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Original Research Article

Serum Vitamin D and Serum Ferritin Levels in Children with ADHD: An Analytical Study

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Abstract

Aim: The aim of the study was to study the association between Serum Vitamin D and Serum Ferritin levels in children with ADHD.

Methods: The study was conducted in the Department of Pediatrics, for the period of 1 year. A total of 100 children meeting the inclusion criteria were enrolled in the study. Subjects included all new or follow-up patients with diagnosed or suspected ADHD and healthy children of the comparable sex and age group attending the pediatric outpatient department (OPD) were taken as controls. Informed and written consent was taken from parents and assent from children above 12 years of age to participate in the study.

Results: 50 cases were diagnosed with ADHD and their results were compared to age and sex matched controls. Serum Ferritin and Vitamin D levels were measured in both cases and controls. Since we matched age, similar age distribution was present in controls. The study found a significant difference in the mean value of serum ferritin levels in cases and controls (p=0.032). No significant difference in the mean value of serum Vitamin D in cases and controls (p=0.555) was noted.

Conclusion: ADHD is a common neurobehavioral disorder presenting in pediatric OPD with higher prevalence in males than females. Combined type was found to be the most dominant type of ADHD in the study population. We observed a significant difference in the levels of Serum Ferritin in children with ADHD and controls.

Keywords: Attention deficit hyperactivity disorder, Iron, Vitamin D

Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most prevalent mental health disorders that affect about 5.3–7.1 percent of children and adolescents. [1] Attention deficiency, hyperactivity and impulsivity are three main symptoms that help diagnose the disorder before the age of twelve years.1,2 Besides, other accompanying secondary symptoms such as aggression, social incompetence, conflict with peers and anti-social behavior other clinically important symptoms. [2,3] So far, drug therapy is the main treatment method. However, there are limitations in drug interventions. For instance, 30 percent of ADHD children do not respond to the drug treatment. [4,5] More effective treatment and strategies are needed to control the disease. [6,7]

The pathophysiology behind ADHD lies in the depletion of neurotransmitters such as dopamine and serotonin in the brain. [8,9] The exact cause of which is elusive; both genetic and environmental risk interdependent relationship. Genetic associations with genes encoding the neurotransmitter dopamine, for example, DRD4, DRD5, and DAT1 and serotonin, for example, 5HTT and 5HTR1B have been proven. Environmental risk factors include psychosocial adversity, maternal stress and substance abuse, exposure to toxins, for example, organophosphate pesticides, polychlorinated biphenyls or lead and dietary factors such as nutritional deficiencies and nutritional surpluses, for example, excessive sugar or artificial food coloring. [10-12]

Micronutrients have imperative roles in neurologic function, including involvement in neurotransmitter synthesis. Iron deficiency is one of the most common cause of anemia in India A decrease in iron concentration causes changes in the normal brain functioning such as changes in conduction of cortical fibers, changes in serotonergic, and dopaminergic systems, as well as in the formation of myelin. [13,14] Iron deficiency impairs cognitive and behavioral functions and is linked with symptoms such as poor attention and hyperactivity. [15] Iron also is a coenzyme of tyrosine hydroxylase, which is required for dopamine synthesis and its degradation. It has been found that iron deficiency is linked with decreased expression of D2 and D4 receptors and dopamine transporter in the brain. [16] These changes in neurotransmitter changes along with basal ganglia dysfunction are believed to be the etiopathogenesis of ADHD. [17]

Vitamin D is a versatile hormone with a major role in calcium and bone metabolism but also plays part in cardiovascular, immune endocrine, and psychiatric diseases. [18] It is important for cerebral function and thought to have a neurotropic and neuroprotective effects. It is important in cerebral function and its deficiency may have role in the etiopathogenesis of ADHD. Vitamin D alters the neurotrophic factors and monoamine levels, facilitating the oxidative stress responses, and changes in neurotransmitters. Vitamin D deficiency, therefore, results in changing in abnormal dopamine regulation, linking it to have a role in etiopathogenesis of ADHD. [19]

The aim of the study was to study the association between Serum Vitamin D and Serum Ferritin levels in children with ADHD. [20]

Materials and Methods

The study was conducted in the Department of Pediatrics, ANMMCH, Gaya, Bihar, India for the period of 1 year. A total of 100 children meeting the inclusion criteria were enrolled in the study. Subjects included all new or follow-up patients with diagnosed or suspected ADHD and healthy children of the comparable sex and age group attending the pediatric outpatient department (OPD) were taken as controls. Informed and written consent was taken from parents and assent from children above 12 years of age to participate in the study.

Diagnosis of ADHD was confirmed. This step was in two-fold- (a) Using child behavior checklist (CBCL) – to rule out other behavior abnormalities. (b) Using INCLEN diagnostic tool for ADHD [INDT-ADHD] for confirmation of ADHD.[20] Blood sample was taken for all the subjects under all aseptic techniques and samples were analyzed for serum ferritin and serum Vitamin D estimation.

Inclusion Criteria for Cases

The following criteria were included in the study:

1. Any child aged between 6 and 15 years diagnosed with
ADHD
1. Any child attending regular schools

Inclusion criteria for controls: 1. Children aged between 6 and 15 years presenting to OPD.

The following criteria were excluded from the study:
1. Any child with seizures
2. Any child with acute febrile illness
3. Any child with intellectual and neurological impairment
4. Any child with other psychiatric disorder
5. Any child with a chronic systemic disease
6. Any child on stimulant medication
7. Any child treated for rickets
8. Any child taking iron or Vitamin D supplements.

Study Tools

Case recording form, CBCL - Child Behavior Checklist, INCLEN diagnostic tool for ADHD [INDT-ADHD], Serum Ferritin estimation: Enzyme Linked Fluorescent Assay technique through VIDAS, Serum Vitamin D estimation: Enzyme Linked Fluorescent Assay via VIDAS Study.

Data Management and Statistical Analysis: The data were collected and entered in MS excel 2010. Different statistical analysis was performed by using statistical package for the social sciences software version 22. The one sample Kolmogorov–Simonov test was employed to determine whether the data sets differed from a normal distribution or not. Normally distributed data were analyzed using parametric tests and non-normally distributed data were analyzed using non-parametric tests. Descriptive statistics was calculated for quantitative variables. Frequency along with percentages was calculated for qualitative and categorical variables. Categorical data were analyzed using chi square test/Fisher Exact test. Student's t-test was used for comparison of quantitative data. Value of $p<0.05$ was said to be statistically significant and $p>0.05$ was said to be statistically insignificant.

Results

Table 1: Age‑ and gender‑wise distribution of children

Age group (Years)	Gender	Cases n=50	Controls n=50
6–9	Male	20	15
	Female	10	12
10–12	Male	6	10
	Female	8	6
13–15	Male	4	4
	Female	2	3

50 cases were diagnosed with ADHD and their results were compared to age and sex matched controls. Serum Ferritin and Vitamin D levels were measured in both cases and controls. Since we matched age, similar age distribution was present in controls.

Table 2: ADHD result on INCLEN tool

Subtype of ADHD	No.	Percentage
Hyperactivity	7	28
Inattention	8	32
Combined	10	40

40% cases were having combined ADHD as compared to hyperactivity and inattention.

Table 3: Serum Ferritin levels and Vitamin D levels in cases and controls

Serum Ferritin levels	Cases n=50	Controls n=50	P value
High	0	8	0.032
Low	22	14	
Normal	28	28	
Vitamin D levels			
Low	40	42	0.555
Normal	10	8	

The study found a significant difference in the mean value of serum ferritin levels in cases and controls (p=0.032). No significant difference in the mean value of serum Vitamin D in cases and controls (p=0.555) was noted.

Table 4: Mean value of S. Ferritin and S. Vitamin D in different subtypes of ADHD

	Inattentive type	Hyperactive type	Combined type	P value
S. Ferritin (ng/ml)	32.48±25.75	25.95±16.24	36.84±20.12	0.670
S. Vitamin D (nmol/L)	35.45±18.02	36.94±12.48	39.71±16.24	0.812

The mean value of serum ferritin levels in cases was observed to be in inattentive type 32.48±25.75 ng/ml, in hyperactive was 25.95±16.24 ng/ml and in combined 36.84±20.12 ng/ml. The mean value of serum ferritin levels in cases was observed to be in inattentive type 35.45±18.02 ng/ml, in hyperactive was 36.94±12.48 ng/ml and in combined 39.71±16.24 ng/ml. The difference was non-significant.

Discussion

Despite being one of the most studied psychiatric disorders, the exact cause of ADHD is still unknown; both genetic and environmental risk factors contribute to the development of ADHD. [21] Iron deficiency is considered a potent cause of poor cognitive impairment, learning disabilities, and psychomotor instability [22], which also supports the hypothesis that iron deficiency may play a role in the pathophysiology of ADHD. [23]

50 cases were diagnosed with ADHD and their results were compared to age and sex matched controls. Serum Ferritin and Vitamin D levels were measured in both cases and controls. Since we matched age, similar age distribution was present in controls. This was in agreement with Bener et al. [24] and Hassan et al. [25] who observed prevalence of ADHD to be more in school age children of 6–9 years than adolescents. Ramtekkar et al. [26] also in their study found the mean age of ADHD to be 7–12 year. The study found a significant difference in the mean value of serum ferritin levels in cases and controls (p=0.032). No significant difference in the mean value of serum Vitamin D in cases and controls (p=0.555) was noted.

Serum ferritin levels are a dependable measure of iron stores in the body tissues and its levels are an early precursor of iron deficiency. Also binding of exogenous ferritin to cell receptors is important pathway for delivery of iron in brain tissue. Low ferritin levels are highly specific for iron deficiency. [27] The range of normal values of ferritin as set by out laboratory was 20–165 ng/ml; therefore, cutoff for low ferritin was set at values <20 ng/ml. We found 44% of cases and 28% of controls to have low ferritin levels. The mean value of serum ferritin levels in cases was observed to be in inattentive type 32.48±25.75 ng/ml, in hyperactive was 25.95±16.24 ng/ml and in combined 36.84±20.12 ng/ml. The mean value of serum ferritin levels in cases was observed to be in inattentive type 35.45±18.02 ng/ml, in hyperactive was 36.94±12.48 ng/ml and in combined 39.71±16.24 ng/ml. The difference was non-significant. No association was found between Vitamin D and subtypes of ADHD. Deficient levels of Vitamin D in majority of both cases and controls could be explained by higher prevalence of vitamin

D deficiency in apparently healthy Indian children as shown in study done by Angurana et al. [28]

Kamal et al. [29] too observed a significantly lower level of Vitamin D in children in ADHD than controls (7.6 vs. 4.6%). Elshorbagy et al. [30] found a greater incidence of Vitamin D deficiency in children with ADHD than controls and proved that supplementation of Vitamin D to children with ADHD can cause an improvement in symptoms of ADHD. Like our results, Gustafsson et al. [31] found no significant difference in cord blood Vitamin D concentration between children with ADHD and controls. There were some limitations to the study. The predetermined sample size could not be taken due to decreased OPD visit of patients during the COVID-19 pandemic. This could lead to underestimation of prevalence of ADHD. Sample size of the study was also not sufficient to establish a causal relationship of S. Ferritin and S. Vitamin D with ADHD. Serum Ferritin levels although being a reliable marker of iron stores in the body its level could be elevated in conditions other than increased iron stores, such as acute inflammatory conditions, cancers, Hemophagocytic lymphohistiocytosis, and hemochromatosis. [27]

Conclusion

ADHD is a common neurobehavioral disorder presenting in pediatric OPD with higher prevalence in males than females. Combined type was found to be the most dominant type of ADHD in the study population. We observed a significant difference in the levels of Serum Ferritin in children with ADHD and controls. There was seen an association between low levels of serum ferritin and ADHD. Therefore, levels of S. Ferritin should be measured in children with ADHD.

References

1. Arnold LE, Hodgkins P, Caci H, Kahle J, Young S. Effect of treatment modality on long-term outcomes in attention-deficit/ hyperactivity disorder: a systematic review. PloS one. 2015 Feb 25;10(2): e011 6407.
2. Matthews M, Nigg JT, Fair DA. Attention Deficit Hyperactivity Disorder. Curr Top Behav Neurosci 2014;16: 235– 66.
3. Gajria K, Lu M, Sikirica V, Greven P, Zhong Y, Qin P, Xie J. Adherence, persistence, and medication discontinuation in patients with attention-deficit/hyperactivity disorder–a systematic literature review. Neuropsychiatric disease and treatment. 2014 Aug 22:1543-69.
4. Leroux JR. Turgay A. Quinn D. Advances in ADHD treatment. Can J Diagn 2009; 26: 49–52.
5. McGough JJ, Biederman J, Wigal SB, Lopez FA, McCracken JT, Spencer T, et al. Long-term tolerability and effectiveness of once-daily mixed amphetamine salts (Adderall XR) in children with ADHD. J Am Acad Child Adolesc Psychiatry 2005; 44(6):530-8.
6. Brooke SG, Molina Stephen P, Hinshaw L, Arnold E, James M, et al. Adolescent Substance Use in the Multimodal Treatment Study of Attention-Deficit/ Hyperactivity Disorder (ADHD) (MTA) as a Function of Childhood ADHD, Random Assignment to Childhood Treatments, and Subsequent Medication. J Am Acad Child Adolesc Psychiatry 2013; 52(3): 250–63.
7. Ghanizadeh A. Predictors of different types of developmental coordination problems in ADHD: the effect of age, gender, ADHD symptom severity and comorbidities. Neuropediatrics 2010; 41(4): 176-81.
8. Sharma A, Couture J. A review of the pathophysiology, etiology, and treatment of attention-deficit hyperactivity disorder (ADHD). Annals of Pharmacotherapy. 2014 Feb;48(2):209-25.
9. Thapar A, Cooper M, Eyre O, Langley K. Practitioner review: what have we learnt about the causes of ADHD?. Journal of Child Psychology and Psychiatry. 2013 Jan;54(1):3-16.
10. Sagiv SK, Epstein JN, Bellinger DC, Korrick SA. Pre-and postnatal risk factors for ADHD in a nonclinical pediatric population. Journal of attention disorders. 2013 Jan;17(1):47-57.
11. Menegassi M, Mello ED, Guimarães LR, Matte BC, Driemeier F, Pedroso GL, Rohde LA, Schmitz M. Food intake and serum levels of iron in children and adolescents with attention-deficit/hyperactivity disorder. Brazilian Journal of Psychiatry. 2010;32:132-8.
12. Sinn N. Nutritional and dietary influences on attention deficit hyperactivity disorder. Nutrition reviews. 2008 Oct 1;66(10):558-68.
13. Lozoff B, Beard J, Connor J, Felt B, Georgieff M, Schallert T. Long-lasting neural and behavioral effects of iron deficiency in infancy. Nutrition reviews. 2006 May 1;64 (suppl_2):S34-43.
14. Oner O, Alkar OY, Oner P. Relation of ferritin levels with symptom ratings and cognitive performance in children with attention deficit–hyperactivity disorder. Pediatrics International. 2008 Feb;50(1):40-4.
15. Kieling C, Goncalves RR, Tannock R, Castellanos FX. Neurobiology of attention deficit hyperactivity disorder. Child and adolescent psychiatric clinics of North America. 2008 Apr 1;17(2):285-307.
16. Gan J, Galer P, Ma D, Chen C, Xiong T. The effect of Vitamin D supplementation on attention-deficit/hyperactivity disorder: A systematic review and meta-analysis of

randomized controlled trials. J Child Adolesc Psychopharmacol 2019;29:670-87.

17. Eyles DW, Burne TH, McGrath JJ. Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease. Frontiers in neuroendocrinology. 2013 Jan 1;3 4(1):47-64.
18. Khoshbakht Y, Bidaki R, Salehi-Abargouei A. Vitamin D status and attention deficit hyperactivity disorder: a systematic review and meta-analysis of observational studies. Advances in Nutrition. 2018 Jan 1;9(1):9-20.
19. Ellison-Wright I, Ellison-Wright Z, Bullmore E. Structural brain change in attention deficit hyperactivity disorder identified by meta-analysis. BMC psychiatry. 2008 Dec;8:1-8.
20. Russell G, Ford T, Rosenberg R, Kelly S. The association of attention deficit hyperactivity disorder with socioeconomic disadvantage: alternative explanations and evidence. Journal of Child Psychology and Psychiatry. 2014 May;55(5):436-45.
21. Thapar A, Cooper M, Eyre O, Langley K. Practitioner review: what have we learnt about the causes of ADHD?. Journal of Child Psychology and Psychiatry. 2013 Jan;54(1):3-16.
22. Konofal E, Lecendreux M, Deron J, Marchand M, Cortese S, Zaïm M, Mouren MC, Arnulf I. Effects of iron supplementation on attention deficit hyperactivity disorder in children. Pediatric neurology. 2008 Jan 1;38(1):20-6.
23. Cortese S, Angriman M, Lecendreux M, Konofal E. Iron and attention deficit/hyperactivity disorder: What is the empirical evidence so far? A systematic review of the literature. Expert review of neurothe rapeutics. 2012 Oct 1;12(10):1227-40.
24. Bener A, Al Qahtani R, Teebi AS, Bessisso M. The prevalence of attention deficit hyperactivity symptoms in schoolchildren in a highly consanguineous community. Medical Principles and Practice. 2008;17(6):440-6.
25. Hassan FM, Soliman MA, Abd El-Nabi SA, Elgazzar GA. Relationship between serum vitamin D and iron level in children with attention-deficit hyperactivity disorder. Menoufia Medical Journal. 2018 Jul 1;31 (3):999.
26. Ramtekkar UP, Reiersen AM, Todorov AA, Todd RD. Sex and age differences in attention-deficit/hyperactivity disorder symptoms and diagnoses: implications for DSM-V and ICD-11. Journal of the American Academy of Child & Adolescent Psychiatry. 2010 Mar 1;49(3): 217-28.
27. Wang W, Knovich MA, Coffman LG, Torti FM, Torti SV. Serum ferritin: past, present and future. Biochimica et Biophysica Acta (BBA)-General Subjects. 2010 Aug 1;1800(8):760-9.
28. Angurana SK, Angurana RS, Mahajan G, Kumar N, Mahajan V. Prevalence of vitamin D deficiency in apparently healthy children in north India. Journal of Pediatric Endocrinology and Metabolism. 2014 Nov 1;27(11-12):1151-6.
29. Kamal M, Bener A, Ehlayel MS. Is high prevalence of vitamin D deficiency a correlate for attention deficit hyperactivity disorder?. ADHD Attention Deficit and Hyperactivity Disorders. 2014 Jun;6:73-8.
30. Elshorbagy HH, Barseem NF, Abdelghani WE, Suliman HA, Al-Shokary AH, Abdulsamea SE, Elsadek AE, Abdel Maksoud YH, Nour El Din DM. Impact of vitamin D supplementation on attention-deficit hyperactivity disorder in children. Annals of Pharmacotherapy. 2018 Jul;52(7):623-31.
31. Gustafsson P, Rylander L, Lindh CH, Jönsson BA, Ode A, Olofsson P, Ivarsson SA, Rignell-Hydbom A, Haglund N, Källén K. Vitamin D status at birth and future risk of attention deficit/hyperactivity disorder (ADHD). PloS one. 2015 Oct 28;10(10):e0140164.