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RESEARCH ARTICLE

AN OVERVIEW OF THE CAUSATIVE RISK FACTORS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER AMONG CHILDREN

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Abstract

Attention deficit hyperactivity disorder is a complicated disorder that affects children's cognition and behavior. The exact cause of ADHD is not known; however, multiple risk factors may be involved. This study aims to provide an overview of the different risk factors involved in the development of ADHD through reviewing and summarizing all recently published researches in this respect. Multiple factors were evaluated to find out their relation to ADHD. Various genetic loci and mutations were found to be linked to ADHD susceptibility. Environmental factors as prenatal smoking, maternal obesity, vitamin D and minerals deficiencies, birth-related problems, pesticides, and lead exposure, artificial food coloring, and sugar consumption were investigated and proven to increase ADHD. Structural brain abnormalities and traumatic brain injury were also involved as risk factors of ADHD. Although the exact causes of ADHD are not discovered, multiple genetic, environmental and structural brain abnormalities proved to play a role in ADHD development. Mutations in Latrophilin 3 (LPHN3) gene linked with increase ADHD susceptibility. Reduced gray matter volume may contribute to ADHD development. Sugar consumption and artificial food colorings increase hyperactivity in both ADHD and normal children.

Introduction:-

Attention deficit hyperactivity disorder (ADHD) is a neurobehavioral disease that is characterized by inattention and hyperactivity-impulsivity with an estimated global prevalence of 2.2 to 17.8%1. ADHD is considered to be a childhood disease; it commonly affects preschool children with a decline in symptoms during maturation to adulthood. According to gender, males are three times more likely to be affected by ADHD than females, and primary school children are twice more likely than adults 2.

Up to date, the exact cause of ADHD is unknown. Most of the studies support that ADHD is a heritable disease associated with multiple gene mutations and many other environmental factors including prenatal as well as perinatal factors 3. These environmental factors include prenatal maternal obesity and Tobacco usage, food additives, preterm birth, white-gray matter distributions abnormalities and chronic deficiencies in certain types of nutrition and minerals, for example, iron, zinc, magnesium and polyunsaturated omega-3 4-7.

The aim of this study is to provide an overview of the different risk factors involved in the development of ADHD through reviewing and summarizing all recently published researches in this respect.This wouldpromote the

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awareness and knowledge of the community about the possibleADHD causativefactors, and help in designing preventive strategies to decrease the incidence of ADHD.

Discussion:-

Genetic background:

ADHD is believed to have a very strong relation with gene abnormalities due to the high incidence rate among families and twins. Its heritability estimated to be 40-90% 8.

Studies confirmed many chromosomal regions that are more likely to be linked with ADHD occurrence, these are 5p, 6q, 7p, 11q, 12q, and 17p, however, studies are still looking at the exact mutations in ADHD susceptible children 9. Many studies demonstrated the high relation between Latrophilin 3 (LPHN3) and ADHD occurrence; LPHN3 can increase the ADHD risk 1.2 folds and the population attributable risk (PAR%) caused by this gene is almost 9%. A case-control study of 290 ADHD patients and 340 controls aged 6-18 years was done with multiple tests to investigate the genes polymorphism and ADHD susceptibility, the results showed that the genetic variants of these four(SLC6A2, SLC6A3, SLC6A4, and LPHN3) genes, particularly LPHN3, was associated with ADHD occurrence 10. Another study was performed in Korea to demonstrate the relation between LPHN3 rs6551665 A/G polymorphism and ADHD, data from 150 ADHD children and 322 controls were collected to investigate the genes by PCR-RFLP, the results confirmed that the LPHN3 rs6551665 GG genotype and G allele cause a significant effect on the ADHD 11.

On the other hand, a meta-analysis study that was done to determine the candidate genes for ADHD; DRD4 and DRD5 were significantly associated with ADHD however, the DAT1 gene did not appear to be involved in ADHD occurrence 12. Many recent studies showed an association between one allele of the serotonin (5-HTT) and ADHD susceptibility13.

Prenatal smoking and nicotine exposure:

In utero exposure to nicotine as a result of tobacco smoking is a subject of concern worldwide. Nicotine exposure includes tobacco smoking, environmental tobacco smoke (ETS) and nicotine replacement therapy. The prevalence of maternal smoking during pregnancy is estimated by European birth cohorts to be ranged from 18 % to 34% 14. Many previously published studies observe the high connection between ADHD symptoms and prenatal smoking. 30,552 parents were surveyed to demonstrate the effect of smoking during pregnancy on ADHD, the results showed that smoking during pregnancy can increase the ADHD risk 2.64 times 15. Yochum C et al. demonstrated the relationship of prenatal cigarette smoking and behavioral abnormalities through the alternation of serotonin, marked reduction of striatal and cortical dopamine level and brain-derived neurotrophic factor (BDNF) these based on authors' studies on rats 16. Linnet KM et al. reviewed 24 studies published between (1973-2002) about the relationship of prenatal smoking and ADHD related symptoms, the results concluded that most of the collected studies support the evidence of this causative risk factor. On the other hand, some researchers found no association between ADHD and maternal smoking 17. Obel C et al. published study in October 2015 by Danish national register-based cohort, the data of 968,665 singletons were collected and analyzed by the International Classification of Diseases (10th version) for the diagnosis of hyperkinetic disorder (HKD) the results of this study suggested no strong association between prenatal smoking and ADHD occurrence 18. Another study was suggested the same idea about the unclear relationship between maternal smoking during pregnancy and ADHD related symptoms, in this study a number of 173 families were surveyed and the data analyzed by Child Behavior Checklist/Teacher Report Form (CBCL/TRF), the results showed that maternal smoking-ADHD relationship was due to familial confounding rather than a real causal effect 19.

Role of maternal obesity:

The prevalence of obesity is increased in the last decades indicating the sedentary lifestyle of all obese people. According to WHO, the last report about the worldwide prevalence of obesity showed that 600 million obese persons complaining from obesity, 15% of them are women 20. Obese pregnant had a two-fold increased risk of having an ADHD child compared with non-obese pregnant 21. A population-based prospective cohort study of 1714 children investigated the relationship between pre-pregnancy obesity and ADHD occurrence by using DSM-IV symptoms list, the study concluded that pre-pregnancy obesity was associated with ADHD-related symptoms 22. Another prospective cohort study of 12,556 school-aged children was conducted to conflict the relationship between pre-pregnancy obesity and AHD, the results showed that increasing BMI in pregnant women may trigger ADHD symptoms 23.

On the other hand, a large population sample of 673, 632 were followed to determine the relation between ADHD and maternal obesity, the study concluded that the association between ADHD and pre-pregnancy obesity that recorded in many previous studies is due to unmeasured family confounding factors rather than a direct effect 24.

Artificial food coloring and sugar consumption:
The relation between Artificial Food Colors (AFCs) and children's behavior is a very ancient concern, over 35 years many studies were conducted to confirm this relation. Most studies concluded that AFCs are not the main cause of ADHD however, they increase the symptoms of hyperactivity in both ADHD and normal children 25. Randomized, double-blinded, placebo-controlled trial was done in order to investigate the relation between AFCs consumption and hyperactivity in 3-years and 8-9 years old children, and the data of 153 3-year old and 144 8-9-year old children were collected to investigate this association, based on drinking of beverages containing sodium benzoate and AFCs; results suggested that sodium benzoate and artificial food coloring diet increase the risk of hyperactivity behavior in children 26. Nigg JT et al.meta-analysis study was conducted by many researchers from Oregon Health and Science University and the Life Sciences Research Organization, they found that elimination of food dyes and food additives from the diet can reduce the symptoms of hyperactivity among ADHD children by 33% 27.

Vitamin D deficiency and ADHD:
Vitamin D deficiency (<30 ng/ml) and chronic deficiency in the body' minerals such as iron, zinc, magnesium and polyunsaturated omega-3 are reported to play a large role in ADHD pathophysiology and are also involved in the development of many other psychiatric diseases including schizophrenia, autism, and depression 28. In a case-control study was conducted in Qatar, a number of 630 children with ADHD and 630 controls both aged 5-18 years old were investigated using multiple of blood tests like iron, ferritin levels, vitamin D, magnesium, calcium and phosphorus levels, the results confirmed that low blood level of iron, ferritin and vitamin D is associated with ADHD 29. Brain iron deficiency is considered to be highly involved in ADHD pathophysiology, 18 ADHD children with 18 controls were investigated by MRI to measure the level of brain iron in pallidum, putamen, caudate, and thalamus and blood sampling to measure the serum ferritin in both ADHD and controls, the results showed that brain iron in thalami is significantly low in ADHD children compared with controls 30. Many studies suggested that low level of blood iron may be related to the pathophysiology of ADHD due to its role in dopamine and noradrenalin production, to evaluate this relation a study on 113 children 5-15 years was conducted, the ferritin level was <20 ng/ml in 59% of children and >20ng/ml in 49%, the results suggested the association between low iron level and ADHD pathophysiology 31.

On the other hand, a meta-analysis study reviewed 17 studies to investigate the relation between serum zinc level and ADHD susceptibility; they included 2177 ADHD children and 2900 controls, the meta-analysis results showed a significant relation($P<0.003$) between ADHD and low serum level of zinc 32. A case-control study was conducted in Egypt to confirm the correlation between serum level of minerals (magnesium, zinc, ferritin, and copper) and ADHD, 58 ADHD children with 25 controls were investigated by lap investigations and the results showed a significant relationship between serum deficiencies of magnesium, zinc, and ferritin and ADHD susceptibility, however, no relation between copper deficiency and ADHD 33. Nutrition deficiency of omega-3 (HUFA) has adverse side effects on the brain and neuron development. A meta-analysis study reviewed 9 studies n=586 to investigate the relation between omega-3 deficiency and ADHD, the results confirmed thisrelation significantly $P<0.001$ 34.

Gray and white matter abnormalities*:*
Gray and white matter abnormalities confirmed by many researchers as a risk factor for ADHD development. Castellanos FX et al. studied the brain volumes using anatomical MRI to identify their relationship with ADHD; a number of 57 boys and 55 healthy control aged 5-18 years were investigated, measurement of brain volume in different regions including globus pallidus, amygdala, cerebellum cerebrum, caudate nucleus, putamen hippocampus and temporal lobe in both halves were obtained; the results showed that ADHD children have 4.7% smaller cerebral volume compared with controls 35. Another MRI study was confirmed the association between gray matter reduction and ADHD 36. Meta-analysis of fourteen neuroimaging studies that were conducted between 2001-2011 comprising 378 ADHD children and 344 controls to investigate the correlation between gray matter volume and ADHD and the effect of stimulant drugs in increasing this volume, the results concluded that ADHD patients had reduced gray matter volume mainly in the basal ganglia due to developmental delay also, the results showed that using stimulants drugs may normalize these structural abnormalities 37. In a voxel-based morphometric study, 25 ADHD children and 25 control aged 6-16 year were investigated, the results showed a general reduction in the brain

global volume 5.4% compared to matched controls and gray matter reduction with no obvious difference between ADHD and control groups in white matter 38. Furthermore, Pastura and his colleagues conducted a study using advanced techniques in magnetic resonance imaging of the brain; they concluded that cortical gray matter reduction is associated with ADHD in children39.

Birth-related problems:
Many recently published studies confirmed the significant relation between ADHD diagnosis and birth-related problems such as very preterm and very low birth weight (VP/VLBW). In 2015, the prevalence of preterm births is estimated by WHO to be 15 million annually. The rate of preterm birth is ranged from 5% to 18% of all born babies 40.

In a longitudinal cohort study, 260 very preterm and low birth weight children were followed from birth to adulthood to investigate the relationship between preterm and low birth weight children and their chance of ADHD diagnosis, the data were collected and assessed in 6, 8 and 26 years old, at each assessment preterm and low birth weight children had a significant attention impairment such as reduced attention span which make them more susceptible for ADHD than their term-born controls 41. Ochiai M et al. longitudinal study in 2015, assessed 160 preterm and low birth weight children from birth to 9 years old, according to ADHD rating scale (ADHD-RC) the results showed a significant relation ($P<0.01$) between ADHD and very preterm children 42. A cohort study of all children born between 1991-2005 was assessed the risk of developing ADHD as a result of preterm birth, a number of 10,321 ADHD children compared with 38,355 controls, the results suggested that the risk of ADHD is markedly higher at children who born at 23 weeks compared with normally born children(38-42 weeks)43. Another study concluded that extremely preterm children are associated with ADHD symptoms 44.

Environmental toxins:
Organophosphate pesticides are potent toxins that target the nervous system of insects, it was believed that exposure to these toxins may cause cognitive decline and behavioral impairment in children. The basic mechanism of organophosphate pesticides is inhibition of acetylcholinesterase, cholinergic signaling and growth factors mediators 45. To determine the relationship between urine concentration of dimethyl alkylphosphate (DMAP) and ADHD, data from 1139 children were collected and analyzed according to DSM-IV criteria, 119children were found to match the diagnostic criteria of ADHD; most of them had a high level of (DMAP). This study concluded that 10-folds increase in urine concentration associated with an odds ratio of 1.55 46. Trichlorophenols (TCPs) is another class of pesticides (organochlorine) which was known for its neurotoxicity effects. Exposure to (TCPs) may lead to behavioral impairment and ADHD in school-aged children 47.

Lead is also considered to be one of the most common environmental toxins. It is almost available everywhere in the environment. High lead concentration in the blood can cause cognitive decline associated with poor IQ scores in children, however, this can also be recorded even when the blood lead level below 10 µg/dl 48. A study was conducted by National Health and Nutrition Examination Survey on 4704 children aged 4-15 years indicated that ADHD diagnosis is four times more likely among high blood lead levels compared to normally developing children 49. Additionally, study was conducted in South Korea on 1778 children to investigate the relationship between blood lead level and ADHD, by using the Korean version of the abbreviated Conners' scale for ADHD diagnosis with exclusion of confounding factors, they found a significant association between BLL >2.5 µg/dl and ADHD development 50. In summary, lead even in small concentrations can act as a risk factor of ADHD.

Conclusion:-

The exact causes of ADHD are not discovered yet; they may vary depending on each individual himself. However, multiple risks may play a role in increasing the susceptibility of children to develop ADHD; these include genetic factors, environmental factors, and structural brain abnormalities. Genetic factors play a central role in the pathophysiology of ADHD with estimated disease heritability of 40-90%.

Latrophilin 3 (LPHN3) is the most common gene that linked with ADHD; mutations in this gene can increase ADHD susceptibility. Multiple environmental factors are proved to be linked to increasing the risk of ADHD development as vitamin D and minerals deficiencies, birth-related problems and pesticides and lead exposure. Prenatal smoking, nicotine exposure, and maternal obesity are the three maternal related risk factors involving in ADHD. Some structural brain abnormalities as the reduced volume of gray matter are proved to be linked to increased ADHD risks. Data regarding the relationship between brain injuries and the development of ADHD are

contradictory. Sugar consumption and artificial food colorings were long believed to be linked to ADHD development; multiple studies have shown that AFCs are not the main cause of ADHD; however, they increase the symptoms of hyperactivity in both ADHD and normal children. More studies may be required to explain the pathophysiologic mechanisms through which these different risk factors lead to ADHD development. Also, large multicenter studies need to be carried out in Arabic populations to find out if there are any particular risk factors are linked to ADHD development in our locality. Data collected from these studies may be the basis of large campaigns to increase community awareness about ADHD and its risk factors.

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