9] It is also reported that children who have suffered a brain injury may show some behaviors similar to those of ADHD. However, only a small percentage of children with ADHD have suffered a traumatic brain injury. Recent British research indicates a possible link between consumption of certain food additives like artificial colors or preservatives, and an increase in activity.[10] Research is under way to confirm the findings and to learn more about how food additives may affect hyperactivity.[4]

ADHD can make life difficult for children. Often struggle in the classroom, which can lead to academic failure and judgment by other children and adults, tend to have more accidents and injuries of all kinds than children who don't have the disorder, having poor self-esteem, more likely to have trouble interacting with and being accepted by peers and adults,[4] at increased risk of alcohol and drug abuse and other delinquent behavior is seen in children suffering from ADHD. ADHD doesn't cause other psychological or developmental problems. However; children with ADHD are more likely than are other children to also have conditions such as learning disabilities, anxiety disorders, depression, bipolar disorder, Oppositional Defiant Disorder (ODD), conduct disorder and Tourette syndrome.[11]

3. Pathophysiology

There are many correlates of ADHD, but correlation does not necessarily mean cause. It is also necessary to develop theories that link the pathological changes to the symptoms. Strong findings include a reduction in total brain size that persists into adolescence.[12] and reduced dimensions of several brain regions,[13-15] including the caudate nucleus, prefrontal cortex white matter, corpus callosum and the cerebellar vermis.[16,17] A decrease in cortical thickness has been reported, which is apparent in childhood and largely resolves during adolescence.[18] Alterations within the frontal and cerebellar white matter have been measured in children and adolescents with ADHD.[19] The anatomical correlates of ADHD are complemented by functional studies that show differences in activation of specific regions during task performance. Studies of dopamine release are particularly relevant to the mechanisms of action of therapeutic drugs in ADHD. However, the precise neuropsychological deficits that characterize this complex and multifactorial condition are not clear yet. Patients with ADHD often present brain abnormalities especially of the right prefrontal cortex (PFC), basal ganglia and cerebellum.[20] These structures are modulated by dopamine (DA) and noradrenaline (NA), which are implicated in the pathophysiology of ADHD.[21] DA is usually associated with reward, learning and motor functions, while NA regulates arousal, attention and mood. The dopamine hypothesis is supported by many pieces of evidence, including gene linkages to transporter and receptors, the actions of stimulant medication on dopamine release and reuptake mechanisms at the synaptic level;[22] a reduction in dopamine synaptic markers associated with symptoms of inattention in ADHD and evidence from functional imaging of hypoactivity of the dopamine system.[23]

In contrast to excitatory neurotransmitters such as glutamate or inhibitory neurotransmitters such as gamma amino- butyric acid (GABA) DA can be excitatory or inhibitory and binds to either D1-like receptors (D1 & D5) or D2-like receptors (D2, D3 or D4).[24] Activation of D1-like receptors results in stimulation of adenylatecyclase but D2-like receptor activation will cause an inhibition of adenylatecyclase which inhibits cyclic AMP production. Thus binding of agonists to D1-like or D2-like receptors serves to depolarise or hyperpolarise the cell membrane respectively. The interpretation of dopaminergic changes in the pathology of ADHD is therefore complicated by the dual excitatory and inhibitory roles of this neurotransmitter. ADHD may in part result from deficits in the dopaminergic system in cortical brain structures such as the prefrontal cortex (PFC) (notably the right-medial side)[25] and subcortical areas such as the nucleus accumbens (NAc) and the striatum.[26]

There are four major dopaminergic pathways in the brain; the mesolimbic, mesocortical, nigrostriatal, and hypothalamic-tuberoinfundibular pathway. The mesolimbic pathway projects from the ventral tegmental area (VTA) to the NAc and is involved in addiction, reward,[27,28] major depression (caused by mesolimbic DA depletion)[29] feeding behavior.[30] and psychosis.[31] The mesocortical pathway projects from the VTA to the cerebral cortex, notably the PFC regulating information processing, selective attention, working memory, language and planning.[32] The nigrostriatal system starts in the substantia nigra pars compacta (SNc) and projects to the striatum regulating motor functions amongst others.[33] The hypothalamictuberoinfundibular (HTI) pathway, which originates in the arcuate nucleus of the hypothalamus and the immediate periventricular nucleus projects mostly to the pituitary gland. The dopaminergic neurons from the HTI pathway regulate the secretion of prolactin and luteinising hormone.[34] The mesolimbic and mesocortical (together called mesolimbocortical pathway) pathways are believed to be involved in ADHD.[25] Mesolimbic DA may be dysregulated in ADHD patients since smaller and immediate rewards are preferred by them compared to larger, but delayed ones.[35] This maladaptive impatience to wait for bigger rewards is one of the aspects of impulsivity called impulsive choice, which is possibly controlled by the

NAc.[36] Mesocortical DA is suggested to be involved in the pathology of ADHD as it plays a role in selective attention and working memory. Whether the mesolimbocortical pathway in ADHD is hyper- or hypofunctional is still open for debate; most animal models favour the hypodopaminergic theory.[37] but others seem to indicate a hyperdopaminergic system.[38,39] The nigrostriatal pathway has also been suggested to contribute to the pathology of ADHD in relation to the hyperactivity. It was demonstrated that the DA transporter (DAT), an important regulator of DA neurotransmission, is lowered in adult ADHD patients by methylphenidate in the striatum.[40] Increased reaction times and speed variability in ADHD patients are also thought to represent nigrostriatal DA dysfunction.[41]

4. Imaging Studies and Neurobiology of ADHD

Modern brain monitoring techniques have established that ADHD can be organically expressed in the brain.[42,43] The techniques include positron emission tomography (PET), single-photon PET (SPECT), quantitative electroencephalography (QEEG), and functional MRI (fMRI). These help quantify brain metabolic activity and correlate it with anatomical differences in the brain, on a real-time basis. Certain QEEG measures do consistently differ between ADHD and normals, but their functional meaning is not yet evident. Measures of event-related potentials document P300 wave differences consistent with ADHD children being deficient in response selection and organization.[43] With PET, abnormal regional blood perfusion is evident in the striatal region of ADHD children.[44] Zametkin obtained similar findings in adults.[45] but fell short of statistical replication in children.[46] Meanwhile, the first SPECT study in children revealed the ADHD group had greater overall metabolic asymmetry, with less activity in the left frontal and left parietal regions.[47] These zones are predominantly dopaminergic, and hypofunction of dopamine pathways is a consistent feature of the disorder. The diagnostic potential of this information is becoming evident. The cerebellum is functionally linked with the prefrontal cortex, and three anatomical measures, namely the right globuspallidus volume, caudate asymmetry, and left cerebellum volume, correlate highly with ADHD in children.[43]

Imaging studies are also beginning to study familial patterns of brain structure and function. Brain endophenotypes refer to brain characteristics shared by ADHD patients and their siblings and likely to be involved in the liability to the disorder. Activation pattern of the ventral prefrontal cortex and reduced striatal activity have been identified as possible brain endophenotype candidates.[48,49]

5. Molecular genetic studies of ADHD

Shared gene effects in ADHD have been demonstrated by family, twin and adoption studies.[50] Understanding the precise involvement of various genes in the pathophysiology of ADHD is however difficult. Two specific genes in particular stress the importance of DA system dysfunctionality in the development of ADHD. These encode for the DAT (SLC6A3) and the D4 receptor (DRD4). The role of other dopaminergic genes possibly with smaller effects remains to be fully elucidated.[51]

Contradicting data on the monoamine degradative enzyme catechol-O-methyltransferase (COMT) with respect to ADHD exists in the literature. COMT catalyses the degradation of catecholamines, especially DA.[52] Polymorphism of COMT influences its catalytic activity; substitution of the valine variant into methionine at codon 108 or 158 decreases enzymatic activity by a factor 3–4.[53] Studies on the effects of COMT polymorphism and its association to ADHD have been confirmed by some studies[54] but rejected by others.[55]

In contrast to the rat D4 receptor, the human D4 receptor is polymorphic, variant repeats of a 48 base-pair (bp) region in exon 3 are found, the most common variants include the two-, four- and seven-fold repeat. The number of repeats was found to influence binding capacity of the D4 receptor, the seven repeat variant for example had different binding properties to clozapine and spiperone when compared to the two and four repeat variants.[56] Interestingly, the seven repeat (7R) allele of the D4 receptor has been associated with ADHD.[57]

Over one hundred molecular genetic studies have recently been reviewed to find associations between ADHD and proposed genes replicating previous findings; a linkage between the DAT, the D4 receptor and ADHD was confirmed. In addition, the D5 and 5-HT transporter were found to be involved.[58] Despite these meta-analyses, a number of individual studies fail in their attempt to link ADHD to the genes encoding for the DAT, D4 and D5 receptors.[59-62]

6. Pharmacological Treatments of ADHD

Psychostimulant medications are generally the first choice in medication of ADHD. Approximately 70 percent of the children treated show improvement in the primary ADHD symptoms.[63,64] Methylphenidate is the drug of choice; other first-line stimulants include dextroamphetamine. The second-line stimulants include methamphetamine, which causes hepatotoxicity in about three percent of subjects treated and can cause death, so must be closely monitored. Methylphenidate targets primarily the DAT glycoprotein; it interacts with and blocks the DAT and interferes with vesicle trafficking in the DA terminal (methylphenidate increases vesicular [3H] DA uptake and the binding of the vesicular monoamine transporter-2 (VMAT2) ligand dihydrotetrabenazine)[65,66] A singlephoton emission computed tomography (SPECT) study performed in rats showed that after methylphenidate administration 78% of the striatal DAT was blocked.[67] Amphetamine is widely used in the treatment of ADHD symptoms. Amphetamine acts less specifically as it can act on both

vesicular storage of DA promoting DA release and directly blocks the DAT but it also releases serotonin (5-HT) which also utilises the DAT to a certain degree.[68] In rats, systemic administration of low doses of amphetamine (0.2 mg/kg) is able to restore attention in PFC-lesioned animals. There was however a trade-off since memory was impaired by challenging the rats with the same (and increased) dosage of amphetamine,[69] suggesting that the degree of PFC dopaminergic tone is critical in influencing the response to amphetamine treatment. Methylphenidate acts on the central nervous system with a dopamine-agonistic effect that is slower in onset but mechanistically almost identical to cocaine and amphetamines.[70-72] Advocates of methylphenidate attest that it works more effectively than any other single intervention to enhance attention span and impulse control.[73] The stimulant drugs used to treat ADHD were short acting (3–4 h) and therefore multiple doses per day were required. It is show the most severe side effects reported: psychic (hypomania, mania, delusions, paranoid delusions, paranoid psychosis, toxic psychosis); hallucinations, auditory and visual; exacerbation of schizophrenia and autism; muteness, extreme withdrawal, partial dissociation; boundary loss, disorganization; nervousness, agitation, terrifying affect, aggressiveness, assaultiveness, anxiety, panic; drug abuse— rebound depression, psychic dependence, increased euphoria, and cocaine-like activity. When methylphenidate is used with antidepressants (such as the tricyclics and Prozac), seizures, hypertension, hypothermia, and convulsions can ensue. Over the long term, weight loss can occur, as can scalp hair loss, vasculitis, leukopenia, visual disturbances, and anemia. Other medications used to treat ADHD include atomoxetine and antidepressants such as bupropion and desipramine. Clonidine andguanfacine have also been shown to be effective.Atomoxetine and antidepressants work slower than stimulants and may take several weeks before they take full effect.[74]

7. Non -pharmaceutical management / Alternative medicine

Nutrients are required by the brain, as they are by every other organ, so virtually any nutrient deficiency can impair brain function.[75] Dietary supplementation can improve academic performance in healthy school-aged children. Pyridoxine, folic acid, thiamin, niacin, and vitamin C are the nutrients most commonly found to be low in children who responded to supplementation with measurable improvement.[76]

Two early controlled trials utilized combinations of B vitamins against ADHD and reported no benefit.[77,78] Treatment with single B vitamins rather than combinations may sometimes be necessary in order to normalize lowered blood levels and selectively increase transmitters in ADHD; for example, pyridoxine can be used to normalize lowered blood serotonin.[79] In 1979, Coleman et al reported that B6 as pyridoxine vitamin improved the behavior of some children with ADHD in a doubleblind crossover comparison with methylphenidate.[80] Blood serotonin levels increased dramatically on B6 supplementation, and teacher ratings showed a 90 percent level of statistical trend in favor of B6 being slightly more effective than methylphenidate. Iron deficiency is the most common of all nutrient deficiencies in U.S. school-age children.[75] which is associated with markedly decreased attentiveness, narrower attention span, decreased persistence, and lowered activity levels, which respond positively to supplementation. According to Galland,[79] the magnesium deficiency status is also often observed in ADHD which features lowered red cell levels of the mineral. A Polish team reported reduced Mg levels in 95 percent of a group of.[81] children with ADHD;[82] dietary supplementation with Mg significantly decreased their hyperactivity.[83]

Several other studies conducted in different countries have found zinc is to be low in ADHD (for references see Galland).[79] Serum zinc can be markedly below normal,[84] and also urinary zinc clearance can be lower; both findings suggestive of poor zinc intake and/or absorption. Findings from one placebo-controlled trial suggest poor zinc status also may predict poor response to amphetamine treatment of the disorder.[81]

Essential fatty acids (EFA) are oily, vitamin-like nutrients which have shown promise in the non-pharmaceutical management of ADHD. The two main classes—omega-3 and omega-6 function as pro-homeostatic constituents of cell membranes and as precursors to smaller molecules (eicosanoids) that transduce information inward to the cell interior, and outward from each cell to influence other cells. Within the ADHD group, a subgroup with higher scores for EFA deficiency also had the lowest levels of plasma EFA.[85] The omega-6 fatty acid GLA (gammalinolenic acid) is a metabolic precursor to AA.[86] GLA was administered to ADHD children in two placebo-controlled studies. In the first, parents' ratings suggested benefit from GLA but teachers' ratings did not.[87] In the second, parents' ratings did not suggest benefit but one teachers' rating of benefit—the Conners Hyperactivity Factor—did achieve statistical significance.[88]

8. Alternative Medicine

There's little research that indicates that alternative medicine treatments can reduce ADHD symptoms. Doing regular yoga routines or meditation and relaxation techniques may help children relax and learn discipline, which may help them manage their symptoms of ADHD. Many of the neurotransmitters are metabolically derived from amino acids. Analyses of plasma amino acid levels determined that phenylalanine, tyrosine, tryptophan, and isoleucine were lower in ADHD patients than in controls.[89] In adults with ADHD, L-tyrosine treatment produced transient improvement.[90,91] Also in ADHD adults, S-adenosyl methionine seemed beneficial in one small, short-term,

uncontrolled study.[92] A complex mixture of bioflavonoids (oligomericproanthocyanidins or OPCs), which have potent antioxidant activity, were reported to benefit ADHD in an undisclosed proportion of children seen in a pediatric practice.[93] The symptom clusters related to attention and distractibility seemingly responded more significantly than hyperactivity and impulsivity. A proprietary mixture of oligosaccharides, which sometimes serve as substrates for probiotic intestinal bacteria, was reported to decrease the severity of ADHD in children during a six-week observation period.[94] With the numerous nutrient deficiencies documented in ADHD, and the promise offered by a range of nutrients in controlled and non-controlled clinical trials, Galland's approach is a proven blueprint for success.[95,79]

So far, studies haven't found a consistent link between diet and improved symptoms of ADHD, though there is some anecdotal evidence that suggests diet changes might make a difference. Neurofeedback training or electroencephalographic (EEG) biofeedback involves regular sessions in which a child focuses on certain tasks while using a machine that shows brain wave patterns. Theoretically, a child can learn to keep brain wave patterns active in the front of the brain which improves symptoms of ADHD. While this treatment looks very promising, more research is needed to see whether it works.[95]

9. ADHD Behavioral Therapy and Counseling

Children with ADHD often benefit from behavior therapy and counseling, which may be provided by a psychiatrist, psychologist, social worker or other mental health care professional. Some children with ADHD may also have other conditions such as anxiety disorder or depression. In these cases, counseling may help both ADHD and the coexisting problem. The counselling may include behavior therapy, psychotherapy, parenting skills training, family therapy and social skills training. The best results usually occur when a team approach is used, with teachers, parents, and therapists or physicians working together. Educate yourself about ADHD, and then work with your child's teachers and refer them to reliable sources of information to support their efforts in the classroom.[11]

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