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Attention Deficit Hyperactivity Disorder

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Abstract

Attention Deficit Hyperactivity Disorder (ADHD) is a developmental disorder which occurs during childhood and persists into adult hood. It is the most common emotional, cognitive and behavioral disorder which is highly heritable and a neurological disorder characterized by Inattention, Hyper activity and Impulsivity. It is a disruptive disorder whose etiology and pathogenesis are poorly under stood, and a multi factorial disorder for which the factors like dietary, environmental, genetic, psychosocial factors contribute to the development of the disorder. It is a chronic disorder which is diagnosed by DSM-IV-TR and is highly responsive to stimulant medication.

Key words: ADHD, neurological disorder, risk factors.

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) represents one of the most prevalent childhood psychiatric disorders [1] which often persists into adolescence and adult hood [2] and is generally considered to be a developmental disorder which is largely neurological in nature affecting about 5% of the world's population [3]. ADHD is highly heritable disorder [4]. According to the recent statistics about 7% of the children from 6-11 years show the incidence of ADHD [5] and it is more prevalent among the children with cerebral issues [6]. It is thought to be a chronic multifactorial disorder [7]. The prevalence of ADHD is 4% greater in those patients with ADHD in the childhood than those with adult patients [7]. Children with ADHD also had problems with sustained attention, impulse control and their motor hyper activity. Patients diagnosed with ADHD are at higher risk for learning, behavioral and emotional problems [8]. A number of studies have shown that individuals with ADHD show 3-4% smaller brain volumes [9]. ADHD also impairs specific aspects of cognition including ability to sustain attention in early childhood [8]. In school aged children it is the most common neuro behavioral problem and

it is a serious medical and behavioral problem [10]. A high incidence of alcohol, cocaine, and nicotine dependence appears to be a higher in ADHD patients [11]. The higher prevalence of ADHD in males may be due to social factors related to identification and diagnosis of ADHD [12].

Types of ADHD:
ADHD is mainly divided into three types: In attentive, Hyperactive-Impulsive and combined types [3].

Symptoms of ADHD:
In healthy infants early infancy feeding and sleeping problems and later speech delay were identified as the early markers for potential ADHD [1]. Children with ADHD were more likely to experience sleep, taking restless sleep, difficulty in initiating sleep, night awakening and snoring. Short sleep duration in adolescents has been reported to be associated with higher risk of ADHD [13]. Children with obstructive sleep apnoea and habitual snoring have presented with inattentive and hyper active symptoms and possibly up to one third of all children with frequent, loud snoring will show significant hyper activity and inattention. With treatment of these respiratory and sleep disturbances, the ADHD symptoms can be improved [13].

Inattentive Type [8]: Children with Inattentive type of ADHD shows:
- Forget full ness in daily activities
- Fails to give close attention to details
- Shows difficulty in sustaining attention to tasks or play activities
- Does not seem to listen when spoken directly
- Does not follow the instructions and fails to finish the home work
- Distracted easily by the external stimuli
- Reluctance to engage in tasks that require sustained mental effort

Hyperactive-Impulsive Type [8]: children with Hyperactive- Impulsive type of ADHD shows:
- Often fidgets with hands or feet
- Often leaves seat in class room
- Often runs about or climbs
- Often has a difficulty engaging leisure activity
- Often acts as if driven by a motor
- Often talks excessively
- Often bursts out answers before questions have been completed
- Often shows difficulty one's waiting turn
- Often interrupts others

Combined Type [3]:
Children with combined type of ADHD show the symptoms of both the inattention and hyperactive-impulsive type.

Risk Factors For ADHD:
- GENETIC FACTORS:

Numerous genetic studies indicate that there is strong genetic influence for ADHD. Approximately 25% of close relatives in the family of children with ADHD also have ADHD [7].

- **Dietary Factors**:

Nutritional factors such as food additives, refined sugars, food allergies, essential fatty acid deficiencies have all been associated with ADHD [7].

- **Perinatal Factors**:

Moderate-to-severe physical illness in the mother during gestation, prenatal and alcohol exposures, miscarriage symptoms, premature delivery symptoms, maternal respiratory viral infections, neonatal seizures, asphyxia or anoxia, severe neonatal illness, mild speech retardation, moderate brain injuries and febrile seizures are the major perinatal factors of ADHD [7]. Neonatal exposure to the high levels of manganese has also been associated with ADHD due to similarity of dysfunction in brain dopamine systems seen with manganese toxicity and ADHD [7]. Pregnancy and delivery complications lie toxemia, eclampsia, and poor maternal health, maternal age, and fetal post maturity, duration of labor, fetal distress, and low birth weight and anti partum hemorrhage appear to have a predisposition for ADHD [14].

- **Thyroid dysfunction:**

In ADHD pathology abnormal thyroid function may also play a major role. This is based on the fact that thyroid hormones are essential to the normal brain development and influence behavioral and cognitive function [7].

- **Environmental factors:**

Environmental factors also contribute to the etiology of ADHD along with other factors [15]. Environmental factors have been correlated with development of ADHD. Physically induced stressors include such factors as malnutrition, toxins, diseases and traumas [16].

- **Brain abnotmalities:**

Children with ADHD show 3%-4% smaller brain volumes in all regions of the brain including the frontal lobes, temporal gray matter, caudate nucleus and cerebellum [7]. Some children who have suffered accidents leading to brain injury may show some signs of behavior similar to that of ADHD [3].

- **Psychosocial factors:**

Psycho social factors that have been implicated in the development of ADHD symptoms include marital distress, family dysfunctions and low socio economic class [16].

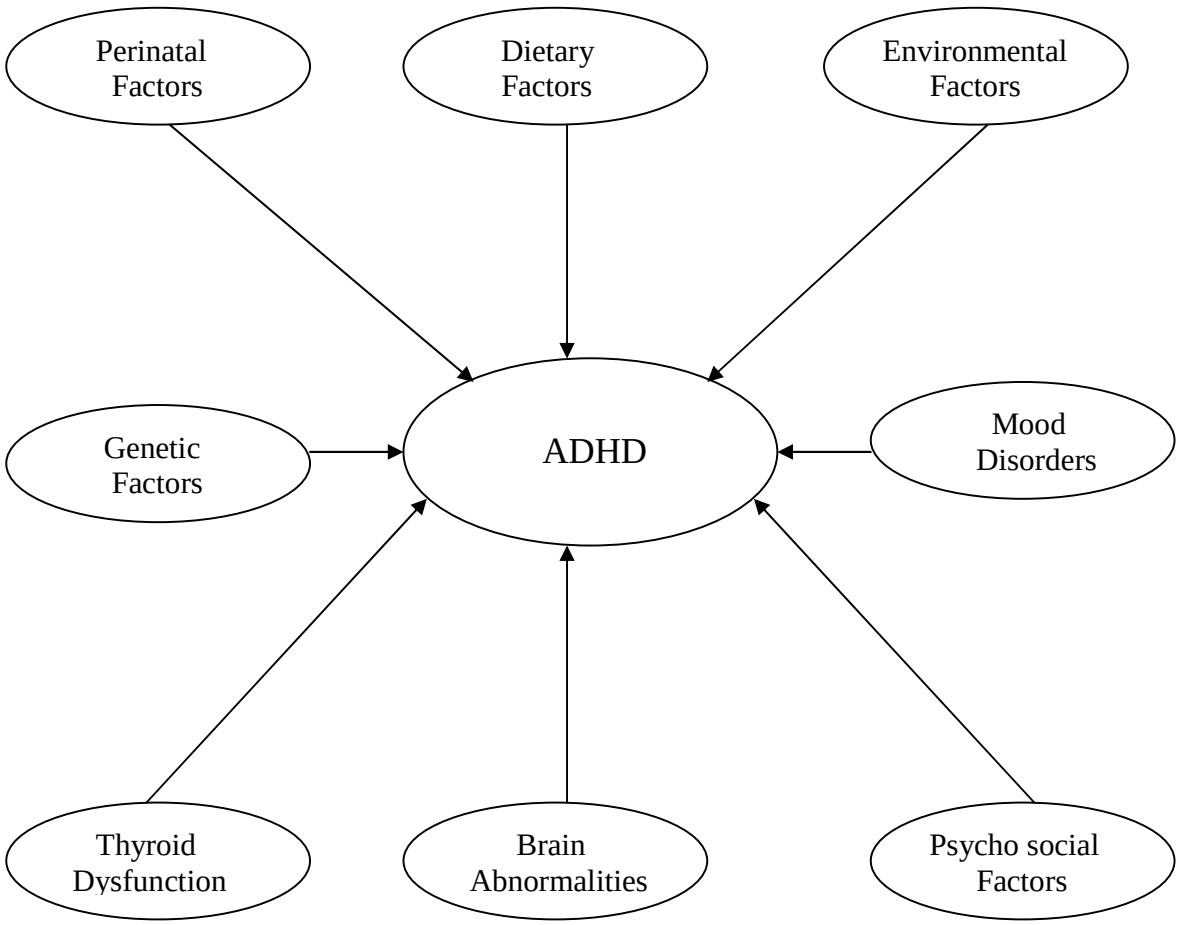
- **Mood disorders:**

Physiologic disturbances such as changes in apetite and weight, abnormal sleep patterns, psychomotor abnormalities, fatigue and diminished ability to think as well as feelings of worthless ness or guilt and suicidal preoccupation [14].

- **Causative Drugs Of ADHD:**

Decreased levels of essential fatty acids decosa hexanoic acid (DHA) is considered to be the cause for ADHD [7]. Higher blood lead concentrations are significantly associated with ADHD [7]. Medication like phenol barbital is also well known to cause hyper activity [17].

Causes for ADHD:



Developmental Course:

- Pre School Children:

ADHD is associated with distinct patterns of challenges at each stage of development. In pre school children with the disorder tend to have great difficulty in managing transitions [18].

- Elementary School Children:

In elementary school children with ADHD continue to experience conflict with peers. They show trouble in organizing school related tasks like doing home work and keeping their desk in order [18].

- Adolescents:

Adolescents with ADHD tend to be immature, get into trouble when not surprised, have poor social skills and engage in higher risk activities [18].

- Adults:

Adults with ADHD experience higher levels of anxiety and depression than the general population. They show increased risk of poor medical health, serious motor vehicle crashes, cigarette smoking and drug abuse. They show changes in employment, poor planning abilities, messiness, dangerous driving and difficulty in organizing their homes [18].

Patho physiology:

The Pathology of ADHD is not clear. The underlying brain regions that are predominantly thought to be involved in ADHD are frontal and prefrontal lobes. The parietal lobe and cerebellum may also be involved [3]. ADHD patho physiology points to dysfunctions of two inter connected brain areas: the prefrontal cortex and the striatum. The prefrontal cortex is believed to play a key role in weighing of consequences and is involved in goal determination and the cognitive steps that go towards achieving these goals such as directing attention, prioritizing actions and creating and executing plans [10]. Neuro biological studies suggest the involvement of neurotransmitters in the patho physiology of ADHD. Dopaminergic, serotonergic and noradrenergic system genes are involved in ADHD [19]. The possible cause of ADHD is abnormalities in functions and structure in connection between the frontal cortex and basal ganglia [29]. ADHD is a syndrome that shows impact on cognitive functions that are essential to the moment-to-moment apprehension of and response to the environment. An influential cognitive theory of ADHD identified that impairment in the executive control of inhibition as being a principal deficit. ADHD has been associated with anomalies in dopamine systems [29].

Neuro biology:

The neuro biology of ADHD is not completely understood [14]. ADHD is a syndrome that impacts the cognitive functions [20]. The core symptoms that characterize the disorder are the imbalances between the Dopaminergic and nor adrenergic systems [16]. The neuro biological substrates of ADHD are derived from neuro psychological, neuro imaging and neuro transmitter studies [19]. Research into the neuro biological features of ADHD in adults has had a substantial impact on establishing the validity of the disorder [20]. Changes in the levels of neuro transmitters and proteins in the brain have been observed using magnetic resonance spectroscopy (MRS) [12]. Abnormalities in different neuro chemicals in ADHD affected children are indicators of different neurological dysfunctions that can be related to lesions and damage from neonatal hypoxic ischemia. N-Acetyl Aspartate (NAA) is indicative of neuronal and axonal density and viability [12]. NAA reductions can be interpreted as evidence for neuronal/axonal loss and dysfunction in a particular area [12]. MRS study investigates the levels of neuro transmitters in brain [12]. Increased levels of glutamate may also be related to changes in dopamine levels associated with ADHD [12]. In ADHD affected children increased levels of glutamate is found in cingluate cortex [12]. Magnetic Resonance Imaging (MRI) based measures shows that cortical gray matter first increases in volume, followed by post adolescent decreases. Volume loss occurs earliest in primary sensory motor areas and later in the dorso lateral pre frontal cortex. These changes in volume of brain tissue are thought to represent developmental processes such as synapse formation and myelination and selective pruning and apoptosis that

are linked to increase in volume later in development [21]. Three regional findings are notable in individuals with ADHD. They are:

- Smaller MRI based volumes of caudate nucleus
- Difference in cerebellum in particular a smaller vermis
- The reductions in cortical gray matter were present in siblings with and with out ADHD [21].

ADHD risk genes directly impacts on fronto striatal gray matter volumes [21]. The concentration of striatal glutamate, glutamate/glutamine and creatinine are greater in patients with ADHD [7]. An imbalance between norepinephrine and dopamine results in ADHD. In patients with ADHD there may be an excess of norepinephrine in the locus ceruleus and deficiency of dopamine in the frontal meso limbic system [10]. The endocrine system is also putatively involves with ADHD [10]. The genes that encode Dopaminergic system includes dopamine transporter gene (dAT1) and dopamine 4 receptor gene (DRD4), Adrenergic receptor includes the genes that encode α2A and α2C and the serotonergic system includes the serotonin receptor 2A genes (HTR2A) and serotonin transporter [19]. Electronic testing like continuous performance tests and neuro psychological tests may contribute to the clinicians over all impressions but neither has good sensitivity nor specificity on their own diagnostic purposes [18]. Structural imaging techniques like computerized tomography of magnetic resonance imaging found the evidence for structural brain abnormalities among ADHD patients, with the most common findings being smaller volumes in frontal cortex, cerebellum and sub cortical structures [14]. ADHD associated fronto cortical system path ways are rich in catechol amines that are involved in the mechanism of action of stimulant medications that are involved in the treatment of the disorder. Imaging studies also implicate the cerebellum and corpus callosum in the patho physiology of ADHD [14]. Functional MRI studies have shown activity in the frontal striatal networks in adults with ADHD and activity in the anterior cingulated gyrus in subjects with out the disorder. Positron emission studies have been shown decreased frontal cortical activity in affected adults [18]. Children with ADHD show significantly lower intra erythrocyte magnesium levels [7]. Lower zinc levels are seen in children with ADHD [7]. ADHD risk genes directly impacts on fronto striatal gray matter volumes [21].

Diagnosis:

The diagnostic assessment process involves documenting the current and past symptoms, establishing that the symptoms cause impairment, obtaining a developmental disorder and psychiatric history and performing physical examination [18]. Current ADHD symptoms can be assessed by using standardized rating scales. Scales for adults typically contain the18 ADHD symptoms from the (Diagnostic and Statistic Manual of Mental Disorders) DSM-IV, each of which is rated on its frequency in past 6 months using a 4-point scale from 0-3 [18].

0-never or not at all
1-some times or some what
2-often or pretty much
3-very often or very much
Given according to the symptoms he or she experienced [18].

ADHD is diagnosed by DSM-IV-TR and it greatly impairs social and cognitive functions in affected individuals [12]. Regarding diagnostic guidelines, ICD-10 and DSM-IV share more similarities than differences [19]. The diagnosis of ADHD is made by careful clinical history.

DSM-III represented a paradigm shift as it began to emphasize inattention as a significant component of the disorder. The DSM-III definition also recognized developmental variability presentation of the disorder at different stages. DSM-III introduced a residual type of ADHD if the remaining symptoms continued to cause significant levels of impairment [14].The two widely used scales are:

1. Narrow scales: used specifically for ADHD
2. Broad scales: measures additional dimensions including co morbidity.

Broad scales are used in separating straight forward and complex cases [14].
Assessment in determining ADHD usually starts with three components:

1. Medical examination followed by
2. A clinical interview, which includes a family and developmental history and
3. A behavioral rating scale which consists of three scales:

- Parent
- Teacher
- Self [16].

Treatment:

The medications that are used for treatment of ADHD should be long acting. The longest acting stimulant medications last for 12 hrs, leaving a child untreated during evening and early in the morning hours. The children may be hyper active and irritable when the effect of drug decreases [22]. The children's compliance could be increased by the medications that are taken once in a day and also these medications can eliminate the need for students to receive a dose of medication at school [22]. Drugs used for treatment of ADHD mainly target dopamine and norepinephrine systems which are thought to be involved in the etiology of ADHD. Dopamine and norepinephrine are catechol amines with similar structures [22]. Nor epinephrine is involved in a number of cognitive functions mainly the signal processing [22]. Norepinephrine source in CNS is locus ceruleus, which induces a wakening alert state and to enhance informational processing and attention to environmental stimuli [22].

Treatment mainly includes:
Psychological
Pharmacological drugs.

Psychological treatment interventions includes education about the disorder, involvement in a support group, skills training like vocational, organizational, time management and coaching [18]. Children and adults with ADHD can have the dual benefit of providing support and social contacts as well as educating the patient about ADHD and useful coping strategies [18]. Behavioral and cognitive behavioral methods dominate all other psychological approaches in the treatment of ADHD [16]. Alternative treatment approaches such as dietary elimination strategies, nutritional supplements and herbal and homeopathic treatments have failed to be effective for treatment of ADHD [23].

Pharmacological treatment:
Medications for ADHD are mainly classified into two. They are:
First line treatment: eg: methyl phenidate, dextro amphetamine
Second line treatment: eg: desipramine, buproprion [18].

The optimal dose is considered when no further reduction in ADHD symptoms occurs and side effects are still judged to be manageable [18].
Conventional therapy is often multimodal including both the behavioral therapies and medication. Many of the approved drugs for ADHD are stimulants, which works by increasing dopamine levels. FDA approved stimulants includes methyl phenidate, amphetamine, dextro amphetamine, dex methyl phenidate, pemoline [7].

Now a days sodium valproate is widely used in the treatment of psychiatric disorders like bipolar I disorder, schizo affective disorder, panic disorder and post traumatic stress disorder [17].

The drugs that are mainly used in the treatment of ADHD are:

- Stimulants
- Tri cyclic anti depressants
- Mono amine oxidase inhibitors
- Buproprion
- Anti hypertensives
- Selective serotonin reuptake inhibitors

- Stimulants:

Eg: Pemoline, Methyl phenidate
Stimulants are the first line treatment. Stimulants such as amphetamines, caffeine and cocaine cause an inhibitory affect on the brain stem circuiting via the descending neural pathways from self regulation region of the brain. This enables a person to ignore new stimuli and hold the attention with in a working memory system where goal setting, self reflection, problem solving and other cognitive processes can take place [16].

Side effects:
Weight loss, stomach ache, headache, initial insomnia, and irritability [22].
Pemoline is used rarely in treatment of ADHD but it is associated with life threatening hepato toxicity [22].

Methyl phenidate:
Methyl phenidate crosses the blood brain barrier rapidly with the most marked reuptake in the striatum [15]. Methyl phenidate is an indirectly acting sympatho mimetic. It is most widely used clinically. It is well absorbed from gastro intestinal tract (GIT) and reaches peak plasma levels in 1-2 hrs. It has a short half life of 2-3 hrs and thus requires multiple daily dosing. It is metabolized completely in liver. It is thought to affect catechol amines, the neuro transmitter systems which are believed to be involved with ADHD patho physiology [10]. It appears that methyl phenidate affects the Dopaminergic system [10]. Methyl phenidate increases dopamine functioning in the basal ganglia in the people diagnosed with ADHD [16]. Short effects on the cardinal symptoms of methyl phenidate on ADHD are increased attention span, increased concentration ability, decreased activity, increased cognitive performance and increased oppositional behaviors [10].
Side effects of methyl phenidate:
Long term side effects are mainly suppression of height and weight gain [16].

- *Tri cyclic anti depressants:*

Eg: Imipramine and Desipramine

Anti depressants are used in ADHD when the patient does not respond to stimulant medication [18]. Tri cyclic anti depressants shown to have greater effect in ADHD than the stimulants [22].tri cyclic anti depressants use in children has declined because of their possible cardiac side effects and associated monitoring [22].
Side effects:
Dry mouth, constipation, sedation and weight gain [22].

- *Mono amine oxidase inhibitors:*

Eg: clorgyline, moclobemide, selegelline
Mechanism of action of mono amine oxidase inhibitors in reducing ADHD symptom severity is probably related to blockage of metabolism of nor epinephrine and dopamine [22].

- *Selective serotonin reuptake inhibitors:*

Eg: fluoxetine, sertraline
These drugs appear to be safe in combination with stimulant therapy and also reduce symptoms of depression [22].

- *Buproprion:*

It is effective in children and adolescents with comorbid psychiatric disorders [22].

- *Anti hypertensives:*

Eg: α2A adrenergic agonists like Clonidine, Guanfacine
These drugs indirectly affect the norepinephrine discharge rates in the locus ceruleus [22].
Side effects:
Rebound hyper tension and sedation [22].

- *Atomoxetine:*

It is the first non stimulant medication to be developed specifically for the treatment of ADHD [18]. A novel compound which is a specific and potent norepinephrine reuptake inhibitor that is similar in structure to fluoxetine [22].
Side effects:
Anorexia, agitation, nausea, restlessness, drowsiness, headache and seizures [24].

- *Cholinergic drugs:*

Cholinergic drugs have also been used in treating ADHD. This is based on nicotine hypothesis of ADHD, because nicotine has been shown to enhance Dopaminergic release [16].

- *Vitamin-B6:*

It is an important cofactor in numerous metabolic reactions including the metabolism of serotonin, gamma amino butyric acid (GABA), nor epinephrine and dopamine [7]. Lower levels of zinc are seen in children with ADHD [7]. Iron significant decrease in ADHD is seen with iron supplementation [7]. In CNS lead may contribute to Dopaminergic dysfunction and may disrupt the structure of the blood brain barrier, which is essential for brain integrity. Iron supplementation protects the integrity of blood brain barrier against lead insults and iron deficiency could increase the toxic effect of lead [7].

Non-research supported ADHD treatment:

- Anti yeast medications
- Chiropractic manipulation
- Dietary manipulation
- Herbal treatments like gingko
- Megavitamin therapy

- Sensory integrative training [24].

CONCLUSION

Attention deficit hyperactivity disorder is a developmental neurological disorder which occurs mainly due to genetic and environmental factors and some medications like Phenobarbital. This disorder can be treated by various medications like stimulants, tri cyclic anti depressants and some herbal treatments like gingko but these cannot cure the disease completely and some side effects are seen with these drugs. Hence research has to be done for the development of drugs which cure the disease completely without showing side effects.

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