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Review Article

A REVIEW ON ASSOCIATION BETWEEN PSYCHIATRIC DISORDERS AND IRON DEFICIENCY ANAEMIA IN A TERTIARY CARE TEACHING HOSPITAL

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ABSTRACT

Iron has an important role in cognitive, behavioral, and motor development. Iron deficiency causes abnormal dopaminergic neurotransmission and may contribute to behavioral disorders. Different types of psychiatric disorders are present in the Indian population. Bipolar disorder, unipolar disorder, schizophrenia, attention deficit hyperactivity disorder, anxiety disorder are some of them. As there are only few studies in Indian literature regarding the association between iron deficiency anaemia and psychiatric disorders, the present review is undertaken. This review is designed to investigate the correlation of iron deficiency anaemia and psychiatric disorders and thus to find out the influence of iron deficiency anaemia in psychiatric disorders. The review shown that there exists a correlation between psychiatric disorders and iron deficiency anaemia.

Keywords: Iron deficiency anaemia, Psychiatric disorders, Iron, Total iron binding capacity, Haemoglobin.

INTRODUCTION

Iron deficiency anemia is a common form of nutritional disorder, iron deficiency results in anemia as iron is necessary to make hemoglobin, key molecule in red blood cells responsible for the transport of oxygen. In iron deficiency anemia, the red cells appear abnormal and are unusually small (microcytic) and pale (hypochromic). The pallor of the red cells reflects their low hemoglobin content. The prevalence of iron deficiency anemia spans all ages and races. In children, iron deficiency causes developmental delays, behavioral disturbances, failure to thrive (grow) and increased infections.

Iron deficiency is a major problem in developed countries such as the US, Canada, the UK and across Europe. In developing countries, iron deficiency anemia is frequently exacerbated by malaria and worm infections. Iron deficiency causes approximately half of all anemia cases worldwide, and affects women more often than men. Iron-deficiency anemia affects nearly 1 billion. Iron-deficiency anemia for infants in their earlier stages of development may have greater consequences than it does for adults. An infant made severely iron-deficient during its earlier life cannot recover to normal iron levels even with iron therapy. In contrast, iron deficiency during later stages of development can be compensated with sufficient iron supplements. Iron-deficiency anemia affects neurological development by decreasing learning ability, altering motor functions, and permanently reducing the number of dopamine receptors and serotonin levels.

Iron deficiency anaemia is characterized by a defect in hemoglobin synthesis owing to significant iron deficiency, resulting in the reduced capacity of the red blood cells to deliver oxygen to body cells and tissues, and many clinical symptoms, such as pale conjunctiva, shortness of breath, dizziness, and lethargy.

Iron is an essential component of hemoglobin, myoglobin, and many enzymes in cellular metabolism and DNA replication and repair. It also plays a crucial role in the development of the central neurological system, autoimmune system, endocrine system, and cardiovascular system. In the development of the brain, iron accounted for the myelination of white matter and the development and functioning of the different neurotransmitter systems, including the dopamine, norepinephrine, and serotonin systems. In vivo microdialysis studies using post-weaning iron-deficient rats and mice demonstrated that they exhibited deficits in intracellular dopamine concentrations and in the density of dopamine and dopamine transporter receptors, with variable amounts of loss by brain region. Anderson et al. showed that decreased iron significantly reduced extracellular concentrations of norepinephrine in the caudate putamen, and altered levels of norepinephrine due to reduced iron levels may be the result of changes in the expression of norepinephrine transport and norepinephrine receptor proteins in the locus ceruleus and basal ganglia. A reduction in serotonin transporter binding was noted in the nucleus accumbens and olfactory tubercle in iron-deficient rats, and the serotonin concentration in the brain was significantly correlated with the non-heme iron level.

Iron deficiency anaemia and iron deficiency were significantly associated with an alteration of monoamine neurotransmitters and the abnormal myelination of white matter, and is probably related to childhood/adolescence-onset psychiatric disorders. There is well documented evidence in the literature that iron deficiency anaemia has a significant influence on cognitive development, intelligence, and developmental delay. Some clinical studies supposed that brain iron deficiency involved in the pathophysiology of attention deficit hyperactivity disorder (ADHD) and ferritin level was related to behavioral symptoms in ADHD patients.

This review is done to understood how various psychiatric disorders are correlated with iron deficiency anaemia based on various studies.

REVIEW OF LITERATURE

Mu-Hong Chen[1] *et al.* (1996-2008) conduct a nation wide population based study on association between psychiatric disorders and iron deficiency anemia among children and adolescents. Utilizing the National Health Insurance Database from 1996 to 2008, children and adolescents with a diagnosis of IDA were identified and compared with age and gender-matched controls (1:4) in an investigation of the increased risk of psychiatric disorders. This study, using a nationwide population-based insurance database with a case–control method and the largest sample size, attempted to clarify the association between IDA and various psychiatric disorders among children and adolescents with IDA. We hypothesized that children and adolescents with ADHD exhibited the higher risk of having a psychiatric disorder.

Statistical Analysis

For between-group comparisons, the independent t test was used for continuous variables and Pearson's X2 test or Fisher's exact test was applied for nominal variables, where appropriate. Multiple logistic regressions were performed to calculate the OR with 95% confidence intervals (CI) after adjusting for ulcer, metrorrhagia, and premenopausal menorrhea (because ulcer and metrorrhagia were two important risks causing IDA of children and adolescents). A two-tailed P-value of less than 0.05 was considered statistically significant. All data processing and statistical analyses were performed with Statistical Package for Social Science (SPSS) version 17 software (SPSS Inc) and Statistical Analysis Software (SAS) version 9.1 (SAS Institute, Cary, NC).

Results

A total of 2957 patients with IDA, with an increased risk of unipolar depressive disorder (OR = 2.34,95% CI = 1.58 ~ 3.46), bipolar disorder (OR = 5.78, 95% CI = 2.23 ~ 15.05), anxiety disorder (OR = 2.17, 95% CI = 1.49 ~ 3.16), autism spectrum disorder (OR = 3.08, 95% CI = 1.79 ~ 5.28), attention deficit hyperactivity disorder (OR = 1.67, 95% CI = 1.29 ~ 2.17), tic disorder (OR = 1.70, 95% CI = 1.03 ~ 2.78),

developmental delay (OR = 2.45, 95% CI = 2.00 ~ 3.00), and mental retardation (OR = 2.70, 95% CI = 2.00 ~ 3.65), were identified. A gender effect was noted, in that only female patients with IDA had an increased OR of bipolar disorder (OR = 5.56, 95% CI = 1.98 ~ 15.70) and tic disorder (OR = 2.95, 95% CI = 1.27 ~ 6.86). We conclude that iron deficiency increased the risk of psychiatric disorders, including mood disorders, autism spectrum disorder, attention deficit hyperactivity disorder, and developmental disorders. Further study is required to clarify the mechanism in the association between IDA and psychiatric disorder.

Sajed Faisal Al-Ali[2] *et al.* (2014) conduct a study on association between autism spectrum disorder and iron deficiency in children diagnosed autism spectrum disorder in the northern west bank. 90 children with an age range of 3 to 13 years participated in a case control study distributed into study group and two control groups. Thirty children diagnosed with autism according to DSMIV and ICD-10 criteria served as a study group, 30 children with mental disorders other than autism served as a control group, and 30 typically developing children taken from the public functioned as a second control group. The three groups were matched for age, gender and geographical area. Serum ferritin, hemoglobin, hematocrit, mean corpuscular volume, and red cell distribution width values were measured and analyzed with food habit survey and demographic data. ID was detected in 20% (N = 6/30) of autistic children based on Serum ferritin level (SF< 10µ/l),compared with 0% for the two control groups (p= 0.0001). Anemia was defined as hemoglobin <110g/l for children under the age of 6 years and hemoglobin <120g/l for children between 6 and 13 years of age.When analysis done for HGB to these six children (children who have low serum ferritin); it was found that 66.6% (4/6) of the children two were pre-school male children (HGB is less than 110g/1), and the other two were one male and one female of school children (HGB is less than 120g/l) have iron deficiency anemia, and the iron deficiency anemia was 13.3% (4\30) for all autistic group. The results indicated that these differences were for males. It was found also that the frequency of low iron intake in these children was associated with feeding difficulties andfood selectivity; there was a significant difference between children in the autistic group who chose foods with a red color as a favorite 23% (7/30) compared to the other two control groups: 0%, respectively (p= 0.0001). The results demonstrated also a significant difference in the frequency of snacks per day (≥ 4) in autistic children 40% (12/30) compared to both mental disorder 16.7 % (n = 5/30) (p = 0.006) and typically developing children 6.7% (n = 2/30) groups (p = 0.001). Results of this study indicated that there is an association between autism, iron deficiency and anemia.

Low levels of serum ferritin in autistic children might be a sign of iron deficiency and an early precursor of iron deficiency anemia. These findings suggest that food selectivity is more common in children with autism than in typically developing children. These findings suggest that ferritin levels should be measured in children with autism as a part of routine investigation.

Shruti Srivastava[3] *et al.* (2010) conduct a cross sectional study on iron profile estimation in children of behavioral disorders. The sample consisted of Forty children in the age group of 5 to 14 years suffering from behavioral disorders. Haemoglobin, Mean Corpuscular Volume, Mean Corpuscular Hemoglobin, Serum Iron, Total Iron Binding Capacity, Peripheral smear, Percentage transferrin saturation, serum ferritin estimations were done. The behavioral symptoms were scored on Achenback Child Behavior Checklist. Statistical analyses were performed using the *t* test and *X*2 test for between-group comparison of biological measures and Pearson test for correlations between symptom severity and serum ferritin levels. The mean age of the sample was 9.72 + 3.19 years with 65% male and 35% female children. Results: Iron deficiency anemia was present in 75% of the children with behavioral symptoms. Serum ferritin was abnormal (<20micrograms/litre) in 67.8% of the children. There was statistically significant association between pica and iron deficiency anemia (p<0.001). Serum ferrittin levels correlated negatively with behavioral symptoms (r=-.067), though not significant. The study concluded that there is a need for correction of Iron

deficiency anemia at a war footing especially in a developing country like India as it leads to behavioral problems.

Rebecca J. Stoltzfus[4] *et al.* conducted comprehensive reviews of published literature linking iron deficiency to disability and death for four potential outcomes: child mortality, perinatal mortality, maternal mortality and mild mental retardation. For all of these outcomes, the best available data were prospective observational studies in which anaemia or haemoglobin concentration was the risk factor. Data on child mortality were not adequate for this task, although a true risk cannot be precluded by the data. Summary relative risks for perinatal mortality (10 studies), maternal mortality (six studies) and mental retardation (five studies) were estimated using random effects models (both mortality outcomes) or a fixed-effects model (retardation) and weighting individual estimates by the inverse of their within-study variance. For mortality outcomes, the bivariate relations between haemoglobin and death were used. In two studies of perinatal mortality, unadjusted and multivariate adjusted odds ratios were compared to assess the potential degree of bias in the unadjusted associations. For mental retardation, published multivariate adjusted relations between haemoglobin and IQ were used. Global anaemia prevalence data were supplied by the World Health Organization (WHO), and converted to mean haemoglobin concentrations, assuming normal distribution and observed standard deviations from a large number of studies. To estimate the haemoglobin distribution if iron deficiency were corrected, we assumed the prevalence of anaemia in women and children would be reduced by 50%. On average, for the world, this would increase haemoglobin concentration by about 0.45 g/dl (range: 0.0 g/dl to 1.28 g/dl).

After adjusting for several important covariates, the OR for mild or moderate mental retardation at school age remained significant in their model, which treated haemoglobin concentration as a continuous risk factor. This finding supports the plausibility of our assumption that the association between mean cognitive scores and anaemia is associated with increased risks of mild mental retardation. The available evidence suggests that iron deficiency anaemia contributes substantially to death and disability in the world. The great majority of this disease burden is in Africa and Asia and derives from anaemia in pregnancy and early childhood. This evidence is based on critical assumptions, most importantly, that the observed prospective relationships are causal in nature, and that the relationships analysed using anaemia as the risk factor pertain equally to iron deficiency anaemia as one particular form of anaemia.

Jyoti Batra and Archana Sood[5] conduct a review on iron deficiency anaemia: effect on congnitive development in children. Studies have indicated that anemic children of less than 2 years have failed to catch up with non anemic children even after iron supplementation. Anemic children of more than 2 years also usually had poorer cognition and school achievements as compared to non-anemic once. They usually catch up in cognition with repeated testing and treatment but not in school achievement. Iron deficiency identifies children at concurrent and future risk of poor development. It is also concluded that iron deficiency is usually associated with many psychosocial, economic and biomedical disadvantages. The iron deficiency during developmental stages of brain (i.e. fetus) may also cause irreversible disturbances and damages to GABA neurotransmitter system. Most of the co-relational and experimental studies done earlier confirmed the hypothesis that iron deficiency of mild to moderate nature has an adverse effect on congnitive development. Therefore, it may be logical to suggest that impairment of higher mental function like cognition and learning in humans may be linked to changes in neurotransmitter receptors and consequent signal transduction process in the nervous system.

Thach Duc Tran[6] *et al.* (2009) conducted a study on psychological and social factors associated with late pregnancy iron deficiency anaemia in rural vietnam: a population-based prospective study. The aim of this study was to examine the relationships between psychological and social factors and late pregnancy IDA among pregnant women in rural Viet Nam. Participants were recruited by a two-stage sampling procedure. First, an independent statistician randomly selected 50 of the 116 communes in the province. Then, all

women who were 12 to 20 weeks gestation living in the selected 50 communes during the enrolment period (from December 2009 to January 2010) were eligible and invited to participate in the study. In total 497/523 (97%) eligible women were recruited and assessed at WI. There were 78 women (16%) lost to follow-up at W2 because they had already given birth (47 women); were away from the area at the time the data collection team visited the commune (15 women); had a stillbirth prior to follow-up (7 women); or withdrew from the study (9 women). At W2, 24 women refused Hb tests and 41 women did not provide a sample of venous blood. Overall, 378 of 523 (72.3%) eligible women provided complete data and were included in the statistical model analyses. There were no significant differences between women who did or did not provide complete data in terms of sociodemographic and reproductive characteristics, exposure to gender-based violence, IDA at W1 (2.4 vs. 2.5, p=0.9) and CMD at either W1 (38.9% vs. 48.7%, p=0.16) or W2 (28.0 vs. 29.3, p=0.87).

The study concluded that Antenatal IDA and CMD are prevalent public health problems among women in Viet Nam. The link between them suggests that while direct recommendations to use iron supplements are important, the social factors associated with common mental disorders should be addressed in antenatal care in order to improve the health of pregnant women and their infants.

Suying Chang [7] *et al.* (2002-2006) conducted a study on effect of iron deficiency anemia in pregnancy on child mental development in rural china. The aim of this study was to determine the impact of iron deficiency anemia (IDA) in pregnancy on young child development. A 2-year follow-up of 850 children born to women who participated in a double-blind cluster randomized controlled trial of prenatal micronutrient supplementation in western rural China. These women were randomly assigned to receive either daily folic acid, iron/folic acid (60 mg iron), or multiple micronutrients (with 30 mg iron) during pregnancy. Children were categorized into the prenatal-IDA and prenatal–non-IDA groups based on the mother's hemoglobin in the third trimester. Each group contained 3 subgroups based on mother's treatment: folic acid, iron/folic acid, and multiple micronutrients. Bayley scales of infant development were administered to the children to assess their development at 3, 6, 12, 18, and 24 months of age. Compared with the prenatal–non-IDA group, the prenatal-IDA group showed a significantly lower mental development index at 12, 18, and 24 months of age. The adjusted mean difference was 5.8 (95% confidence interval [CI], 1.1–10.5), 5.1 (95% CI, 1.2–9.0), and 5.3 (95% CI, 0.9–9.7), respectively. Further analysis showed that the mental development indexes in the prenatal-IDA group and prenatal–non- IDA group were similar with supplementation of iron/folic acid but were significantly lower in the prenatal-IDA group with supplementation of folic acid or multiple micronutrients. The study concluded that prenatal IDA in the third trimester is associated with mental development of the child. However, prenatal supplementation with sufficient iron protects child development even when the woman's IDA was not properly corrected in pregnancy.

CONCLUSION

Iron is an essential nutrient not only for the normal growth, health, and survival, but also for normal mental and motor development and cognitive functioning. Iron deficiency (ID) is a major public health problem affecting more than 2000 million persons worldwide. Iron deficiency with anaemia is associated with significantly poorer performance on psychomotor and mental development scales and behavioral ratings in infants, children and adolescents. A large number of studies have been conducted to examine the effects of iron deficiency and iron deficiency anaemia on mental outcomes. This review concluded that there exists an association between iron deficiency anaemia and various psychiatric disorders.

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