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Role of Vitamin B12 in Autistic Spectrum and Attention Deficit Hyperactivity Disorders: A Scoping Review

Review Article

Rawat S[1]*, Nagpal J[1] and Jain T[2]

[1]*Sitaram Bhartia Institute of Science and Research, B-16, Qutab Institutional Area, New Delhi, India*

[2]*Amity Institute of Food Technology, Amity University, Amity Road, Sector-125 Noida-201301, Uttar Pradesh, India*

***Corresponding author:** Rawat S, Department of Research and Clinical Epidemiology, Sitaram Bhartia Institute of Science and Research, B-16, Qutab Institutional Area, New Delhi, India Email: swapnil.rawat@gmail.com

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Abstract

Vitamin B12 plays a vital role in normal brain functioning. Its deficiency is associated with developmental delays, irritability, and failure to thrive in children. Several studies have evaluated the possibility of B-12 deficiency leading to ASD/ADHD with inconsistent results. This review summates the available literature on B12 deficiency/supplementation and ASD/ADHD in children. The literature search was conducted in Medline and Extended Medline using the following search words (Vitamin B12 or Cobalamin or Methylcobalamin or Cyanocobalamin) and (Autism, Autistic spectrum disorder or attention deficit hyperactivity disorder or ASD or ADHD). Total of sixteen studies were retrieved of which four were clinical trials. Most of the observational studies report an association between B-12 deficiency and Autism. Studies on ADHD are fewer, and the association is weaker. Intervention studies were only available for ASD. Three of these reported improvement in biochemical and/or clinical behavior ratings for ASD children while one study did not show any improvement in either. There is observational data documenting the relationship between B-12 dfefficiency and ASD. Studies on ADHD are fewer and less conclusive. Intervention studies using B-12 in ASD children document biochemical improvement. There is paucity of trial literature on the clinical impact of B-12 supplementation in ASD especially in terms of behavior ratings. Further work should be urgently considered to address these lacunae.

Keywords: Vitamin B12; Autism; Attention Deficit Hyperactivity Disorder

Introduction

Vitamin B12 is a water-soluble vitamin required for the development and initial myelination of central nervous system and normal functioning of the brain. Vitamin B12 (B12) is an essential cofactor for two enzymes involved in one-carbon metabolism: methylmalonyl CoA mutase (reduced function of this enzyme results in increased serum methylmalonyl acid (MMA) levels) and methionine synthetase (this enzyme catalyzes the remethylmation of homocysteine to methionine). A serum B12 level below the normal expected range may indicate B12 deficiency [1]. Levels of B12 along with methlymalonic acid (MMA) and homocysteine are usually measured to detect the B12 deficiency [2]. Well-documented adult consequences of B12 deficiency include pernicious anemia, megaloblastic anemia, peripheral neuropathy neuropsychiatric syndromes and subacute combined degeneration of spinal cord [2,3,4]. Vitamin B12 (cobalamin) deficiency has been previously thought to be rare in children; however, recent studies suggest that the condition is more common than previously recognized [5]. Vitamin B12 deficiency in children is known to present with nonspecific manifestations, such as developmental delay, irritability, weakness, and failure to thrive. B-12 deficiency is becoming increasingly critical in India with the high prevalence of deficiency and the rising prevalence of vegetarianism. Recently many researchers have attempted to evaluate the potential role of the deficiency in childhood neurological syndromes like Autistic spectrum and Attention Deficit Hyperactivity Disorder. The current review seeks to summate the current evidence in this regard.

Metabolism

Vitamin B12 is found primarily in foods of animal origin.

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When consumed, vitamin B12 is released from food proteins in the stomach and binds to R-binder proteins, made in the saliva and stomach. After exposure to pancreatic proteases, vitamin B12 is released from the R proteins in the small intestine and forms a complex with intrinsic factor, produced in gastric parietal cells. The intrinsic factor-vitamin B12 complex is taken up in the terminal ileum, after recognition by specific ileal receptors. The complex dissociates in the enterocyte, and the free vitamin enters the portal circulation bound to transcobalamin II, which transports vitamin B12 to tissues. Vitamin B12 is secreted in bile and reabsorbed in the ileum, conserving B12 in individuals with normal absorption [5]. Although the adult recommended dietary allowance for vitamin B12 is 2.4 μg/d, an adult stores about 2 to 3 mg (primarily in the liver) [6].

Dosage and mode of administration

Table 1 lists the current Recommended Dietary Allowances (RDA) by National Institute of Nutrition, 2020 for vitamin B12 across all age groups [7].

Safety profile

The Institute of Medicine (IOM) did not establish a Upper Limit for vitamin B12 because of its low potential for toxicity. In Dietary Reference Intakes, the IOM states that "no adverse effects have been associated with excess vitamin B12 intake from food and supplements in healthy individuals" [6].

Therapeutic dosages

In patients with vitaminB12 deficiency, two oral regimens have been shown to achieve neurologic and hematologic response in the short term. Effective dosages were 2,000 µg daily or 1,000 µg daily for 10 days, then weekly and monthly [8].

Contraindications and cautions [9]

Vitamin B12 is contraindicated in known hypersensitivity to the vitamin or to cobalt. Patients who have early Leber's disease develop severe and swift optic atrophy on treatment with vitamin B12. Hypokalemia and sudden death are reported when severe megaloblastic anemia is treated aggressively. Indiscriminate administration of vitamin B12 may mask the true diagnosis of pernicious anemia. Multiple vitamin deficiency is expected in any dietary deficiency.

Drug interactions

Most antibiotics, methotrexate and pyrimethamine invalidate folic acid and vitamin B 12 diagnostic microbiological blood assays. Chloramphenicol may antagonize the hematopoietic response to vitamin B12. Hematopoietic response in such patients should be monitored.

Table 1: Recommended Dietary Allowances (RDAs) for Vitamin B12 [7].

Age group (y)	RDA (µg/day)
Infant (0-6 months)*	Breast milk
Infants and pre-school children (6m-5yrs)	1.2
School children and adolescents (5-17yrs)	2.5
Adults	2.5
Pregnant (Additional)	0.25
Lactating (Additional)	1.0

Colchicine, aminoglycosides, certain anticonvulsants (e.g., Phenytoin, Phenobarbital, Primidone), para-aminosalicylic acid or excessive alcohol intake may impair the absorption of vitamin B12. Vitamin C may destroy vitamin B12. Patients should avoid ingesting large amounts of vitamin C within 1 hour of oral vitamin B12 administration.

Histamine2-Receptor Antagonists (cimetidine, ranitidine, nizatidine, famotidine)

May cause vitamin B12 insufficiency by reducing gastric acid cleavage of vitamin B12 from food sources. This may be important in patients with low stores of vitamin B12 or in patients taking H2-antagonists for extended periods of time (>2 years).

Pregnancy

No adverse effects have been reported.

Lactation

Vitamin B12 is distributed into the milk of nursing women in concentrations that approximate the maternal blood vitamin B12 concentration. No adverse effects have been reported.

Autistic spectrum and attention deficit hyperactivity disorder

Autism Spectrum Disorder (ASD) is a neurological and developmental disorder characterized by impaired social interaction, abnormal communication and repetitive or unusual behavior [10,11]. Prevalence of ASD is reported to be 1 in 160 children globally [12]. ASD begins from childhood and tends to persist into adolescents and adulthood. By the age of three, all typical symptoms such as impaired social reciprocity, poor communication skills and restricted for repetitive behavior, affecting three major domains are observed. Associated co-morbidities include epilepsy, bowel disorder, intellectual disability and type -I diabetes. ADHD on the other hand includes attention difficulty, hyperactivity and impulsive behavior. Children with ADHD have difficulty in concentrating on single task or sitting still for long period of time [13]. Its presence increases difficulties in academic performance and social interactions besides leading to low self-esteem. Up to 9.4% of United States children are diagnosed with ADHD [14].

Role of B12 in ASD and ADHD

Vitamins and minerals are required for normal growth and development of children. Vitamin B-12 is known to be necessary for the synthesis of myelin in the body. The development and pattern of myelination follows a well-described neuroanatomical arc [15], progressing in a posterior-to-anterior and centre-outwards spatiotemporal pattern that corresponding to maturing cognitive functions [16]. That is, there is a strong overlap in the emergence of a specific cognitive function and the myelination of brain regions and networks sub serving that function.

Hence it was hypothesized by several researchers that childhood neurodevelopmental anomalies like ASD or ADHD could be related to a deficiency of Vitamin B-12. Hence we undertook a review of literature of the subject to define the scope of existing knowledge on the subject.

Citation: Rawat S, Nagpal J, Jain T. Role of Vitamin B12 in Autistic Spectrum and Attention Deficit Hyperactivity Disorders: A Scoping Review. Indian J Nutri. 2021;8(3): 243.

Search strategy

We conducted searches in Medline, Extended Medline (1950 to 22 July 2020) using the following search words (Vitamin B12 or Cobalamin or Methylcobalamin or Cyanocobalamin) and (Autism, Autistic spectrum disorder or attention deficit hyperactivity disorder or ASD or ADHD). We imposed no age or language restrictions. We also reviewed reference lists of identified articles and hand-searched reviews, bibliographies of books, and abstracts. We scanned the titles and abstracts of the trials identified in the computerized search to exclude studies that were obviously irrelevant. We scrutinized the full texts of the remaining studies and identified relevant observational and interventional studies. The studies identified by this exercise are presented in Table 2.

Observational studies

Several observational studies have documented that children with ASD or ADHD are deficient in B-12 as reflected in the biochemical B-12 parameters [17-27]. Table 2 summaries the observational data on the subject. As presented Pasca et al and Altun et al noted that children with autism have significant higher levels of total homocysteine and lower levels of B12 in plasma as compared to age matched controls [17,26]. A study of Omani children found that ASD have low dietary intake of B12 and thus have low serum B12 levels compared to neurotypical controls [20]. Another research on homocysteine levels in urine found to be significantly higher in autism children [18]. While most studies on ASD children document B-12 deficiency in children with ASD the results of Chen et al and Guo et al differed from this general trend. Chen J, in China studied 68 ASD children and documented that maternal serum levels of vitamin B12 and homocysteine were not significantly associated with risk of ASD.23 Guo et al, in China studied 371 children (274 ASD) aged 2-7 years using the Autism Behavior Checklist and their Social responsiveness scale. No significant difference was found regarding vit B12 between ASD group and control group (p = >0.106) [26].

Two studies report observational data on B-12 levels in children with ADHD. Both recorded lower B-12 levels in ADHD children than in controls but the levels in ADHD were higher than those of children with ASD. Bala et al analysed and compared B-12 levels in ASD (n=34) [22], ADHD (n=16) and controls (n=27) and noted that the ASD group had the lowest vitamin B12 levels, whereas the vitamin B12 levels of the ADHD group were significantly lower compared to the controls. Similarly, Yektas et al compared vitamin B12, folate and homocysteine concentrations in ASD (n=48), ADHD (n=35) and controls (n=35) [28]. ASD had the lowest vitamin B12 and the highest homocysteine levels while ADHD had intermediate levels. They also noted that Oppositionality and hyperactivity and/or impulsivity may be related to vitamin B12 and homocysteine levels in children with ADHD.

Clinical trials

Pubmed search yielded only 4 Intervention studies using B-12 in children with ASD/ADHD (all were for ASD). Of these only two studies report the impact of supplementation on behavioral rating and biochemical B-12 status together. Hendren et al randomized 57 children with ASD to receive either 8 weeks of treatment with methyl B12 (75 mcg/kg) or saline placebo every 3 days in a subcutaneous injection [29]. The primary outcome measure was overall improvement in symptoms of ASD as measured by the Clinical Global Impressions-Improvement (CGI-I) score. Secondary outcome measures included changes in the Aberrant Behavior Checklist (ABC) and the Social Responsiveness Scale (SRS). Laboratory measures of methionine methylation and antioxidant glutathione metabolism were assessed at baseline and 8 weeks. The primary outcome measure - the clinician rated CGI-I score -was statistically significantly better (lower) in the methyl B12 group (2.4) than in the placebo group (3.1) (0.7 greater improvement in the methyl B12 group, 95% CI 1.2–0.2, p = 0.005). Clinical improvement among children treated with methyl B12 was positively correlated with increases in plasma methionine (p = 0.05), decreases in S-adenosyl-l homocysteine (SAH) (p = 0.007) and improvements in the ratio of S-adenosylmethionine (SAM) to SAH (p = 0.007), indicating an improvement in cellular methylation capacity. No improvements were observed in the parent-rated ABC or SRS.

However, Bertoglio et al in a cross over trial did not find any statistically significant differences in the overall [30]. However, Nine (9 of 30) subjects (30%) demonstrated clinically significant improvement on the Clinical Global Impression Scale and at least two additional behavioral measures. More notably, these responders exhibited significantly increased plasma concentrations of GSH and GSH=GSSG means for behavior or glutathione endpoints between active and placebo groups. This led the authors to conclude that methyl B12 may alleviate symptoms of autism in a subgroup of children, possibly by reducing oxidative stress. An increase in glutathione redox status (GSH=GSSG) may provide a biomarker for treatment response to methyl B12. Also, the cross-over design of the study may not be most appropriate to answer the study question given that cobalamin could be stored in the liver for a long time up to 2 to 3 years.

The other two studies primarily evaluated the impact of supplementation on biochemical parameters. James SJ, et al. in 2009, supplemented 40 autistic children with 75 μg/kg methylcobalamin (2 times/wk) and 400 μg folinic acid (2 times/d) for 3 months [31]. Plasma concentrations of transmethylation/ transsulfuration metabolites and glutathione redox status in autistic children were measured as compared to controls. There were significant increases in cysteine, cysteinylglycine, and glutathione concentrations (P < 0.001). The oxidized disulfide form of glutathione was decreased and the glutathione redox ratio increased after treatment (P < 0.008). Kaluzna et al recruited 51 children (30 ASD and 21 controls) [32]. Autistic children were supplemented daily with Group A1: vitamins B6, B12, and folic acid and Group A2: vit B6 and B12 in the dose of 200 mg, 1.2 μg, and 400 μg, respectively. All children followed a sugar-free diet. Pre vs post-treatment (A1 and A2) in autistic children: Homocysteine levels:

2.41 ± 1.10 vs 1.13 ± 0.44 and 1.33 ± 0.39 mmol/mol creatinine for A1 and A2 groups, respectively. The authors concluded that the intake of vitamins B6 and B12, together with folic acid, was more effective in lowering the levels of urinary homocysteine than the intake of vitamins B6 and B12 alone.

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Table 2: Clinical Efficacy of Vitamin B-12 in children with ASD and/or ADHD.

S.No.	Author	Country	Subjects/ Selection	Study Design	Study group/ Methods	Outcome variables	Results	Conclusion
1	Pąsca SP, 2006 [17]	Romania	Total(n)= 21 Autism(n)= 12 Control(n)= 9 Diagnostic Criteria: DSM-IV	CCS	2 groups: cases and controls. Cross-sectional data	tHcy and vitamin B12 in plasma	*Autism vs Control:* Hcy levels 9.83 ± 2.75 vs. 7.51 ± 0.93 μmol/L (P = 0.01) respectively B12 levels assayed only in the autistic group were found to be suboptimal for 7 children (of a total of 12) and lower for 2 of them (of a total of 12) compared to the age-matched reference ranges (9 children).	Children with autism had higher levels of tHcy and suboptimal levels of vitamin B12
2	Kałużna-Czaplińska J, 2011 [18]	Poland	Total (n)= 55 Autism (n) =34 Control (n) =21 Age= 4-11yrs Diagnostic Criteria: DSM-IV	CCS	2 groups: cases and controls Overnight urine samples were collected at 9 am once a week, for up to three consecutive months for both groups	Homocysteine (Hcy) levels in urine for both groups	*Autism vs Control*: Hcy levels 2.36 ± 1.24 vs. 0.76 ± 0.31 (mmol/mol creatinine) (P< 0.05) respectively.	The level of urinary homocysteine for autistic children is significantly higher than that for healthy ones.
3	Ali A, 2011 [19]	Oman	Total (n)= 80 ASD=40 Control=40 Age=3-5yrs Diagnostic Criteria: DSM-IV- TR	CCS	2 groups: cases and controls Fasting blood samples for serum homocysteine, serum folate and Vit B12 were measured in both groups	Serum homocysteine, folate and Vit B12	*ASD vs Control:* serum Hcy levels 20.1 ± 3.3 vs. 9.64 ± 2.1 (μmol/L) (P < 0.05)serum folate 1.8 ± 0.4 vs. 6.1±0.6 (μg/L) (P < 0.05) vitamin B(12) levels 191.1 ± 0.9 vs. 288.9 ± 1.3 (pg/mL) (P < 0.05)	High fasting serum homocysteine and low folate /vitamin B(12) levels could be used as biomarkers for an early diagnosis of ASD
4	Al-Farsi 2013 [20]	Oman	Total (n)= 80 ASD=40 Control =40 Age= 3-5yrs Diagnostic Criteria: Childhood Autism Rating Scale based on DSM-IV-TR	CCS	2 groups: a hospital-based case- control study Participants mother was interviewed for data collection from both groups	· Dietary intake through food diary and Reduced Dietary Questionnaire · Serum levels of folate, B12 and homocysteine	*ASD vs Control:* Dietary intake of B12 1.3 vs. 2.2 (μ/d) (P=0.02) and folate 136.3 ±5.2 vs. 230.5±3.7 (μ/d) (P=0.04) Serum B12 183.6 vs. 341.2 (pg/mL) (P=0.001), Folate 2.1±0.3 vs. 7.3±0.4 (μg/L) (P=0.001) and Hcy 6.59± 0.6 vs. 3.92±0.5 (μmol/L) (P=0.004)	Omani children with ASDs exhibit significant deficiencies in folate and vitamin B12
5	Bala KA, 2016 [21]	Van, Turkey	Total (n)= 42, ASD= 21, Control=21 Age= 2-18yrs Diagnostic Criteria: (DSM-V) and (DSM-IV-TR)	CCS	2 groups: cases and controls	Plasma amino acid, B12 level and vitamin D levels	*ASD vs Control*: Vitamin B12 levels 233.62±60.7 and 428.5±173.8 (P<0.001)	Both vitamin B12 and D were significantly lower in the ASD group compared to controls.
6	Bala KA, 2016 [22]	Van, Turkey	Total (n)= 77 children and adolescents, ADHD (n) = 34, ASD (n) = 16, Controls (n) = 27 Diagnostic Criteria: DSM-V and DSM-IV	CCS	The blood samples were obtained between 8:00 and 9:00 a.m. for all groups	Serum vitamin B1, Folate and 25(OH) vitamin D	*ADHD vs. ASD vs. Control:* B12 levels 371.72±160.63 vs. 235.13±68.68 vs. 424.04±167.94 (pg/ml) (P=0.001) Folate levels 10.16± 2.93 vs 9.17 ±3.96 vs 8.52 ±3.75 (ng/mL) (P>0.05) 25 OH D 19.49±8.53 vs. 15.11±7.47 vs. 28.73±9.04 (ng/dL) P<0.001)	ASD group had the lowest vitamin B12 levels, whereas the vitamin B12 levels of the ADHD group were significantly lower compared to the controls

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7	Chen J, 2016 [23]	China	Total (n)= 136; ASD=68; Controls=68 Age:3-7yrs Diagnostic Criteria: DSM-V	CCS	Archived maternal blood samples (11-13 weeks gestational age) were identified for participants and compared with their offspring	maternal serum B12 and homocysteine levels first trimester were compared with ASD in offspring	*ASD vs Control :* Vit B12 levels 568.5 (487.4-633.1) vs. 555.4 (482.4- 622.8) (pg/ml)(P=0.42) HCY 13.8 (11.4-14.9) vs. 13.5 (10.6-14.8) (*μ*mol/l) (P= 0.63)	Maternal serum levels vit B12, and HCY were not significantly associated with the risk of ASD.
8	Meguid NA, 2017 [24]	Egypt	Total (n)= 160 ASD: 80 Control: 80 Age: 4-6yrs Diagnostic Criteria: DSM-IV- TR, CARS, ADI-R	CCS	2 groups: cases and controls Anamnestic interviews and health status, FFQ and 3 days food diary was noted, and fasting blood samples were taken for B12 for both groups	Serum B12, FFQ, 3 day food diary	*ASD vs Control :* Dietary B12 intake 0.39 ± 0.12 vs. 0.85 ± 0.15 (*μ*g/day) (P=0.001) Correlation between dietary intake of B12 and its level in serum (r=0.605)	Children with autistic disorder had significantly low intake of vitamin B12. Also, significantly lower levels of vitamin B12 in children with autistic disorder compared to controls.
9	Raghavan R, 2018 [25]	Human	1257 mother-child pair ASD=87 Neurotypical group =1171 ASD: Children who concomitantly had ASD and ADHD, ASD and other developmental disabilities, Children without ASD constituted the 'neurotypical' group	Cohort	Recruited at birth, maternal plasma folate and B12 were measured from samples taken 2-3 days after birth. Cases were followed through childhood	Exposures of maternal vitamin B12 supplementation during preconception, first, second, and third trimesters were corelated with ASD	very high B12 (≥536.8 pmol/L) and plasma folate (≥60.3 nmol/L) showed 2.5 times increased risk; 95% CI (1.4, 4.5), (1.3, 4.6) respectively	Extremely high maternal plasma folate and B12 levels at birth were associated with ASD risk.
10	Altun H, 2018 [26]	Turkey	Total (n)= 105 ASD=60 Control= 45 Age= 3-12 yrs Diagnostic Criteria: DSM- IV-TR	CCS	2 groups: cases and controls Venous blood was collected between 8:00 and 10:00 AM for both groups	• homocysteine • vitamin B12 • vitamin D, • vitamin D receptor (VDR), • vitamin B6 • folate	*ASD vs Control :* Hcy levels 8.90±0.19 vs. 7.46±0.21 (*μ*mol/L) (*P*<0.001) Vitamin B12 levels 181.5±41.61 vs. 382.06±71.34 (pg/ml) (P<0.001) Vitamin D levels 13.79±1.03 vs. 16.58±1.06 (ng/ml) (P<0.001) VDR 1.24±0.11 vs. 1.92±0.26 (ng/ml) (P<0.001) Vitamin B6 25.17±3.64 vs. 53.06±7.95 (ng/ml)(P<0.001) Folate 121.16±8.04 vs. 172.31±17.19 (pg/ml) (P<0.001)	The study shows that low serum levels of vitamins D, B6, B12, folate and VDR as well as high homocysteine are important in the etiopathogenesis of ASD.
11	Guo M, 2018 [27]	China	Total (n)= 371 ASD= 274 Control= 97 Mean age= 2-7 yrs Diagnostic Criteria: DSM-V, The symptoms of the patients were assessed with the ABC , SRS and neurodevelopment was evaluated with GDS	CCS	Fasting blood samples were taken	Mineral and vitamin status of autistic children and its relationship with autistic symptoms	No significant difference was found regarding Vit B12 between ASD group and control group (p = 0.106)	No significant correlations between SRS, GDS or subscale scores and Vit B12

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12	Yektaş Ç, 2019 [28]	Turkey	Total (n)= 118 ADHD=48 ASD=35	CCS	Serum vitamin B12, folate and homocysteine concentrations were measured	Serum concentrations of vitamin B12, folate and homocysteine	*ASD vs ADHD vs Control:*	ASD had the lowest vitamin B12 and the highest homocysteine levels
			controls=35					Oppositionality and hyperactivity and/or impulsivity may be related to vitamin B12 and homocysteine levels in children with ADHD
			Diagnostic Criteria: CARS, Turgay-DSM-IV and DBDRS				Vitamin B12 268 (407) *vs* 929 (774) *vs* 1611 (357)	
							(pg/mL)	
							Folate 1315(302) vs. 1229 (701) *vs.* 1319 (155)	
							(ng/ml)	
							Homocysteine 1912 (598) *vs* 1582 (238) *vs* 1297	
							(487) (*μ*mol/L)	
13	James SJ, 2009 [29]	Human, US	Total (n)= 82 Autistic children=40 Control: 42	CT	40 autistic children were treated with 75 *μ*g/kg methylcobalamin (2 times/wk) and 400 *μ*g folinic	Plasma concentrations of transmethylation /transsulfuration metabolites and glutathione redox status in autistic children as compared to controls	There were significant increases in cysteine, cysteinylglycine, and glutathione concentrations (P < 0.001). The oxidized disulfide form of glutathione was decreased and the glutathione redox ratio increased after treatment (P < 0.008).	The significant improvements observed in trans- methylation metabolites and glutathione redox status after treatment suggest that targeted nutritional intervention with methylcobalamin and folinic acid may be of clinical benefit in some children who have autism
			Age: 2-7yrs		acid (2 times/d) for 3 mo.			
					Results were measured before and after treatment and compared with values measured in age- matched control children			
			Diagnostic Criteria: DSM-IV and					
			CARS >30					
14	Bertoglio K, 2010 [30]	US	Autistic children(n) =30	CT	6 weeks of placebo and 6 weeks of methyl B12 at a dose of 64.5 mcg/kg every three days administered subcutaneously into the buttocks	Blood for GSH analysis and behavioral assessments at baseline, week 6, and week 12.	No statistically significant differences in the overall means for behavior or glutathione endpoints were identified between active and placebo groups	Methyl B12 is ineffective in treating behavioural symptoms of autism
			Control: 21 Age: 3-8yrs	(Crossover)	Fasting blood sample were			
			Diagnostic Criteria: DSM-IV and nonverbal IQ>= 49		collected			
15	Kałużna-Czaplińska J, 2011 [31]	Poland	Total (n)= 51	RCT	For each autistic child, the homocysteine level in urine was measured twice:	Homocysteine levels in urine:	Non-autistic homocysteine levels: 0.76 ± 0.31 mmol/mol creatinine	The intake of vitamins B6 and B12, together with folic acid, was found to be more effective in lowering the levels of urinary homocysteine than the intake of vitamins B6 and B12 alone.
			Autistic (n)= 30		Autistic Children were supplemented daily with Group A1: vitamins B6, B12, and folic acid and Group A2: vit B6 and B12 in the dose of 200 mg, 1.2 μg, and 400 μg, respectively. All children followed a sugar-free	1. Baseline for all	Pre vs post-treatment (A1 and A2) in autistic children:	
			Control (n)= 21		diet.	2. 3 months after supplementation for autistic children (A1 and A2)	Homocysteine levels: 2.41 ± 1.10 vs 1.13 ± 0.44 and	
			Age: 4-11 years				1.33 ± 0.39 mmol/mol creatinine for A1 and A2 groups, respectively	
			Diagnostic Criteria: DSM-IV					

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16	Hendren RL, 2016 [32]	California	Total ASD (n)= 57 Intervention (n)= 28 Placebo (n)= 29 Age: 3-7yrs Diagnostic Criteria: ADI-R and the ADOS	RCT	8 weeks of treatment with methyl B12 (75 μg/kg) or saline placebo every 3 days in a subcutaneous injection.	Clinical Global Impressions-Improvements (CGI-I) score	*Intervention vs Placebo:* Mean CGI-I score 2.4, lower-better *vs* 3.1 (0.7 greater improvement in the methyl B12 group, 95% CI 1.2- 0.2, p = 0.005)	Methyl B12 treatment improved clinician-rated symptoms of ASD that were correlated with improvements in measures of methionine metabolism and cellular methylation capacity.

Foot notes: ABC: Autism Behavior Checklist; ASD: Autism Spectrum Disorder; ADHD: Attention Deficit Hyperactivity Disorder; ADI-R: Autism Diagnosis Intervention-Revised; ADOS: Autism Diagnostic Observation Scale; CCS: Case Control Study; CARS: Childhood Autism Rating Scale; CT: Clinical Trial; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; DSM-V: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; DBDRS: Disruptive Behavior Disorder Rating Scale; FFQ: Food Frequency Questionnaire; GDS: Gesell Developmental Scale; HCY: Homocysteine; RCT: Randomized Control Trial; SRS: Social Responsiveness Scale; thcy: Total homocysteine

Conclusion

In conclusion, there is strong theoretical basis for the role of Vitamin B-12 in DNA methylation and nerve myelination and hence it is a potential suspect for neurodevelopmental disorders of childhood like ASD and ADHD. Deficiency of B-12 is common worldwide and especially in India. The deficiency is reported to be particularly severe in vegetarian populations. There is ample observational data (with a few exceptions) from developed countries documenting the relationship between B-12 deficiency and ASD. Studies on ADHD are fewer and hence less conclusive. Intervention studies using B-12 in ASD children have consistently demonstrated biochemical improvement. There is paucity of trial literature on the clinical impact of B-12 supplementation in cases with ASD in terms of behavior ratings. The few existing studies were only from developed countries and support a potential role for B-12 supplementation in children with ASD although the evidence is not strong. The studies were conducted with small sample sizes, showed weak differences and were weak in design. While it is possible that B-12 might be the effect of restricted dietary preferences in neurologically compromised children. It is also possible that some of the neurological effects of deficiency at a developmentally sensitive stage may not be reversible. None of the studies were conducted in micro-nutritionally high-risk settings or in developing countries. Also, none of studies have evaluated the preventive or longer-term impact of supplementation. Further work should hence be urgently considered to address these lacunae.

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