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Nervous System Lesion in Infants with Vitamin B12 Deficiency Anemia

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Abstract

Introduction: Vitamin B12 deficiency affects not only the bone marrow but also the nervous system. Usually, B12 hypovitaminosis develops slowly to over several years, although infants may also have this disorder.

Patients and Methods: We performed a retrospective analysis of clinical symptoms and results of routine laboratory testing in patients with vitamin B12 deficiency anemia. Our sample included 19 children from 3 - 24 months of age. All patients were treated at Krasnoyarsk Regional Clinical Center for Maternal and Child Health from 2012 to 2019. All participants had serum levels of vitamin B12 < 83 pg/mL.

Results: All patients were found to have nervous system disorders, including muscular hypotonia (100%), hypo- or adynamia and neurodevelopmental retardation (63%), and hyporeflexia (42%). One-third of children (32%) developed involuntary movements during treatment with cyanocobalamin.

A case is reported of an 8 month old boy with developmental regression and brain atrophy secondary to severe vitamin B12 deficiency. Timely cyanocobalamin treatment can prevent irreversible neurological injury.

Conclusion: Vitamin B12 deficiency in infants may manifest itself with neurological disorders that do not correlate with the degree of anemia. Children with muscular hypotonia and delayed psychomotor development should be tested for their serum level of vitamin B12 if all other potential causes of these disorders have been excluded. It is also important to perform differential diagnoses with paroxysmal conditions, including those induced by cobalamin therapy.

Keywords: *Infants; Vitamin B12 Deficiency Anemia; Involuntary Movements; Neurological Findings; Cyanocobalamin*

Introduction

The physiological role of vitamin B12 is unique in human body. Vitamin B12 is a cofactor of the important intracellular reactions (synthesis of DNA and succinyl-CoA) [1-3]. In case of pathological disorder of these reactions because of the vitamin B12 deficiency the cell proliferation is changed. Also excess of C15 and C17 fatty acids are formed. These leads to anomalous lipids structure of the nerves myelin [3-5]. On the contrary the methylmalonate (MMA) and homocysteine (Hct) are accumulated. These metabolites (MMA and Hct) have neurotoxic effects (demyelization, axon degeneration, neuron necrosis) [1,3,7-9]. Regardless of the cause of deficiency, this influences the function of all cells. The vitamin B12 deficiency is a multiple pathology condition but the bone marrow and the mucosa of gastric tract are suffered first of all. The main clinical features of vitamin B12 deficiency are macrocytic anemia, pancytopenia, gastrointestinal disorders,

cardiomyopathy, reproductive dysfunction and hard neurological deviations as seizures, coma, depressions, psychosis, atrophic changes in brain and optic nerve [2,10-14]. Neurological disorders occur independently of hematological in any age [1,6,8].

Vitamin B12 is not synthesized in the human body. Adults may tolerate vitamin B12 deficient diets for many years without apparent symptoms due to their endogenous stores [3]. The vitamin B12 deficiency can occur in infancy in case of vitamin B12 deficiency of mothers because of low cobalamin fetus store level and low concentration in the breast milk [3,7,10,11,14,16].

Purpose of the Study

An analysis of the signs and symptoms of the nervous system damage in infants with vitamin B12 anemia was performed.

Materials and Methods

Infants admitted to regional hospital (Krasnoyarsk Regional Clinical Center for Maternity and Childhood Protection) between 2012 to 2019 and suffered from vitamin B12 deficiency anemia were included in this study.

Retrospective analysis of clinical symptoms was performed. All infants were assessed by clinical and neurological examinations. Laboratory investigations included blood count, peripheral blood smear, serum screening as well as vitamin B12 and folic acid level. Serum vitamin B12 level was < 83 pg/mL in all cases. The level of folic acid was normal.

Cranial ultrasound was performed in all children. Electroencephalography (EEG) was performed in 15 children. Computer tomography (CT) was performed in 6 patients.

The treatment was performed by next regime: cyanocobalamin form in solution 0,5 mg/ml (Russian Federation) 5 mcg/kg every day by intramuscular or intravenous injection until reticulocytes increasing achieved, then 1 injection every other day until the normalization of hemoglobin level. Then the treatment has been continued in outpatient department.

Statistic analysis included correlation analyses by Spearman's rank coefficients (r_s) to identify the relationship between the parameters, and Wilcoxon T-test account for evaluation of the dynamics of test results after cyanocobalamin treatment. The median (Me), upper (Q1) and lower quartile (Q3) are used to describe nonparameric parameters.

Results of the Study

Of 19 patients aged 3 - 24 month (Me - 8 mo, Q1-5,5 mo, Q3-15 mo), 10 children were males and 9 - females. All children had been exclusively breast fed. Disease experience was from 2 week to 6 months. The patients condition was severe. Clinical signs and symptoms are presented in table 1. All children had changes in neurological status (Table 1). The main neurological symptoms were hypotonia (in 100% cases), low muscular activity (63%). 32% children had adynamia. The correlation analysis is refuted the possible connection of the detected motor disorders and muscular hypotension with the degree of anemia (r_s = 0,02, p = 0,5). On 12 children (63%) had retardation in motor activities (regress of acquired skills). 2 children had seizures, 3 infants - tremor before cobalamin treatment.

Symptom	Proportion (%)
Somatic status	
Fatigue	19/19 (100%)
Low-grade fever	1/19 (5%)
Weight loss	10/19 (53%)
Pallor	19/19 (100%)
Waxy skin	13/19 (68%)
Icteric skin	6/19 (32%)
Hyperpigmentation	5/19 (26%)
Petechiae	6/19 (32%)
Gunther glossitis	8/19 (42%)
Aphthous stomatitis	1/19 (5%)
Tachycardia at rest	13/19 (68%)
Vomiting	8/19 (42%)
Dysphagia	5/19 (26%)
Hepatomegaly at palpation	11/19 (58%)
Splenomegaly (+1,5-2 см)	7/19 (37%)
Constipation for 3 to 7 days	3/19 (16%)
Neurological status	
Muscular hypotonia	19/19 (100%)
Hypo- and adynamia	12/19 (63%)
Lowed tendon reflexes (bicipital and patellar)	8/19 (42%)
Lowed abdominal reflexes	7/19 (37%)
Reduced palatal reflex	7/19 (37%)
Tremor	3/19 (16%)
Structural epilepsy including West syndrome	2/19 (11%)
Involuntary movements due to therapy with cyanocobalamin	6/19 (32%)

Table 1: *Clinical symptoms in infants with vitamin B12 anemia.*

Cranial CT (in 6 children) detected brain atrophy and demyelination features. Laboratory changes presented in table 2 and 3. Thrombocytopenia was in 63% patients. Leucopenia and pancytopenia was in 26% patients. Hemolytic process was detected in 79%.

Parameter	Me (Q1-Q3)
Baseline	
Hb, g/L[1]	67 (60-80)
Ht, %	24,0 (19,2-24,6)
RBCs, x 10^{12} cells/L	2,2 (1,9-2,8)
Reticulocytes, %[1]	5 (3-12)
MCV, fL	102,2 (94,3-106,3)
MCH, pg	32,9 (29,4-35,1)
MCHC, g/L	33,0 (32,1-33,6)
RDW-CV, %	22,3 (19,9 - 25,8)
WBCs, x 10^9 cells/L	5,6 (4,1 - 6,8)
Leukopenia < 3500 cells/μL (proportion, %)	5/19 - 26%
Hypersegmented neutrophils detection (proportion, %)	9/19 - 47%
Platelets, x 10^9 cells/L	102 (60-296)
Thrombocytopenia < 150 cells/μL (proportion, %)	12/19 - 63%
Pancytopenia (proportion, %)	5/19 - 26%
Days 8-9 of vit. B12 administration	
Hb, g/L[1]	103 (91 - 115)
Reticulocytes, %[1]	25 (15 - 53)

Table 2: *Complete blood count in infants with vitamin B12 anemia.*

[1] - The increase in Hb and reticulocyte levels was significant, p < 0,01, Wilcoxon T-test: T = 3.

Parameter	Me (Q1-Q3)
Serum iron, μmol/L	25,3 (12,9 - 29,5)
Total bilirubin, μmol/L	23 (16,5 - 38)
Indirect hyperbilirubinemia, (proportion, %)	6/19 - 32%
LDH, U/L	1415 (758 - 1789)
Elevated LDH (proportion, %)	15/19 - 79%
AST, U/L	62 (35 - 97)
Elevated AST (proportion, %)	12/19 - 63%
ALT, U/L	36 (15 - 68)
Elevated ALT (proportion, %)	10/19 - 52%

Table 3: *Main biochemical parameters in infants with vitamin B12 anemia.*

During cyanocobalamin therapy in dose 5 mcg/kg/daily the involuntary movements were occurred in 6 children (32%) such as tremor and myoclonus: 2 children - on fourth day, 3 children - on fifths day, 1 children - on sixes day. During cobalamin replacement therapy improvement was achieved on 2 - 5 days: general activity, increasing appetite, muscular tone gross, motor skills rehabilitation. Repeated control analysis of complete blood count on 8 - 9 days of vitamin B12 therapy was demonstrated that Hemoglobin (Hb) and Reticulocytes were increased. Increase in Hb and reticulocyte levels was significant (p < 0,01, Wilcoxon T-test). All children were discharged from the hospital in good condition under the outpatient doctor attention.

Clinical case

An 8-month-old boy was admitted to our hospital. The boys mother had complains which had developed over the two months: lethargy, absence of spontaneous motor activity, weight loss (500 gr per mo). The boy passively laid in the crib and did not have interest in toys and surrounding people. Also, the child had dysphagia, vomiting, stools no more than 1 time a week. The boy eventually stopped feeding (only maternal breast milk randomly in a day). There was regression of motor skill development (boy lost the ability turn over and sit).

History: Gestation age was 40 weeks. Birth weight - 3950g. Apgar score - 8/9. The boy had exclusively breast fed. Motor skills: keeping the head upright - from 1 mo, turning over - 4 mo, sitting - 6 mo. The vaccination had been in term.

Objectively: Patient condition was very severe. Voice was very weak and squeaky. There was negative emotional reaction even from a doctor touch. The skin was pallor with wax color. The hyperpigmentation was detected in skin folds, nipples and scrotum. The mucous membrane of the oral cavity, upper palate and tongue had specific crimson color. The Gunther glossitis and aphthous stomatitis were revealed. The patient had loss of subcutaneous fat. Respiratory rate 28 per minutes. No breath abnormality. Heart rate - 150 per minutes. Heart tone were normal. Weak systolic noise. The boy had asymmetrically enlarged belly because of constipation, hepatomegaly + 5 sm over the costal and splenomegaly (+ 1,5 sm). The boy had total muscle hypotonia and tendon hyporeflexia.

Blood count: Hb 101 g/L, red blood cells (RBCs) 2,5 x 10^{12} cells/L, mean corpuscular volume (MCV) 111,5 fL, mean concentration hemoglobin (MCH) 40,3 pg, mean corpuscular hemoglobin concentration (MCHC) 36,1 g/L, red cell distribution width (RDW-CV) 28,9%, white blood cells (WBCs) 5,3 x 10^{9} cells/L, Platelets 307 x 10^{9} cells/L. Serum vitamin B12 level was < 83 pg/mL. The maternal vitamin B12 level was < 83 pg/mL also.

Cranial CT revealed cerebral atrophy and moderate enlargement of the ventricle and subarachnoid liquor structures (Figure 1). EEG excluded epileptic activity. So, diagnosis of the vitamin B12 deficiency was defined. The treatment of cyanocobalamin was started by intramuscularly (See material and methods). On the next day we fixed dramatic improvement in baby's condition: his muscle tone improved significantly and patient could sit by himself. On the fourth day after vitamin B12 treatment onset involuntary movements were occurred such as tremor and myoclonus of the facial muscles, tongue, arms and legs. But cobalamin therapy did not interrupted. Involuntary movements were regressed spontaneously. The patient was invited to examination in 9 months. There were revealed no pathologic symptoms in somatic and neurological status. Cranial CT detected the regress of the atrophic changes (Figure 2).

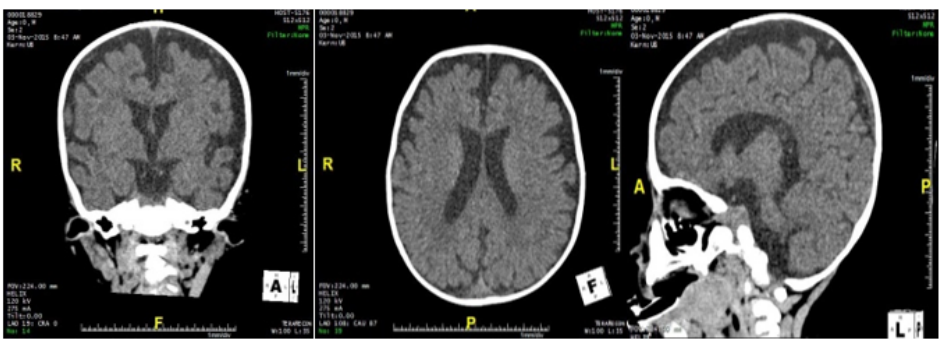

Figure 1: *Baseline CT-scan. Cerebral atrophy and moderate enlargement of the ventricles and subarachnoid liquor structures have been detected.*

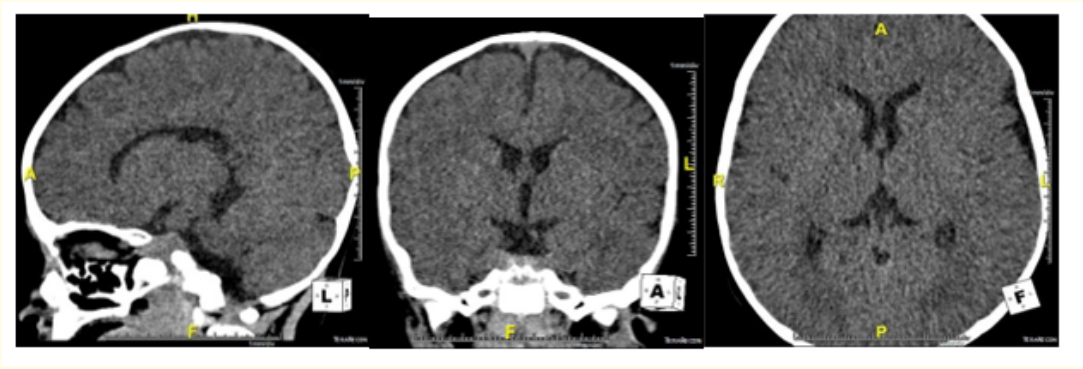

Figure 2: *CT-scan in 9 months of cobalamin administration. Regress of the atrophic changes has been detected.*

Discussion

Damage of the nervous system in infancy secondary to severe vitamin B12 deficiency was reported widely [2,7,10,12-14,18-20]. Neurological lesions were revealed in all infants in our study. Neurological disorders can formed earlier and more frequent than anemia develops [10,12,13,19]. The reason of neurological disturbance lies in the demyelination in fetus and infants in case of vitamin B12 deficiency. Myelination starts in 4 mo intrauterine period and progresses gradually to puberty [11].

The involuntary movements due to cobalamin therapy is discussed widely in publications [7,10,12,16,18-20,23]. We observed these hyperkinesis in 32% infants. Epilepsy was excluded in all cases. Disbalance of glycaemia is the possible cause of this phenomenon as glutamate influence and inflammatory cytokines activation [3,7,10,23]. Also, the unequal conducting an electrical pulse through remyelination nerve is discussed [3]. The genesis of involuntary movements during therapy of cobalamin is unknown yet finally [7].

The fact of the positive response to cobalamin therapy onset is the marker of the adequate replacement treatment [12,20].

Conclusion

The clinical features associated with vitamin B12 deficiency are non-specific [3]. In early aged children the neurological symptoms have expressed significant and regardless of the degree of anemia. We agree with the recommendation that the vitamin B12 serum level must be estimated in every infant with hypotonia and developmental delay if all other potential causes of these disorders have been excluded [1,3,10]. Also, patients with detected vitamin B12 anemia must be subjected to estimate of nervous system function (as neurovisualization methods as EEG registration). Involuntary movements during cobalamin therapy need to be differentiated from seizures of another etiology. Early identification and treatment can prevent irreversible brain injury [2,3,9,16-19].

Conflict of Interests

Authors have not conflicts.

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Bibliography

1. Hvas AM and Nexo E. "Diagnosis and treatment of vitamin B 12 deficiency. An update". *Haematologica* 91.11 (2006): 1506-1512.
2. Hunt A., *et al*. "Vitamin B 12 deficiency". *British Medical Journal* 6 (2014): 23-29.
3. Smith J and Coman D. "Vitamin B12 deficiency: an update for the general paediatrician". *Pediatrics and Therapeutics* 4.1 (2014): 188.
4. Frenkel EP. "Abnormal fatty acid metabolism in peripheral nerve of patients with pernicious anaemia". *Journal of Clinical Investigation* 52 (1973): 1237-1245.
5. Mansoor M., *et al*. "Early biochemical and hematological response to intramuscular cyanocobalamin therapy in vitamin B 12-deficient patients". *Annals of Nutrition and Metabolism* 62 (2013): 347-353.
6. Boldyrev A., *et al*. "Why is homocysteine toxic for the nervous and immune systems?" *Current Aging Science* 6.1 (2013): 29-36.
7. Ìncecik F., *et al*. "Neurological findings of nutritional vitamin B 12 deficiency in children". *The Turkish Journal of Pediatrics* 2.1 (2010): 17-21.
8. Devalia V., *et al*. "Guidelines for the diagnosis and treatment of cobalamin and folate disorders". *British Journal of Haematology* 166 (2014): 496-513.
9. Langan R and Goodbred A. "Vitamin B12 Deficiency: Recognition and Management". *American Family Physician* 96.6 (2017): 384-389.
10. Yilmaz S., *et al*. "Different neurological aspects of nutritional B 12 deficiency in infancy". *Journal of Child Neurology* 31.5 (2015): 1-4.
11. Black M. "Effects of vitamin B12 and folate deficiency on brain development in children". *The Food and Nutrition Bulletin* 29.2 (2008): 126-131.
12. Goraya J., *et al*. "Neurology of nutritional vitamin B 12 deficiency in infants: case series from India and literature review". *Journal of Child Neurology* 30.13 (2015): 1831-1837.
13. Honzik T., *et al*. "Clinical presentation and metabolic consequences in 40 breastfed infants with nutritional vitamin B12 deficiency - What have we learned?" *Journal of the European Paediatric Neurology* 14.6 (2010): 488-495.
14. Kocaoglu C., *et al*. "Cerebral atrophy in a vitamin B12-deficient infant of a vegetarian mother". *Journal of Health, Population and Nutrition* 32.2 (2014): 367-371.
15. National Institutes of Health. Office of Dietary Supplements (2020).
16. Karabayir N., *et al*. "The infant with vitamin B 12 deficiency". *Çocuk Dergileri* 17.3 (2017): 136-138.
17. Dror DK and Allen LH. "Vitamin B-12 in human milk: a systematic review". *Advances in Nutrition* 9 (2018): 358S-366S.
18. Demir N., *et al*. "Clinical and neurological findings of severe vitamin B12 deficiency in infancy and importance of early diagnosis and treatment". *Journal of Paediatrics and Child Health* 49 (2013): 820-824.
19. Taşkesen M., *et al*. "Neurological presentations of nutritional vitamin B 12 deficiency in 42 breastfed infants in Southeast Turkey". *The Turkish Journal of Medical Sciences* 41.6 (2011): 1091-1096.
20. Acıpayam C., *et al*. "Cerebral atrophy in 21 hypotonic infants with severe vitamin B 12 deficiency". *Journal of Paediatrics and Child Health* 56.5 (2020): 751-756.

21. Glaser K., *et al*. "Psychomotor development following early treatment of severe infantile vitamin B 12 deficiency and West syndrome – is everything fine? A case report and review of literature". *Brain and Development* 37.3 (2015): 347-351.

22. Malbora B., *et al*. "Two infants with infantile spasms associated with vitamin B12 deficiency". *Pediatric Neurology* 51.1 (2014): 144-146.

23. Zanus C., *et al*. "Involuntary movements after correction of vitaminB12 deficiency: a video-case report". *Epileptic Disorders* 14.2 (2012): 174-180.

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