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Extremely severe vitamin B12 deficiency – case presentation and review of literature

Ekstremno teška deficijencija vitamina B12 – prikaz slučaja i pregled literature

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Abstract. ***Aim:*** Vitamin B12 (cobalamin) is nutrient from the vitamin B complex family. It is essential in the human body for deoxyribonucleic acid (DNA) synthesis and for cellular energy production. Vitamine B12 deficiency is decrease in its serum concentration below 220 pmol/L, and it can be present in various range of hematologic and systemic symptoms and signs. The aim of this article is to provide extensive information on extreme forms of deficiency of vitamin B12. ***Case report:*** 83-year-old men presented with fatigue, intolerance of physical activity, vertigo, paresthesia in fingers, dispersion, epigastric pain, vomitting and loss of apetite. Vital parameters were within normal range, and physical examination did not reveal any patological findings, except icterus of sclera and subicterus of skin. Urgent laboratory findings showed erythrocytes 1.18 x 10^{12}/L (4.34-5.72 x 10^{12}/L), hemoglobin 50 g/L (138-175 g/L), mean corpuscular volume (MCV) 123.6 fL (83.0-97.2 fL), vitamin B12 < 61 pmol/L (220-665 pmol/L). Patient started parenteral therapy with vitamin B12. After 5 days, rapid increase in reticulocyte count was observed, with haemogram stabilization within 6 weeks. In a follow-up period of two years, the patient had no symptoms. ***Conclusion:*** We presented patient with extreme deficiency of vitamin B12. Screening for vitamin B12 deficiency should be established in each patient with macrocytic anemia, even with slightly elevated MCV.

Key words: megaloblastic anemia; therapeutics; vitamin B 12 deficiency

Sažetak. ***Cilj:*** Vitamin B12 (kobalamin) je nutrijent iz porodice vitamina B-kompleksa. U ljudskom organizmu esencijalan je za sintezu deoksiribonukleinske kiseline (DNK) i proizvodnju energije u stanicama. Deficijencija vitamina B12 jest pad njegove koncentracije u serumu ispod 220 pmol/L, a može se prezentirati u širokom rasponu hematoloških i sistemskih simptoma i znakova. Cilj ovog članka je pružiti ekstenzivnu informativnost o ekstremnim oblicima deficijencije vitamina B12. ***Prikaz slučaja:*** Pacijent u dobi od 83 godine javio se zbog iznemoglosti, intolerancije napora, vrtoglavica, trnaca u prstima, dekoncentracije, bola u epigastriju, povraćanja i gubitka apetita. Bio je normalnih vitalnih parametara, a fizikalnim pregledom nije pronađeno patološkog nalaza, osim žutice. Hitni laboratorijski nalazi bili su: eritrociti 1.18 x 10^{12}/L (4.34 – 5.72 x 10^{12}/L), hemoglobin 50 g/L (138 – 175 g/L), prosječni volumen eritrocita (MCV) 123.6 fL (83.0 – 97.2 fL), vitamin B12 < 61 pmol/L (220 – 665 pmol/L). Započeta je parenteralna terapija s vitaminom B12. Nakon 5 dana zapažen je rapidan rast retikulocita, uz stabilizaciju hemograma u roku od 6 tjedana. U kontrolnom razdoblju od dvije godine nakon liječenja pacijent nije imao simptoma. ***Zaključak:*** Prikazali smo pacijenta s ekstremnom deficijencijom vitamina B12. Probir na deficijenciju vitamina B12 trebao bi biti proveden kod svakog pacijenta s makrocitnom anemijom, čak i s blago povišenim MCV-om.

Ključne riječi: megaloblastična anemija; terapija; vitamin B 12 deficijencija

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INTRODUCTION

Vitamin B12 (cobalamin) is a water-soluble essential nutrient from the vitamin B complex family, which is essential in the human body for hematopoiesis, neural metabolism, deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis, and carbohydrate, fat and protein metabolism. Vitamin B12 deficiency is decrease in its serum concentration below 220 pmol/L[1]. Based on serum levels, it classifies as mild (201-220 pmol/L), moderate (150-200 pmol/L) or severe (<150 pmol/L).

Patients who are treated for secondary haematological manifestations of vitamin B12 deficiency are resistant to administered therapy, and progression of the disease is possible meanwhile.

Simptomatology progresses proportionally to the level of deficiency, and it can be present in various range of symptoms and signs – from asymptomatic mean corpuscular volume (MCV) increase to severe hematologic, neuropsychiatric and digestive manifestations. Hematological clinical picture is mainly characterized by megaloblastic anemia[2]. The causes of vitamin B12 deficiency can be different, such as autoimmune chronic gastritis (pernicious anemia), malnutrition, malapsorption syndrome, vegetarianism, surgical resection of the gastrointestinal system, consumption of drugs that interfere with the metabolism of vitamin B12 (tuberculinostats, cytostatics, metformin), and in many cases etiology is unknown[3,4]. Various researches suggest that homozygosity for methylentetrahydrofolate reductase (MTHFR) C677T polymorphism could be associated with elevated risk of vitamin B12 deficiency, and it is supported by the fact that this mutation can be found in 15-28% of patients with reduced serum concentrations of vitamin B12[5,6].

Although the lack of vitamin B12 is a common condition, especially in the elderly population, its progression to extremely low levels is a rare case. Due to symptomatology that progresses proportionally with decrease of vitamin B12 level in serum, this disorder is usually manifested, detected and treated well before the terminal phase. Below we present the case of extremely low vitamin B12 deficiency, with comparison to cases of authors who reported such cases in the literature. The aim of this article is to give an insight into clinical repercussions of extreme forms of vitamin B12 deficiency.

CASE REPORT

An 83-year-old man presented with fatigue, intolerance of physical activity, vertigo, paresthesia in fingers, dispersion, epigastric pain, vomitting and loss of apetite. Symptoms started 2-3 months before admission, with progression over time. During this period the patient lost 6 kg. He had lisinopril in chronic therapy. In addition to arterial hypertension, from anamnesis and medical records there was no data on other comorbidities, operative procedure, alcohol abuse or diet programs.

On admission, vital parameters were within normal range, and physical examination did not reveal any patological findings, except icterus of sclera and subicterus of skin. Urgent laboratory tests were made (Table 1). Based on laboratory results, suspicion on megaloblastic anemia was set. Aditional laboratory diagnostics showed reticulocyte count 5 x 10^9/L (22-97 x 10^9/L), haptoglobin 0.4 g/L (0,26-1,85 g/L), *lactate dehydrogenase* (LDH) 1937 U/L (<241 U/L), folate 7.9 µg/L (2-20 µg/L), vitamin B12 <61 pmol/L (220-665 pmol/L). Parenteral therapy with vitamin B12 was introduced (500 mcg 1x1 intravenosus). Peripheral blood smear showed expressed anisocytosis, hypochromacy, poikilocytosis and macrocystosis. Direct Coombs test was negative. Esophagogastroduodenoscopy showed an atrophy of the gastric mucosa, with angiodysplasia of corpus. Intrinsic factor and parietal cell antibodies were not analyzed, as well as the Schilling test. Hepatitis markers were negative. Bone marrow aspiration was consistent with megaloblastic anemia – hypercelular bone marrow, with the presence of megaloblasts and large metamyelocytes. Immunophenotyping, cytogenetics and histopathological bone marrow analysis excluded myelodysplastic syndrome.

After 5 days of parenteral treatment with vitamin B12, rapid increase in reticulocyte count was observed, with haemogram stabilization within 6

Table 1. Laboratory findings upon arrival

Test required	Result	Unit	Reference range
Rbc	1.18	x 10^{12}/L	4.34-5.72
Hemoglobin	50	g/L	138-175
Hematocrit	0.146	L/L	0.415-0.530
MCV	123.6	fL	83.0-97.2
MCH	42.1	pg	27.4-33.9
MCHC	340	g/L	320-345
RDW-CV	26.0	%	14.6-16.5
Thrombocytes	228	x 10^{9}/L	158-424
MPV	11.5	fL	6.8-10.4
Wbc	7.0	x 10^{9}/L	3.4-9.7
Glucose (s)	7.2	mmol/L	4.4-6.4
Urea (s)	16.0	mmol/L	2.8-8.3
Creatinine (s)	125	µmol/L	79-125
Na^+ (s)	139	mmol/L	137-146
K^+ (s)	4.8	mmol/L	3.9-5.1
Cl^- (s)	103	mmol/L	97-108
Total bilirubin (s)	99	µmol/L	3-20
Direct bilirubin (s)	26	µmol/L	0-5
Indirect bilirubin (s)	73	µmol/L	3-15
AST (s)	49	U/L	11-38
ALT (s)	63	U/L	12-48
ALP (s)	36	U/L	60-142
GGT (s)	21	U/L	11-55
Alpha-amylase (s)	46	U/L	23-91
CRP (s)	1.4	mg/L	0.0-5.0

Rbc – red blood cells, MCV – mean corpuscular volume, MCH – mean corpuscular hemoglobin, MCHC – mean corpuscular hemoglobin concentration, RDW-CV – red blood cell distribution width, MPV – mean platelet volume, Wbc – white blood cells, Na^+ – sodium, K^+ – potassium, Cl^- – chloride, AST – aspartate aminotransferase, ALT – alanine aminotransferase, AP – alkaline phosphatase, GGT – gamma-glutamyl transferase, CRP – C-reactive protein, (s) – serum.

Table 2. Laboratory parameters during hospitalization and on outpatient controls

Day	Rbc (x 10^{12}/L)	Hbg (g/L)	Hct (L/L)	MCV (fL)	MCH (pg)	MCHC (g/L)	Trc (x 10^{9}/L)	Wbc (x 10^{9}/L)	Ret (x 10^{9}/L)	T Bil (µmol/L)	I Bil (µmol/L)
1	1.18	50	0.146	123.6	42.1	340	93	6.7	5	99	73
5	2.25	76	0.232	103.1	33.7	327	235	4.4	101	26	16
10	2.46	74	0.240	97.5	29.9	307	286	5.0	168	/	/
20	3.95	113	0.374	94.7	28.7	303	489	11.9	28	21	16
50	5.30	144	0.462	87.2	27.2	312	203	7.1	22	11	8
60	5.05	138	0.430	85.0	27.3	321	229	6.7	33	8	7
120	5.21	139	0.446	85.5	26.7	313	190	7.6	57	/	/
250	5.38	147	0.452	84.0	27.4	326	174	6.2	/	15.4	/

Rbc – red blood cells, Hbg – hemoglobin, Hct – hematocrit, MCV – mean corpuscular volume, MCH – mean corpuscular hemoglobin, MCHC – mean corpuscular hemoglobin concentration, RDW-CV – red blood cell distribution width, Trc – thrombocytes, Wbc – white blood cells, Ret – reticulocyte count, T Bil – , total bilirubin, I Bil – indirect bilirubin. Reticulocyte count reference range: 22-97 x 10^{9}/L; for other parameters reference range is listed in Table 1.

weeks (Table 2). Patient was discharged home after 14 days of hospitalization. Therapy at discharge was: intramusculary vitamin B12 a 500 mcg 1x1 per day (for 7 days), than per week (for 30 days), then per month (for lifetime). In a follow-up period of 2 years, the patient had normal hematological parameters, and no permanent nor reccurent symptomes.

DISCUSSION

We presented a case of extreme vitamin B12 deficiency. The immeasurable concentration of vitamin B12 (<61 pmol / L) in our patient's serum is one of the lowest reported in the literature[7]. The clinical picture that can present in vitamin B12 deficiency consists of a wide spectrum of hematological, neurological, psychiatric, oral, dermatological and other symptoms and signs[2]. Since the severity of the clinical picture is usually proportional to the degree of vitamin B12 deficiency, we have analyzed the literature only of those cases with extremely low levels of vitamin B12 in serum (in this review the concentrations of vitamin B12 below the level of measurability, ie <61 pmol / L or <82.7 mg / ml or ng / L, are considered extremely low).

The review of literature provided a total of 40 applicable cases (Table 3). Review involved 17 (42,5%) females and 23 (57,5%) male patients. All cases included adults in the age range of 18-88 years. The identified causes of B12 deficiency included lack of intrinsic factor in 18 (45%) cases, vegetarianism in 4 (10%) cases, malnutrition in 3 (7,5%) cases, nitrous oxide exposure in 1 (2,5%) case, metformin therapy in 1 (2,5%) case, malabsorption in 1 (2,5%) case, and 12 (30%) cases did

Table 3. Characteristics of patients with extreme deficiency of vitamin B12, review of literature

Case number	Age	Sex	Symptoms	Serum V B12	Etiology	Treatment	Ref number
1	83 years	Male	• Fatigue • Vertigo • Paresthesia in fingers • Dispersion • Epigastric pain • Vomitting • Loss of weight	<61 pmol/L	Unknown	IM (B12) 500 mcg daily for 1 week, then weekly for 1 month, then monthly for a lifetime	(presented case)
2	56 years	Male	• Acute onset of paresthesia involving both hands and feet • Difficulty walking • Inability to feel the ground	75 pg/mL	Lack of IF	Parenteral administration of vitamin B12	8
3	40 years	Male	• Acute onset of irrelevant speech and inability to comprehend • Involuntary movements of upper extremities • Unsteady gait • Hyperpigmentation of hands and feet	63 pg/mL	Vegetarianism	Parenteral (B12) 3000 µg/day for 1 month, then 1000 µg/month for 1 month	9
4	21 years	Male	• Progressive gait instability • Weakness in legs • Paresthesia in feet • Difficulty concentrating	55 pmol/L	Malnutrition (poor diet)	IM (B12) for 1 week, weekly injections for 1 month, then monthly injections	10
5	35 years	Male	• Progressive unsteadiness • Slurring of speech • Alteration in mood • Numbness in both legs	<44 pg/mL	Lack of IF	IM (B12) 1 mg daily for 1 week, then monthly injections	11
6	37 years	Female	• Burning pain in lower limbs	51 ng/L	Lack of IF	IM (B12) 5000 µg/ week for 1 month than 1000 µg/week	12

Case number	Age	Sex	Symptoms	Serum V B12	Etiology	Treatment	Ref number
7	61 years	Female	• Pain • Cramps • Distal parethesias in lower limbs	53 ng/L	Lack of IF	IM (B12) 1000 µg/ day	12
8	38 years	Female	• Fatigue • Electric dysesthesia with neck flexion (Lhermitte's sign)	<50 pg/mL	Lack of IF	(B12) 500 µg biweekly	13
9	44 years	Male	• Fatigue • Numbness in extremities • Intermittent electric dysesthesia associated with neck flexion (Lhermitte's sign)	42 pg/mL	Lack of IF	B12 therapy	13
10	44 years	Male	• Shortness of breath • Fatigue • Paresthesia • Numbness and tingling in fingertips bilaterally	70 ng/L	Lack of IF	IM (B12) 1000 µg/ day for 1 week, then weekly for 1 month, then monthly	14
11	55 years	Male	• Bradykinesia • Tremors of hands	5 pg/mL	Lack of IF	IM (B12) 1000 mg/ day for 3 days then 1/week for 4 weeks	15
12	55 years	Male	• Weakness and numbness in extremities • Difficulty walking • Deterioration of mental activities	<30 pg/mL	Lack of IF	IM (B12) 1000 µg/ day for 7 days, then 1000 µg/ week	16
13	77 years	Male	• Unstable gait • Urinary urgency • Clumsiness of hands • Tingling sensations in legs • Occasional dizziness	38 pg/mL	Lack of IF	IM (B12) 1mg/day for 1 week then 1 mg/month	17
14	65 years	Male	• Problems walking • Memory loss • Disorientation in time • Disturbance of executive functioning	<30 ng/L	Nitrous oxide exposure	Replacement B12 therapy	18
15	60 years	Male	• Behavior changes • Tingling numbness of both hands and feet	60 pg/mL	Metformin therapy	IM (B12) once a week for 4 weeks	19
16	38 years	Female	• Progressive hand numbness and tingling • Numbness of feet	72 pg/mL	Unknown	Parenteral B12 therapy	20
17	76 years	Female	• Forgetfulness • Reading difficulty • Headaches • Fatigue • Weight loss • Visual impairment • Gait abnormalities	78 pg/mL	Unknown	IM (B12) 1000 µg monthly	21
18	27 years	Male	• Forgetfulness • Social withdrawal • Paucity of speech • Decreased interest • Apathy • Weight loss	<50 pg/mL	Vegetarianism	IM (B12) injections	22

Case number	Age	Sex	Symptoms	Serum V B12	Etiology	Treatment	Ref number
19	33 years	Female	• Sad mood • Fatigue • Lack of interest • Sleep disturbances • Weight loss	82 pg/mL	Vegetarianism	IM (B12) 1000 ng/ day for 10 days	23
20	72 years	Male	• Apathy • Irritability • Deterioration of attention and memory • Psychotic episodes • Paranoid thoughts • Jealous delusions	54 pg/mL	Lack of IF	IM (B12) 1000 µg 3x/week for 45 days, weekly for 45 days, then monthly	24
21	35 years	Female	• Manic symptoms • Gradiosity • Hyperactivity • Sexual indiscretion • Hyperphagia • Irritable mood • Reckless behavior • Flight of ideas • Overbearing manner	<60 pg/mL	Unknown	IM (B12) 1000 µg/ day for a week, weekly for one month, then monthly	25
22	78 years	Female	• Visual hallucinations • Emotional distress • Paranoia	44 pmol/L	Unknown	Oral vitamin (B12) 1mg daily	26
23	54 years	Female	• Stomatitis • Glossitis	<44 pmol/L	Unknown	(B12) 1 mg/day IM for 5 days, followed by 1 mg monthly	27
24	36 years	Male	• Migratory glossitis	<44 pmol/L	Unknown	(B12) 1 mg/day IM for 5 days, followed by 1 mg monthly	27
25	33 years	Female	• Acute glossitis	<44 pmol/L	Unknown	(B12) 1 mg/day IM for 5 days, followed by 1 mg monthly	27
26	68 years	Female	• Glossitis	25 pmol/L	Unknown	(B12) 1 mg/day IM for 5 days, followed by 1 mg monthly	27
27	31 years	Female	• Recurrent aphthous stomatitis (canker sores)	< 50 pg/mL	Lack of IF	IM (B12) 1000 µg/ day for 1 week, followed by once every two weeks	28
28	88 years	Female	• Tongue and mouth discomfort • Oral epithelial dysplasia	60 ng/L	Unknown	IM (B12) 1 mg every 3 days	29
29	25 years	Female	• Blackish discoloration of the skin on knuckles	31.6 pg/mL	Vegetarianism	Oral B12 replacement	30
30	54 years	Male	• Darkening of hands, feet, and tongue (hyperpigmentation)	35 pg/mL	Malnutrition	IM (B12) 1 mg every week for 2 months, then every month for 3 months	31
31	43 years	Male	• Increased skin pigmentation • Progressive weakness • Weight loss	34.3 pg/mL	Lack of IF	IM (B12) 100 mg/ day for 7 days, then 2x/week for 3 weeks, then 100 mg once a month	32

Case number	Age	Sex	Symptoms	Serum V B12	Etiology	Treatment	Ref number
32	26 years	Female	• Gradual and painless visual loss • Headaches • Increasing breathlessness on exertion	54 ng/L	Malnutrition (poor diet)	B12 supplementation	33
33	22 years	Female	• Malaise • Anorexia • Exercise intolerance	52 pg/mL	Lack of IF	IM (B12) 100 µg/ day for 10 days, followed by monthly injections	34
34	26 years	Male	• Complex partial seizures • Social withdrawal • Memory impairment • Impaired concentration • Visuospatial disorientation • Constructional apraxia • Impaired distal sensations • Impaired deep tendon reflexes	26 pg/mL	Lack of IF	IM (B12) injections	35
35	52 years	Male	• Shortness of breath • General weakness • Weight loss • Sore tongue	52 pmol/L	Lack of IF	IM (B12) for 7 days, then weekly for 4 weeks, then once a month	36
36	18 years	Male	• Short stature • Prepubertal sexual maturation • Exertional dyspnea • Vertigo	60 pg/mL	Malabsorption	IM (B12) 100 µg/ day for 14 days, then 50 µg every other week	37
37	44 years	Female	• Acute confusional state/ delirium • Weakness • Paraesthesias of the lower limbs • Palpitations • Exertional dyspnea	62.9 pg/ml	Unknown	IM(B12) 1 mg daily for one week,then 1 mg monthly	38
38	46 years	Male	• Fatigue • Arthromyalgia • Upper finger paresthesia • Mild abdominal pain • Tinnitus • Recurring headache	< 36.9 pmol/L	Unknown	IM (B12) injections	39
39	55 years	Male	• Postural instability • Fatigue • Generalized weakness • Weight loss	22 pmol/L	Lack of IF	IM (B12) for 7 days, then weekly for 4 weeks, then once a month	40
40	43 years	Male	• Fatigue • Weight loss • Jaundice	38 pg/mL	Lack of IF	IM (B12) injections	41

V – vitamin; IM – intramuscular, IF – intrinsic factor, Ref – reference

not report a definitive cause of vitamin B12 deficiency. A total of 28 (70%) cases involved patients with B12 deficiency who had neurological impairment, 11 (27,5%) patients had psychiatric abnormalities, 7 (17,5%) patients had oral manifestations, 4 (10%) patients had dermatological manifestations, and 4 (10%) patients had other rare manifestations. All patients had hematological abnormalities. The most common symptoms of disease were paresthesia/weakness/numbness in limbs in 14 (35%) cases, fatigue in 13 (32,5%) cases, vertigo/gait abnormality in 11

(27,5%) cases and anorexia/weight loss in 9 (22,5%) cases. All patients were treated with various schemes of vitamin B12 supplemental therapy. 31 patients received vitamin B12 intramuscularly, 3 parenterally, 2 per os, while the way of treatment was not reported in 4 cases[8-41].The lowest reported concentration of serum vitamin B12 was that of 5 pg/ml[15].

When comparing the presented case with data from the literature review we come to the conclusion that our patient was presented with a typical clinical picture of extreme deficiency of vitamin B12. Age of the presented patient was above the average age of reviewed cases, and only one patient was older[29]. Of the 4 most frequent symptoms listed above, our patient was presented with all 4. Although the etiology of deficiency has not been proven, considering the findings of gastroduodenoscopy, it is possible that it was a case of pernicious anemia. In an elderly patient, it is not always imperative to find the cause of the deficiency. Given that treatment is universal (and also very simple and efficient), patients from this population are often not psychologically and physically motivated for the extensive diagnostic treatment needed to detect the etiology of the disease. Analysing table 3 it is apparent that from 7 patients aged >65 years, 5 patients had undefined cause of vitamin B12 deficiency[17,21,24,26,27,29]. Treatment applied by intramuscular injections in our case is in accordance with other authors. From the tabular review (Table 3) it is seen that doses for intramuscular B12 therapy ranged from 100 µg to 1000 µg. Like in all reviewed cases, our patient had a very satisfactory response to therapy[8-41]. There is still a question about the depth of deficiency, given that laboratory analysis at the treatment facility was unable to provide information on the concentration of vitamin B12 below 61 pmol/L. The indicator on the severity of disease could be hemoglobin level of 50 g / L. A study from US authors over 2083 patients with very low hemoglobin levels (<80 g/L) who rejected the blood transfusion (mostly Jehovah's Witnesses) showed that mortality rapidly increases with a hemoglobin decrease below 50-60 g/L[42,43]. Considering that our patient had one of the lowest hemoglobin levels among the reviewed cases, it is believed that the concentration of vitamin B12 in his serum was well below 61 pmol/L.

Differential diagnosis of extreme vitamin B12 deficiency should include other hematologic conditions such as myelodysplastic syndrome and acute leukemia, but also systemic diseases such as alcoholic liver disease, peripheral neuropathy, dementia, depression, multiple sclerosis, etc.[44-46]. Patients who are treated for secondary haematological manifestations of vitamin B12 deficiency are resistant to administered therapy, and progression of the disease is possible meanwhile[47]. It is not a rare case that anemia caused by vitamin B12 deficiency is misdiagnosed with hemolytic anemia. Vitamin B12 deficiency can manifest with increase of hemolysis parameters, which is explained by the mechanism of ineffective erythropoiesis. The organism attempts to compensate for anemia by increased erythropoesis in the bone marrow, but at the same time one part of the megaloblasts collapses before it turns into more mature forms and erythrocytes[48,49]. Vitamin B12 in essential coenzyme in DNA and RNA production, so other blood cells can be affected by its deficit, with consequent leukopenia, thrombocytopenia or pancytopenia. If hemolysis is accompanied by thrombocytopenia, in clinical practice diagnosis of thrombotic thrombocytopenic purpura is often suspected. Actually, a rare complication of vitamine B12 deficiency known as "pseudo" thrombotic microangiopathy occurs[50,51]. It happens due to damage of vascular endothelium by homocysteine, causing microangiopathic hemolysis. Vitamine B12 is a cofactor of two enzymes in human body cells – *methylmalonyl- coenzyme A* mutase and *methionine synthetase* (catalyzes the conversion of homocysteine into methionine) and deficiency of these en-

In the context of urgent diagnostics at the emergency department, the indication for analysis of vitamin B12 (and folate) should be established in each patient with macrocytic anemia, even with slightly elevated MCV (present in prodromal stages of megaloblastic anemia), especially in elderly patients.

zymes caueses accumulation of homocysteine and methylmalonic acid in the serum. It is believed that homocysteine acts prooxidatively on erythrocytes and vascular endothelium, i.e. as hemolytic toxin[41,45].

In the context of urgent diagnostics at the emergency department, the indication for analysis of vitamin B12 (and folate) should be established in each patient with macrocytic anemia, even with slightly elevated MCV, especially in elderly patients[52]. Normal MCV does not exclude anemia caused by vitamin B12 deficiency – with associated iron deficiency, erythrocytes are normocytic[53]. On the other hand, elevated MCV can also be found within another pathology – reticulocytosis within hemolytic anemia, aplastic anemia, myelodysplastic syndrome, multiple myeloma, etc[54]. With supplemental therapy of vitamin B12 in its deficiency, a rapid increase in reticulocyte count (reticulocyte crisis) occurs after 3-5 days. In refractory cases, the treatment is enhanced with blood transfusions. Complete recovery usually occurs within 6 weeks, although neurological impairments can persist much longer or even be irreversible[55].

CONCLUSION

Extreme deficiency of vitamin B12 presents in a wide range of severe symptoms of different body systems. There are no pathognomonic signs of disease and clinical course can be very deceitful, with progression to profound psychophysical disability. All patients with anemia that have elevated MCV and red blood cell distribution width (RDW) should be carefully evaluated for possible vitamin B12 and folate deficiency. Prevention, early detection and admission of supplemental treatment have a crucial role in stopping the negative clinical course and development of long-term effects of vitamin B12 deficiency.

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