North Clin Istanb 2023;10(6):790–796
doi: 10.14744/nci.2022.33279

Original Article PEDIATRICS

Just a vitamin? Should cobalamin (Vitamin B12) levels be checked in children with neurological disadvantages?

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ABSTRACT

OBJECTIVE: The assay of serum cobalamin (Cbl) level is commonly used to diagnose Cbl deficiency. Unexpectedly, the elevated Cbl levels may be determined in some of the patients and its interpretation is difficult. We investigated the association between elevated Cbl levels and a variety of clinical entities in patients presenting with various neurological symptoms.

METHODS: The data were obtained from the patients' electronic medical records in a tertiary hospital affiliated with a university. The pediatric patients with serum Cbl levels above 1000 pg/mL were included in the study. The patients with serum Cbl levels below 900 pg/mL and above 200 pg/mL constituted the control group.

RESULTS: The mean Cbl level of the patients with neurological problems was 1424.2±354.2 pg/mL, whereas the average Cbl level of neurologically healthy was 1316±317.8 pg/mL, and the difference was statistically significant. While the rate of having neurological deficits or symptoms in the study group was found to be 24%, this rate was only 18% in the control group. Unexpectedly, despite elevated Cbl level, the high mean corpuscular volume rate was higher in the study group compared to the control group.

CONCLUSION: This study highlights the importance of the disorders of Cbl metabolism in patients presenting with various neurological symptoms. In children with neurological deficits, serum Cbl levels should be checked. In case of high Cbl level is determined, patients should be followed up closely, and further investigations should be performed in terms of Cbl metabolism disorders.

Keywords: Diagnostic strategy; elevated cobalamin level; neurological deficit; vitamin B12.

Cite this article as: *Kocaoglu C, Akturk S. Just a vitamin? Should cobalamin (Vitamin B12) levels be checked in children with neurological disadvantages? North Clin Istanb 2023;10(6):790–796.*

Cobalamin (Cbl) synthesization lacks in humans and exists only in animal foods. Such food includes dairy products, meat, fish, and eggs. 2–3 mg of Cbl is stored primarily in the liver [1]. In infancy, while the recommended dietary intake of Cbl is 0.4 μg/day for the ages of 0–6 months and 0.5 μg/day for 7–12 months of age, the daily requirement for children and adolescents ranges from 0.7 to 2 μg/day [2]. The uptake of Cbl takes place in the terminal ileum with the aid of the intrinsic factor. After the uptake by the ileum, while about 20% of Cbl binds to transCbl II, most of the remaining Cbl binds to circulating haptocorrin. The amount of free Cbl in the circulation is negligibly low. Haptocorrin is predominantly synthesized by myeloid cells. There are two forms of this synthesis: The sialic acid-rich form and the sialic acid-poor form. It is considered that the former is produced by myeloid precursor cells, whereas the latter is produced more by mature granulocytes [3]. The function of haptocorrin has yet to be elucidated. However, it may be playing a role in

Received: June 13, 2022 *Revised:* November 20, 2022 *Accepted:* December 13, 2022 *Online:* November 20, 2023

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the defense against microorganisms [4]. Vitamin B12 or Cbl has a variety of biological functions in mammalians. Especially, Cbl role plays in the nervous system as a cofactor methionine synthesis from homocysteine (methionine synthase pathway) and in hematopoiesis as cofactor succinyl-CoA synthesis from methylmalonyl-CoA (methylmalonyl-CoA mutase pathway). Cbl deficiency in children may present as megaloblastic anemia or a variety of neurological symptoms such as hypotonia, irritability, lethargy, developmental delay, cerebral atrophy, convulsion, and movement disorders. Even further, mental deterioration, encephalopathy, and extrapyramidal signs may also be seen in some patients. Favorable response is generally achieved through Cbl support therapy, and especially neurological symptoms may improve in a few days, although the recovery rates may vary from one patient to another [5, 6].

The assay of serum Cbl level is commonly used to diagnose Cbl deficiency. Unexpectedly, the elevated Cbl levels may be determined in some of the patients and its interpretation is difficult. In our study, the source of inspiration was the patients admitted to the pediatric intensive care unit due to various reasons and found to have high values of mean corpuscular volume (MCV) during the routine examinations. It was noteworthy that as opposed to the expectations, serum Cbl values were high in some of these patients; moreover, most of these children had neurological deficits. Although Cbl deficiency is frequently discussed in the literature, the number of publications is very limited concerning children with high Cbl levels. However, some studies have recently reported that elevated serum levels of Cbl might be a sign of serious and life-threatening diseases, such as myeloproliferative disease, acute hepatitis, severe alcoholic liver disease, and cirrhosis [4, 7–9].

Our primary motive was to understand the unexpected elevated Cbl levels and its clinical significance in the patients suspected of Cbl deficiency. In this context, we investigated the association between elevated Cbl levels and a variety of clinical entities, including neurological deficits, psychiatric disorders, and visual impairment.

MATERIALS AND METHODS

The pediatric patients with serum Cbl levels above 1000 pg/mL were included in the study and called as the study group. The control group was composed of randomized among children whose Vitamin B12 levels were found to be normal during the study period.

Highlight key points

- The mean serum Cbl level of the group with neurological problem was higher than those of neurologically healthy.
- While high MCV was detected as 20.8% among those with neurological deficits, the rate of having high MCV was only 3.9% among those without any neurological deficits.
- Children with neurological deficits may have defects in the metabolism and use of Cbl.
- In patients presenting with various neurological symptoms, the Cbl metabolism disorder should be kept in mind, and serum Cbl levels should be checked.

Patients with serum Cbl levels below 900 pg/mL and above 200 pg/mL were considered normal. Cbl and folate levels were measured by Simens Advia Centaur® XP immunoassay system using the chemiluminescence method. Those who were vegetarian received medicine containing Cbl or valproate, and the patients with thalassemia were excluded from the study. There were no patients with hepatitis, alcoholic liver disease, cirrhosis, rheumatoid arthritis, cystic fibrosis, or any malignancy in the entire study group (the study group and control group). In the study group, three patients were excluded due to the use of drugs containing Cbl, two patients due to thalassemia major, and one patient due to chronic kidney disease (CKD). In the control group, two patients were excluded from the study due to CKD, one patient for type I diabetes mellitus, and one patient for heredofamilial amyloidosis. The data were obtained from the patients' electronic medical records in a tertiary hospital affiliated with a university. All medical charts were examined by the same investigator. The neurological deficits and the secondary pathologies (psychiatric and ophthalmological) of patients were recorded as well as their serum Cbl, folate levels, and hematologic parameters. The patients who presented with the change of consciousness, personality change, convulsion, paresis, and paralysis were defined as having neurological deficits. Ophthalmological (misting, bloodshot, eye pain, flashes of light, and sensitivity to light) and psychiatric (learning disorders, attention deficit, hyperactivity, and behavioral disorders) problems were determined according to the patient's application to the relevant polyclinics with any complaints.

The study was approved by the local ethics committee with the number E-86737044-806.01.03. The study was conducted by the Declaration of Helsinki.

Statistical Analysis

The statistical analyses were performed using the Statistical Package for the Social Sciences for Windows, release 22.0 (SPSS, Chicago, IL, USA). The results were accounted for as mean±standard deviation or median interquartile range (IQR), and the statistical significance was accepted as $p<0.05$. While the normality of data was tested using the Kolmogorov–Smirnov test, the Mann–Whitney U test, or t-test was used to compare the mean values. The Pearson or Spearman correlation analysis was utilized to determine the correlations.

RESULTS

The data of 4360 patients were scanned and analyzed retrospectively in terms of serum Cbl levels between 2016 and 2020. The percentage of those with elevated serum Cbl level was determined as 4.6%. A total of 300 patients constituted the entire study, including 200 in the study group and 100 in the control group. In the entire study group, the median age was calculated as 4 years (min 0, max 16) (IQR 1–10), and 41.7% (n=125) and 58.3% (n=175) were males and females, respectively.

In the study group, the median age was 3 years (min 0, max 16) (IQR 1–8), and 45% (n=90) and 55% (n=110) were composed of males and females, respectively. In this group, the mean Cbl level was detected as 1342±329.3 pg/mL (min 1000, max 2280), 95% confidence interval of 1296.1–1387.9. In the control group, the median age was 4 years (min 0, max 16) (IQR 2-13), and 35% (n=35) and 65% (n=65) were males and females, respectively. In this group, the mean Cbl level was calculated as 364.3±144.9 pg/mL (min 109, max 918), 95% confidence interval 335.6–393.1. The age and gender distributions of the study and control groups were similar ($p>0.05$).

The rate of having neurological deficits or symptoms in the study group was found to be 24% (n=48) (Table 1). In addition, of the patients in this group, 7% had psychiatric, 18.5% ophthalmological, and 10.5% had both psychiatric and ophthalmological symptoms. While the rate of those with normal MCV was 50.5%, the rate of those with MCV low and high was 41.5% and 8%, respectively. The rate of having neurological deficits or symptoms in the control group was 18% (n=18). In addition, 6% of the patients in the control group had psychiatric, 28% had ophthalmologic and 9% had both psychiatric and ophthalmologic symptoms. While the rate of MCV of the normal was 70%, the rates of MCV low and high were 28% and 2%, respectively.

Table 1. Incidence of signs or symptoms in the study and control groups

Symptoms	Study group		Control group		p
	n	%	n	%	
Neurological	48	24	18	18	>**0.05**
Low MCV rate	83	41.5	28	28	<**0.05**
Normal MCV	101	50.5	70	70	<**0.05**
High MCV rate	16	8	2	2	<**0.05**

MCV: Mean corpuscular volume.

Table 2. Comparison of cobalamin levels of groups in terms of neurological deficits and secondary pathologies

	Neurological deficits (+)	Neurological deficits (-)	p
Cbl level of study group	1424.2±354.2	1316±317.8	<**0.05**
Cbl level of control group	344.4±121.5	368.7±149.8	>**0.05**

Cbl: Cobalamin.

In the study group, the mean Cbl level of the patients with neurological deficits was 1424.2±354.2, whereas the average Cbl level of those without any neurological deficits was 1316±317.8, and the difference was statistically significant ($p<0.05$) (Table 2). However, in the control group, the mean Cbl level of those with neurological deficits was detected as 344.4±121.5, whereas the average Cbl level of those without any neurological deficits was 368.7±149.8, and this difference was not statistically significant ($p>0.05$). While 9 (18.8%) of 48 patients with neurological deficits in the study group were fed with enteral nutrition products, three (16.7%) of 18 patients with neurological deficits in the control group were fed with enteral nutrition products.

In the study group, while the mean Cbl level of the patients with secondary pathologies was 1348.2±326.1, the average Cbl level among those without any secondary pathologies was 1338.5±332.3, and this difference was not statistically significant ($p>0.05$). In the control group, the mean Cbl level of those with secondary pathologies was 398.6±156.1, whereas the average Cbl level of those without any secondary pathologies was found to be 338.4±131.3, and the difference was statistically significant ($p<0.05$). The data including MCV,

TABLE 3. Mean levels of folate, iron, iron-binding capacity and ferritin, and mean corpuscular volume

	Study group		Control group		p
Folate	13.5±6.3		11.3±4.8		>**0.05**
Iron	46.8±27		76.9±68.4		<**0.002**
IBC	306.4±67.2		286.6±81.5		>**0.05**
Ferritin	59.8±133.8		29.6±32.9		<**0.05**
MCV	75.2±17		78±7.6		>**0.05**
	Neurological deficits (+) n=48	Neurological deficits (-) n=152	Neurological deficits (+) n=18	Neurological deficits (-) n=82	
Folate	12.3±6.9	14.2±5.8	11.2±4.4	11.5±5.5	>**0.05**
IBC	281.5±65.2	318.6±65.6	326.7±80	263.5±74.4	<**0.05***
High MCV rate	20.8% (n=10)	3.9% (n=6)	2.4% (n=1)	2% (n=2)	<**0.001****

IBC: Iron-binding capacity; MCV: Mean corpuscular volume; *: The difference was between the groups with neurological deficits (+) and (-) in the control group; **: The difference was between the groups with a neurological deficit (+) and (-) in the study group.

mean folate, iron, iron-binding capacity (IBC), and ferritin level of both groups are shown in Table 3. Compared to the control group, the mean serum iron level of the study group was found to be statistically significantly lower, whereas the average ferritin level was higher. There was no difference among MCV, mean folate, and IBC levels of both groups.

When the average folate levels were compared, no difference was observed between those with and without neurological deficits in both the study and control groups (Table 3). In the study group, among those with neurological deficits, the rate of the patients with high MCV was 20.8% (n=10), whereas the rate of having high MCV was only 3.9% (n=6) among those without any neurological deficits. However, among those with neurological deficits in the control group, the rate of those with high MCV was 2.4% (n=1), whereas the rate of having high MCV was only 2% (n=2) among those without any neurological deficits.

DISCUSSION

The unknown physiopathological basis for neurologic dysfunction in patients with elevated Cbl levels and the frequent divergence between the neurologic and hematologic manifestations inspired us to plan and carry out this work. Elevated serum concentration of Cbl is mostly considered to be non-hazardous in clinical practice and is usually underestimated due to there is no complete consensus regarding the assessment of high serum Cbl levels. However, elevated Cbl levels may be associated with various life-threatening situations. Recently, the number of studies investigating the relationship between neurological development and Cbl has increased [10–12]. We also observed that serum Cbl levels were higher in the patients with neurological deficits. Although the reason for low Cbl levels can be explained by poor nutritional status, it is not always likely to explain high Cbl levels, given the nutritional problems of children with neurological deficits. While the active form of Cbl constitutes approximately 6–20% of total serum Cbl, the remaining major part is bound to haptocorrin (also named holohaptocorrin) and is stored in the liver [13, 14]. Some authors have reported that the unexpectedly high values are due to increasing holohaptocorrin levels and tried to explain the situation by the probable holohaptocorrin leakage into the circulation due to the destruction of hepatocytes. Alternatively, the reduced uptake of holohaptocorrin by injured hepatocytes may contribute to elevated serum Cbl levels [15]. Consequently, elevated serum Cbl level consists of metabolically inactive haptocorrin complexes.

The relationship between Cbl and various neurological disorders has yet to be understood fully. It can be speculated that Cbl dysfunction and the resulting lack of activity of methionine synthase and methylmalonyl-CoA mutase, the accumulation of inactive Cbl analogs, and concurrent abnormalities in folate metabolism can

play a role in the development of different neurological symptoms. However, the roles of both methionine synthase and methylmalonyl-CoA mutase pathways in the pathogenesis of neurocognitive dysfunction have yet to be supported consistently in experimental animal and human studies [16, 17]. In addition, in animal models, the role of Cbl analogs inhibiting Cbl-dependent enzymes has not been confirmed yet. On the other hand, relatively increased serum folate, S-adenosylmethionine, cysteine, and cysteine-glycine levels in patients with pernicious anemia and neurologic deficits suggest a role for folate-mediated inhibition of glycine N-methyltransferase in the pathogenesis of neurologic symptoms [18]. Observations in gastrectomized rats with Cbl deficiency implicate the cytokines and growth factors as mediators of neurologic disorders [19]. The myelinolytic cytokines and tumor necrosis factor are increased in the spinal fluid of these animals, while the neurotrophic cytokines, epidermal growth factor, and interleukin 6 are decreased. Furthermore, it has been shown that neurologic lesions can be prevented in Cbl-deficient rats by intraventricular injections of tumor necrosis factor antibodies, epidermal growth factor, or interleukin 6 and induced in rats without Cbl deficiency by intraventricular injections of epidermal growth factor antibodies or tumor necrosis factor. In addition, increased tumor necrosis factor and decreased epidermal growth factor levels have been determined in Cbl-deficient humans and improved with the supportive treatment of Cbl [20].

Megaloblastic anemia is one of the most common signs of Cbl deficiency. However, neurologic changes sometimes occur in the absence of hematologic abnormalities [21]. In our study, 200 patients with high Cbl levels were described as the study group. Serum Cbl level in all cases was above 1000 pg/mL in this group, and MCV was above 90 fL in 36 (8%) patients. Especially given the roles played by Cbl as a cofactor both in the methionine synthase pathway in the nervous system and methylmalonyl-CoA mutase pathway in hematopoiesis, this made us think that there may be a disorder in Cbl metabolism. The fact that a higher elevation of MCV was detected in the patients with neurological deficits both in the study and control groups supported our hypothesis. In addition, hyperglycinemia has been considered a causative factor for neurological disturbances in x-linked Cbl disorders, and it has been shown that the clinical conditions of these patients can be improved with Cbl treatment.

In various previous studies, elevated Cbl levels were reported in acute hepatitis, severe alcoholic liver disease, cirrhosis, cancer, rheumatoid arthritis, cystic fibrosis, and myeloproliferative diseases, such as chronic myeloid leukemia, polycythemia vera, and hypereosinophilic syndrome [11, 12, 15, 22, 23]. While most studies investigating elevated Cbl levels have been carried out with adults, there are few studies performed on children. While one study suggested that increased immunoglobulin G level may cause elevated Cbl levels, in another study, it was reported that higher Cbl levels were seen in children receiving valproate therapy [24, 25]. In addition, in the study by LeBlanc et al. [26], high Cbl levels were associated with excessive production by gut bacteria. The data of our study showed that the patients with high Cbl levels have higher neurological deficit rates. Theoretically, elevated serum Cbl levels may be associated with functional disorders of Cbl metabolism. It should be kept in mind that Cbl metabolism-induced disorders may be the main reason for hospital admission, or such disorders may change the symptoms of the current disease. Thus, it may be appropriate to check Cbl levels in admission to the hospital, especially in patients with neurological deficits. While Carmel et. al. [23] reported the rate of elevated serum Cbl levels as 14% in the study performed in adults, the rates of elevated Cbl levels were reported as 13% in those with "moderate-to-high" (600–1000 pmol/L) and 7% in those with "very high" in a recent study by Arendt and Nexo [27]. In our study, the elevated serum Cbl ratio was found to be 4.6% in scanned hospital records, and our finding was compatible with that reported by the study of Arendt and Nexo.

As a result, elevated serum Cbl levels are a quite common laboratory finding, especially among children with neurological deficits, compared to the neurologically healthy population. Given that these children are often in a nutritional deficiency state, neurological deficits can sometimes be accompanied by signs of Cbl deficiency, such as megaloblastic anemia. Therefore, this made us consider a functional deficiency of Cbl, such as tissue uptake or action. However, it may be proposed that elevated serum Cbl levels may be due to the increased holohaptocorrin, or as Stenberg et al. [22] have speculated, subclinical gut inflammation may be playing a role in this increase. In addition, the changes in gut microbiota may have caused the increase. However, these mechanisms do not explain the MCV elevation seen more commonly in patients having elevated Cbl levels. The shortage of current knowledge leads to numerous unanswered questions and challenges. Therefore, clinicians should focus

on what to consider, when unexpectedly encountering elevated levels of Cbl in a patient evaluated for Cbl deficiency. The abovementioned situations, such as liver diseases, hematologic disorders, and the use of vitamin preparations containing Cbl should be ruled out in patients with unexpectedly elevated Cbl levels.

In the study group, while high MCV was detected as 20.8% among those with neurological deficits, the rate of having high MCV was only 3.9% among those without any neurological deficits. In the control group, however, these rates were 2.4% and 2% in those with and without neurologic deficits, respectively. Given that the study group consisted of patients with high Cbl levels, such a finding was surprising. It can be hypothesized that children with neurological deficits also have deficits in the metabolism and use of Cbl. However, it is difficult to determine whether such a deficit in Cbl metabolism is a reason or a result.

Our results do not allow us to conclude whether elevated Cbl levels could be a marker for a specific diagnosis. However, our study showed that more comprehensive investigations including other parameters of Cbl metabolism (total and Cbl-saturated transCbl, total haptocorrin, soluble TC receptor, sCD320, and methylmalonic acid) are needed to determine the further investigation indications and the clinical strategies to be followed on the discovery of elevated Cbl levels.

Conclusion

This study demonstrated the importance of interpreting serum Cbl levels in patients presenting with various neurological symptoms. We suggest that children with neurological deficits also have deficits in the Cbl metabolism. More comprehensive studies are needed to elucidate the changes in Cbl metabolism in patients with neurological disadvantages.

Acknowledgements: Authors thank Numan Duran for language editing.

Ethics Committee Approval: The Konya Provincial Health Directorate granted approval for this study (date: 05.03.2021, number: E-86737044-806.01.03).

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Authorship Contributions: Concept – CK; Design – CK; Supervision – CK; Materials – SA; Data collection and/or processing – SA; Analysis and/or interpretation – CK, SA; Literature review – CK, SA; Writing – CK; Critical review – CK, SA.

REFERENCES

1. Chalouhi C, Faesch S, Anthoine-Milhomme MC, Fulla Y, Dulac O, Chéron G. Neurological consequences of vitamin B12 deficiency and its treatment. Pediatr Emerg Care 2008;24:538–41. [CrossRef]
2. Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and its Panel on Folate, Other B Vitamins, and Choline. Dietary reference intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. 9, Vitamin B12. Washington (DC): National Academies Press (US); 1998.
3. Gimsing P. Cobalamin metabolism in chronic myelogenous leukemia. Dan Med Bull 1998;45:459–79.
4. Ermens AA, Vlasveld LT, Lindemans J. Significance of elevated cobalamin (vitamin B12) levels in blood. Clin Biochem 2003;36:585–90.
5. Graham SM, Arvela OM, Wise GA. Long-term neurologic consequences of nutritional vitamin B12 deficiency in infants. J Pediatr 1992;121:710–4. [CrossRef]
6. von Schenck U, Bender-Götze C, Koletzko B. Persistence of neurological damage induced by dietary vitamin B-12 deficiency in infancy. Arch Dis Child 1997;77:137–9. [CrossRef]
7. Karakurt N, Albayrak C, Yener N, Albayrak D. Does vitamin B12 deficiency in infants cause severe clinical symptoms necessitating intensive care? J Pediatr Emerg Intensive Care Med 2019;6:134–9. [CrossRef]
8. Solomon LR. Disorders of cobalamin (vitamin B12) metabolism: emerging concepts in pathophysiology, diagnosis and treatment. Blood Rev 2007;21:113–30. [CrossRef]
9. Baker H, Leevy CB, DeAngelis B, Frank O, Baker ER. Cobalamin (vitamin B12) and holotranscobalamin changes in plasma and liver tissue in alcoholics with liver disease. J Am Coll Nutr 1998;17:235–8. [CrossRef]
10. Kocaoglu C, Akin F, Caksen H, Böke SB, Arslan S, Aygün S. Cerebral atrophy in a vitamin B12-deficient infant of a vegetarian mother. J Health Popul Nutr 2014;32:367–71.
11. Bicakci Z. Growth retardation, general hypotonia, and loss of acquired neuromotor skills in the infants of mothers with cobalamin deficiency and the possible role of succinyl-CoA and glycine in the pathogenesis. Medicine (Baltimore) 2015;94:e584. [CrossRef]
12. Scalais E, Osterheld E, Weitzel C, De Meirleir L, Mataigne F, Martens G, et al. X-linked cobalamin disorder (HCFC1) mimicking nonketotic hyperglycinemia with increased both cerebrospinal fluid glycine and methylmalonic acid. Pediatr Neurol 2017;71:65–9. [CrossRef]
13. Refsum H, Johnston C, Guttormsen AB, Nexo E. Holotranscobalamin and total transcobalamin in human plasma: determination, determinants, and reference values in healthy adults. Clin Chem 2006;52:129–37. [CrossRef]
14. Brada N, Gordon MM, Wen J, Alpers DH. Transfer of cobalamin from intrinsic factor to transcobalamin II. J Nutr Biochem 2001;12:200–6.
15. Sugihara T, Koda M, Okamoto T, Miyoshi K, Matono T, Oyama K, et al. Falsely elevated serum vitamin B12 levels were associated with the severity and prognosis of chronic viral liver disease. Yonago Acta Med 2017;60:31–9. [CrossRef]
16. Metz J. Cobalamin deficiency and the pathogenesis of nervous system disease. Annu Rev Nutr 1992;12:59–79. [CrossRef]
17. Allen RH, Stabler SP, Savage DG, Lindenbaum J. Metabolic abnormalities in cobalamin (vitamin B12) and folate deficiency. FASEB J 1993;7:1344–53. [CrossRef]
18. Carmel R, Melnyk S, James SJ. Cobalamin deficiency with and without neurologic abnormalities: differences in homocysteine and methionine metabolism. Blood 2003;101:3302–8. [CrossRef]

19. Scalabrino G, Buccellato FR, Veber D, Mutti E. New basis of the neurotrophic action of vitamin B12. Clin Chem Lab Med 2003;41:1435–7. [CrossRef]
20. Peracchi M, Bamonti Catena F, Pomati M, De Franceschi M, Scalabrino G. Human cobalamin deficiency: alterations in serum tumour necrosis factor-alpha and epidermal growth factor. Eur J Haematol 2001;67:123–7. [CrossRef]
21. Aaron S, Kumar S, Vijayan J, Jacob J, Alexander M, Gnanamuthu C. Clinical and laboratory features and response to treatment in patients presenting with vitamin B12 deficiency-related neurological syndromes. Neurol India 2005;53:55–9. [CrossRef]
22. Stenberg R, Böttiger A, Nilsson TK. High levels of vitamin B12 are fairly common in children with cerebral palsy. Acta Paediatr 2020;109:1493–4. [CrossRef]
23. Carmel R, Vasireddy H, Aurangzeb I, George K. High serum cobalamin levels in the clinical setting--clinical associations and holo-transcobalamin changes. Clin Lab Haematol 2001;23:365–71. [CrossRef]
24. Jeffery J, Millar H, Mackenzie P, Fahie-Wilson M, Hamilton M, Ayling RM. An IgG complexed form of vitamin B12 is a common cause of elevated serum concentrations. Clin Biochem 2010;43:82–8. [CrossRef]
25. Keenan N, Sadlier LG, Wiltshire E. Vascular function and risk factors in children with epilepsy: associations with sodium valproate and carbamazepine. Epilepsy Res 2014;108:1087–94. [CrossRef]
26. LeBlanc JG, Milani C, de Giori GS, Sesma F, van Sinderen D, Ventura M. Bacteria as vitamin suppliers to their host: a gut microbiota perspective. Curr Opin Biotechnol 2013;24:160–8. [CrossRef]
27. Arendt JF, Nexo E. Unexpected high plasma cobalamin: proposal for a diagnostic strategy. Clin Chem Lab Med 2013;51:489–96. [CrossRef]