









**Table 3: Clinical biochemistry baseline value among ADHD and control subject**

Variables	Reference normal value	ADHD Mean±SD (N=630)	Control	P
Vitamin D (ng/ml)	30-80	16.81 (7.84)	22.18 (9.00)	<0.01
Serum iron (µg/dL)	37-158	82.11 (13.61)	85.60 (12.47)	<0.01
Ferritin (ng/ml)	15-150	36.26 (5.93)	38.19 (5.61)	<0.01
Hemoglobin (g/dL)	11.2-16.5	12.06 (2.13)	12.89 (2.02)	<0.01
Magnesium (mmol/L)	0.65-1.05	0.82 (0.08)	0.88 (0.06)	<0.01
Potassium (mmol/L)	3.4-4.7	4.62 (0.50)	4.57 (0.55)	0.21
Calcium (mmol/L)	2.10-2.5	2.35 (0.12)	2.39 (0.14)	<0.01
Phosphorous (mmol/L)	0.4-1.3	1.47 (0.30)	1.54 (0.26)	<0.01
<b>n (%)</b>				
Supplement vitamin D		233 (37.0)	295 (46.8)	<0.01
Severe deficiency 25(OH) D<30 ng/ml		116 (18.4)	78 (12.4)	<0.01

ADHD: Attention deficit hyperactivity disorder, SD: Standard deviation, 25(OH) D: 25-Hydroxyvitamin D

**Table 4: Multivariate logistic regression analysis as predictors for ADHD children**

Independent variables	Odds ratio	95% confidence interval	P
Vitamin D deficiency (ng/ml)	3.27	1.65-5.90	<0.01
Serum iron deficiency (ng/ml)	2.81	1.72-4.53	<0.01
Physical activity	2.67	1.68-4.26	<0.01
Ferritin (ng/ml)	2.53	1.81-3.45	<0.01
Serum calcium level	2.04	1.01-3.58	<0.01
Nervous behavior	1.73	1.14-2.56	<0.01
Consanguinity	1.49	1.16-1.92	<0.01
BMI in percentiles	1.38	1.15-1.54	<0.01
Child order	1.08	1.12-3.36	<0.01

BMI: Body mass index, ADHD: Attention deficit hyperactivity disorder

in many developed and developing countries, the majority of children who have ADHD are undiagnosed and there is limited recognition of child mental health problems in primary care.<sup>[1-3,5,6]</sup> Teachers and parents may be well placed to identify unrecognized children and to facilitate their referral to medical health care services hence the use of assessments by them become very important and relevant. The association between iron deficiency, ferritin deficiency and ADHD in young children have been previously reported in the literature but, the potential associated risk factors never been discussed.<sup>[9-24]</sup> Therefore, the current study conducted and explored an association between important circulating levels of iron deficiency, ferritin and vitamin D deficiency and their impact on ADHD and study outcome supported strong correlations among those variables.

As Konofal *et al.*,<sup>[14]</sup> had reported that iron deficiency has been previously considered a potent cause of poor cognitive impairment, learning disabilities, and psychomotor instability it is worth considering that iron deficiency (low serum ferritin level) could lead to ADHD symptoms in relationship with central dopaminergic dysfunction. Furthermore, iron supplementation<sup>[8-16,29]</sup> and vitamin D<sup>[21-24]</sup> may form a first-line treatment for children with ADHD and iron deficiency. Furthermore, Konofal *et al.*,<sup>[12]</sup> have shown that the mean serum ferritin levels, were lower in children with ADHD [mean (SD), 23 (13) ng/ml] than in the controls [mean (SD), 44 (22) ng/ml;  $P < 0.01$ ], while serum iron, hemoglobin, and hematocrit levels were within normal ranges in both children with ADHD and controls and did not differ between groups and serum ferritin levels were inversely correlated with the severity of ADHD. They suggest that low iron stores may explain as much as 30% of ADHD severity. This correlation suggests that the iron deficient children are mainly inattentive and distractible and suffer from learning disabilities, a finding consistent with the role of iron deficiency in cognitive deficits and mental retardation.<sup>[30]</sup> Another aspect worth bearing in mind and further exploration is that the iron deficiency can be easily corrected. A causal relationship between iron deficiency and poor cognitive development and/or behavioral problems has been well-established over the past 3 decades.<sup>[29-33]</sup> Finally, there was a trend toward a correlation between the hyperactivity sub-scores and serum ferritin levels, the children with more severe iron deficiencies suffering from increased motor restlessness.<sup>[11]</sup> Previous studies have revealed that iron was associated with ADHD which affect the social-emotional development and functioning of children. In our study, an increased risk of ADHD was noted among those with IDA, which was compatible with a recent meta-analysis result.

More recently, a study from India<sup>[13]</sup> showed that serum ferritin levels newly diagnosed children with ADHD showed low levels of ferritin in comparison with controls-similar findings to the present study. There was also a significant inverse correlation between serum ferritin levels and oppositional subscores on Conner's Rating Scale. Our study also confirms findings from Israel.<sup>[9]</sup>

The current study suggests that low iron deficiency and ADHD pathophysiology could related to several multifactor. It is worth considering that iron deficiency (low serum ferritin level) could lead to ADHD symptoms in relationship with genetics, environmental risk factors, absence of iron supplementation, and lack of low nutritional foods. A causal relationship between iron deficiency and ADHD and poor cognitive development and/or behavioral problems has been well-established over the past 3 decades.<sup>[29-33]</sup> Previous studies have revealed that iron was associated with ADHD which affect the socioemotional development and functioning of children.<sup>[29,32]</sup>

The correct recognition of ADHD and prompt treatment has major international public health implications.<sup>[5,6]</sup> This study

highlights standard laboratory assessments, which may give a clue toward the diagnosis and treatments. One important limitation is major diagnostic issues and implications of such diagnoses on children, teachers, peers, families and parents, and society at large must be explored further. Recognition of ADHD, even if accurate, may be harmful through labeling, stigmatization, scapegoating, and effects on self-perception. It has been argued that such over-medicalization enables both adults and children to avoid taking responsibility for a range of behaviors.<sup>[32]</sup> Current study revealed the importance of careful investigations and potential for early treatment for affected children and their families. Hyperactivity carries a considerable developmental risk even when considered in dimensional terms.

Although our study included a large sample of participants and it is case-controlled, it has some limitations. As confounding factors, we cannot exclude the possibility that they have contributed, to some extent, in determining the in the association of serum iron, ferritin levels, vitamin D, and ADHD. This study did not include data on children kept on avoidance/restriction diet. It is known that avoidance or restriction diet is one of the modalities of therapy in some case of ADHD and for a relatively short period of time. However, it is unlikely that the majority of ADHD patients in our study were on avoidance diet, or for prolonged time of dietary restrictions as the nutritional parameters (BMI) and laboratory biomarkers (serum iron, ferritin levels, and serum albumin) do not indicate evidence avoidance long enough to affect vitamin D status and iron deficiency. Hyperactivity and impulsivity are some of the main characteristic features of ADHD disease in children.

## Conclusions

The association between lower serum levels of various factors needs to be explored further in longitudinal studies. This study indicates that low serum iron, ferritin levels and vitamin D deficiency may be associated with ADHD pathophysiology and therefore must be assessed. Furthermore in addition, education for the parents, teachers, families, and society at large is absolutely vital if the burden of disease related to ADHD is to be reduced. It may also be that various chemicals in the diet may be interfering with the absorption of various protectors and this must be explored as a matter of urgency.

### What this study adds?

The correlation between iron, ferritin, vitamin D deficiency, and ADHD in young children has previously not been reported in the literature. However, data is lacking regarding the association between iron deficiency and ADHD. This study reveals that those deficiencies were higher in ADHD children compared with healthy children. Supplementing infants with iron and vitamin D might be a safe and effective strategy for reducing the risk of ADHD.

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