Original Article

Study of the relationship of serum Vitamin D and ferritin levels in children with attention deficit hyperactivity disorder

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ABSTRACT

Background: Attention deficit hyperactivity disorder (ADHD) is one of the most prevalent mental health disorders among school-age children in India. Etiopathogenesis is attributed to abnormal dopamine regulation which is influenced by both genetic (genes encoding dopamine-DRD4, DRD5, and DAT1) and environmental factors. Micronutrients such as iron and Vitamin D play imperative roles in neurologic function, neurotransmitter synthesis, and regulation. **Aim:** The aim of the study was to study the association between Serum Vitamin D and Serum Ferritin levels in children with ADHD. **Materials and Methods:** This case–control study was conducted in the outpatient department of a tertiary care hospital, from October 2019 to May 2021. Subjects (n=30) included patients with the diagnosis of ADHD (using child behavior checklist and INDT–ADHD). Healthy children of the comparable age group were taken as controls. Statistical analysis was performed using Statistical Package for the Social Sciences software version 22. **Results:** The mean value of serum ferritin levels in cases was observed to be 32.55±31.97 ng/ml and in controls was 143.43±260.40 ng/ml. The study found a significant difference in the mean value of serum ferritin levels in cases and controls (p‒0.024). No significant difference in the mean value of serum Vitamin D in cases and controls (p–0.229) was noted. **Conclusions:** An association between low levels of serum ferritin and ADHD was seen.

Key words: Attention deficit hyperactivity disorder, Iron, Vitamin D

Attention deficit hyperactivity disorder (ADHD) is one of the most prevalent mental health disorders among school-age children in India, estimated to affect 11.32% of primary school-going children in India [1]. It is usually diagnosed in childhood and is likely to persist to adulthood. This disorder can severely affect scholastic and social performance and has poor long-term social and emotional outcomes. In addition, ADHD is commonly associated with comorbidities such as other psychiatric, behavioral, and developmental problems, including autistic spectrum disorders and developmental delay which make the diagnosis and management difficult [2].

The pathophysiology behind ADHD lies in the depletion of neurotransmitters such as dopamine and serotonin in the brain [3,4]. 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 [5-7].

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 [8,9]. Iron deficiency impairs cognitive and behavioral functions and is linked with symptoms such as poor attention and hyperactivity [10]. 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 [11]. These changes in neurotransmitter changes along with basal ganglia dysfunction are believed to be the etiopathogenesis of ADHD [12].

Vitamin D is a versatile hormone with a major role in calcium and bone metabolism but also plays part in cardiovascular, immune,

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endocrine, and psychiatric diseases [13]. 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 [14]. Vitamin D receptors and 1α-hydroxylase enzyme are responsible for the formation of the active form of Vitamin D, and these are found to be widely distributed in the central nervous system, mainly in the neuronal cells of the substantia nigra, hippocampus, hypothalamus, prefrontal cortex, and cingulated gyrus [14-16]. Most of these regions have seen to be associated in the pathogenesis of ADHD [16,17]. Recommended treatment for ADHD is multimodal including medication, parent training, skills training counseling, behavioral therapy, and educational support. Despite treatment only 30–70% of patients respond to currently available ADHD therapies [18]. As both iron and Vitamin D deficiencies have been implicated in the etiopathogenesis of ADHD, this study is being carried to determine the variations in the Serum ferritin and Serum Vitamin D levels and to find their association with ADHD.

Study Protocol

The study was conducted in the Department of Pediatrics, Himalayan institute of Medical sciences from October 2019 to May 2021. 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.

Study Design

Type of study

Case–control study.

Sample Size

n=2 (Z1-α12 + Z1-β) 2σ (μ1–μ2) 2Zα=1.96 at 5% level of significance Zβ=1.28 at 95% power of test σ=pooled standard deviation μ1=mean of case group μ2= mean of control group. Then n=52 in each group Total sample=104 of which – Cases=52 and Controls=52 Due to unprecedent COVID-19 pandemic and lockdown resulting in disruption of OPD, the number of patients presenting to OPD were limited. Ultimately 30 cases and 30 controls were enrolled for the study who met the inclusion criteria.

Selection of Subject

Inclusion criteria for cases

The following criteria were included in the study:
1. Any child aged between 6 and 15 years diagnosed with ADHD
2. Any child attending regular schools inclusion criteria for controls: 1. Children aged between 6 and 15 years presenting to OPD.

Exclusion criteria for both cases and controls

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

A total of 60 children meeting the inclusion criteria were enrolled in the study. 30 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. Prevalence of ADHD in children in our pediatric OPD was estimated to be 1.2%. Since we matched age, similar age distribution was present in controls (Table 1).

DISCUSSION

This was one of the first studies to determine the prevalence of ADHD in children presenting to tertiary care center in state of Uttarakhand, India. According to our findings, prevalence of ADHD was estimated to be 1.2%. Our value was considerably lower as compared to that found by Joseph and Devu determined the prevalence of ADHD in India to be 7.1% in childhood [19]. Compared to a worldwide prevalence of 5.29% [2,20], prevalence in our center was lower. These findings could be attributed to decreased number of patients presenting to OPD during COVID pandemic. Furthermore, schools were closed for most part of the 2020–2021, which could have led to delayed recognition of inattentive and hyperactive symptoms outside of a classroom setting. A social stigma attached to mental and behavioral disorders and decreased awareness among general population could be a potential cause of non-recognition of symptoms of ADHD and delayed treatment. In our study, the prevalence of ADHD in children with age group 6–9 years was more than in adolescent age children (Table 1). It was 60% in school going children of 6–9 years, 20% in early adolescents (10–12 years) and 20% in middle adolescents (13–15 years of age). This was in agreement with Bener *et al*. [21] and Hassan *et al*. [22] who observed prevalence of ADHD to be more in school age children of 6–9 years than adolescents. Ramtekkar *et al*. [23] also in their study found the mean age of ADHD to be 7–12 year.

INDT-ADHD tool was used for confirmation of diagnosis of ADHD, after ruling out other psychiatric and behavioral disorders by use of CBCL. Using INDT-ADHD tool we could determine the dominant subtype of ADHD (whether the symptoms are hyperactive impulsive type, inattentive type or combined type). The present study found 36.67% to have combined type, 33.33% to have inattentive type and 30% to have hyperactive type of ADHD (Table 2). When these results were associated with gender, girls with ADHD had predominant inattentive type, whereas hyperactive-impulsive type was more common in boys. To assess for iron levels in body, serum ferritin levels were measured both in cases and controls. 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 [24]. 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 46% of cases and 20% of controls to have low ferritin levels (Table 3).

In our study, 73% of cases and 63% of controls had low levels of Vitamin D (Table 4). Mean value of vitamin D was 37.77±16.05 nmol/L in cases and 63.87±116.43 nmol/L in controls. We observed slightly lower mean value in cases as compared to controls but the difference was not statistically significant. We found no association between Vitamin D levels and ADHD. On assessing mean Vitamin D values among different subtypes of ADHD, lowest value was observed in cases with Inattentive type ADHD (33.49±18.01 nmol/L), followed by hyperactive type (37.93±13.67 nmol/L) and combined types (39.74±17.20 nmol/L) (Table 5). The difference observed in the mean values of Vitamin D was not statistically 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*. [25]. Goksugar *et al*. [15] also found lower mean serum Vitamin D level in the ADHD group (20.9±19.4 ng/ml) than control groups (34.9±15.4 ng/mL) but in their study there was a significant difference in both the levels. Kamal *et al*. [26] too observed a significantly lower level of Vitamin D in children in ADHD than controls (7.6 vs. 4.6%). Elshorbagy *et al*. [27] 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*. [28] 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

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

Age group (Years)	Gender	Cases (n=30)		Controls (n=30)	
		No.	Percentage	No.	Percentage
6–9	Male	10	60	18	60
	Female	6			
10–12	Male	4	26.66	8	26.66
	Female	5			
13–15	Male	3	13.33	4	13.33
	Female	1			

Table 2: ADHD result on INCLEN tool

Subtype of ADHD	No.	Percentage
Hyperactivity	9	30.00
Inattention	10	33.33
Combined	11	36.67

Table 3: Serum Ferritin levels in cases and controls

Serum ferritin	Cases	Controls	*P* value
High	0 (0)	4 (13.33)	0.037
Low	14 (46.67)	7 (23.33)	
Normal	16 (53.33)	19 (63.33)	
Total	30	30	

Table 4: Vitamin D levels in cases and controls

Serum Vitamin D	Cases with ADHD	Controls	*P* value
Low	22 (73.33)	20 (66.67)	0.573
Normal	8 (26.67)	10 (33.33)	
Total	30	30	

Table 5: Mean value of S. Ferritin and S. Vitamin D in different subtypes of ADHD

	Inattentive type (n=10)	Hyperactive type (n=9)	Combined type (n=11)	*P* value
	Mean	Mean	Mean	
S. Ferritin (ng/ml)	33.49±31.79	24.98±20.38	37.88±40.50	0.679
S. Vitamin D (nmol/L)	35.45±18.01	37.93±13.67	39.74±17.20	0.838

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 [24]. Therefore, to overcome this limitation cases and controls who had any systemic illness or those who were on iron supplements were excluded from the study. Still, some children with undiagnosed underlying systemic illness can have falsely elevated ferritin levels.

CONCLUSIONS

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.

AUTHOR CONTRIBUTION

Ashima Mehta – Conceptualized the study and collected the data under the guidance of Dr B.P. Kalra and Dr Malini Srivastava.

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