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

Ana Pupić-Bakrač, Antea Pervan, Jure Pupić-Bakrač, Jakov Končurat

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. Vitamin 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, vomiting and loss of appetite. Vital parameters were within normal range, and physical examination did not reveal any pathological 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


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. Based on serum levels, it classifies as mild (201-220 pmol/L), moderate (150-200 pmol/L) or severe (<150 pmol/L).

CASE REPORT

An 83-year-old man presented with fatigue, intolerance of physical activity, vertigo, paresthesia in fingers, dispersion, epigastric pain, vomiting and loss of appetite. 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 pathological 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. Additional 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 intravenous). Peripheral blood smear showed expressed anisocytosis, hypochromacy, poikilocytosis and macrocytosis. 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 – hypercellular 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

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


Table 2. Laboratory parameters during hospitalization and on outpatient controls

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

weeks (Table 2). Patient was discharged home after 14 days of hospitalization. Therapy at discharge was: intramuscular 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 recurrent symptoms.

**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. 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. 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>
<thead>
<tr>
<th>Case number</th>
<th>Age</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Serum V B12</th>
<th>Etiology</th>
<th>Treatment</th>
<th>Ref number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>83 years</td>
<td>Male</td>
<td>• Fatigue • Vertigo • Paresthesia in fingers • Dispersion • Epigastric pain • Vomiting • Loss of weight</td>
<td>&lt;61 pmol/L</td>
<td>Unknown</td>
<td>IM (B12) 500 mcg daily for 1 week, then weekly for 1 month, then monthly for a lifetime</td>
<td>(presented case)</td>
</tr>
<tr>
<td>2</td>
<td>56 years</td>
<td>Male</td>
<td>• Acute onset of paresthesia involving both hands and feet • Difficulty walking • Inability to feel the ground</td>
<td>75 pg/mL</td>
<td>Lack of IF</td>
<td>Parenteral administration of vitamin B12</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>40 years</td>
<td>Male</td>
<td>• Acute onset of irrelevant speech and inability to comprehend • Involuntary movements of upper extremities • Unsteady gait • Hyperpigmentation of hands and feet</td>
<td>63 pg/mL</td>
<td>Vegetarianism</td>
<td>Parenteral (B12) 3000 µg/day for 1 month, then 1000 µg/month for 1 month</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>21 years</td>
<td>Male</td>
<td>• Progressive gait instability • Weakness in legs • Paresthesia in feet • Difficulty concentrating</td>
<td>55 pmol/L</td>
<td>Malnutrition (poor diet)</td>
<td>IM (B12) for 1 week, weekly injections for 1 month, then monthly injections</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>35 years</td>
<td>Male</td>
<td>• Progressive unsteadiness • Slurring of speech • Alteration in mood • Numbness in both legs</td>
<td>&lt;44 pg/mL</td>
<td>Lack of IF</td>
<td>IM (B12) 1 mg daily for 1 week, then monthly injections</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>37 years</td>
<td>Female</td>
<td>• Burning pain in lower limbs</td>
<td>51 ng/L</td>
<td>Lack of IF</td>
<td>IM (B12) 5000 µg/week for 1 month than 1000 µg/week</td>
<td>12</td>
</tr>
<tr>
<td>Case number</td>
<td>Age</td>
<td>Sex</td>
<td>Symptoms</td>
<td>Serum V B12</td>
<td>Etiology</td>
<td>Treatment</td>
<td>Ref number</td>
</tr>
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<td>-------------</td>
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<td>-------</td>
<td>---------------------------------------------------------------------------</td>
<td>-------------</td>
<td>--------------</td>
<td>------------------------------------------------</td>
<td>------------</td>
</tr>
</tbody>
</table>
| 7           | 61   | Female| • Pain  
• Cramps  
• Distal paresthesias in lower limbs                                  | 53 ng/L     | Lack of IF   | IM (B12) 1000 µg/day                              | 12         |
| 8           | 38   | Female| • Fatigue  
• Electric dysesthesia with neck flexion (Lhermitte's sign)            | <50 pg/mL   | Lack of IF   | (B12) 500 µg biweekly                             | 13         |
| 9           | 44   | 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   | Male  | • Shortness of breath  
• Fatigue  
• Paresthesia  
• Numbness and tingling in fingertips bilaterally                          | 70 ng/L     | Lack of IF   | IM (B12) 1000 µg/day, then weekly, then monthly | 14         |
| 11          | 55   | 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   | 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   | 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   | Male  | • Problems walking  
• Memory loss  
• Disorientation in time  
• Disturbance of executive functioning                                       | <30 ng/L    | Nitrous oxide exposure  
Replacement B12 therapy                                                  | 18         |
| 15          | 60   | 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   | Female| • Progressive hand numbness and tingling  
• Numbness of feet                                                           | 72 pg/mL    | Unknown      | Parenteral B12 therapy                            | 20         |
| 17          | 76   | Female| • Forgetfulness  
• Reading difficulty  
• Headaches  
• Fatigue  
• Weight loss  
• Visual impairment  
• Gait abnormalities                                                        | 78 pg/mL    | Unknown      | IM (B12) 1000 µg monthly                           | 21         |
| 18          | 27   | Male  | • Forgetfulness  
• Social withdrawal  
• Paucity of speech  
• Decreased interest  
• Apathy  
• Weight loss                                                               | <50 pg/mL   | Vegetarianism  
IM (B12) injections                                                     | 22         |
<table>
<thead>
<tr>
<th>Case number</th>
<th>Age</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Serum V B12</th>
<th>Etiology</th>
<th>Treatment</th>
<th>Ref number</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>33 years</td>
<td>Female</td>
<td>• Sad mood • Fatigue • Lack of interest • Sleep disturbances • Weight loss</td>
<td>82 pg/mL</td>
<td>Vegetarianism</td>
<td>IM (B12) 1000 ng/day for 10 days</td>
<td>23</td>
</tr>
<tr>
<td>20</td>
<td>72 years</td>
<td>Male</td>
<td>• Apathy • Irritability • Deterioration of attention and memory • Psychotic episodes • Paranoid thoughts • Jealous delusions</td>
<td>54 pg/mL</td>
<td>Lack of IF</td>
<td>IM (B12) 1000 µg 3x/week for 45 days, weekly for 45 days, then monthly</td>
<td>24</td>
</tr>
<tr>
<td>21</td>
<td>35 years</td>
<td>Female</td>
<td>• Manic symptoms • Gradiosity • Hyperactivity • Sexual indiscretion • Hyperphagia • Irritable mood • Reckless behavior • Flight of ideas • Overbearing manner</td>
<td>&lt;60 pg/mL</td>
<td>Unknown</td>
<td>IM (B12) 1000 µg/day for a week, weekly for one month, then monthly</td>
<td>25</td>
</tr>
<tr>
<td>22</td>
<td>78 years</td>
<td>Female</td>
<td>• Visual hallucinations • Emotional distress • Paranoia</td>
<td>44 pmol/L</td>
<td>Unknown</td>
<td>Oral vitamin (B12) 1mg daily</td>
<td>26</td>
</tr>
<tr>
<td>23</td>
<td>54 years</td>
<td>Female</td>
<td>• Stomatitis • Glossitis</td>
<td>&lt;44 pmol/L</td>
<td>Unknown</td>
<td>(B12) 1 mg/day IM for 5 days, followed by 1 mg monthly</td>
<td>27</td>
</tr>
<tr>
<td>24</td>
<td>36 years</td>
<td>Male</td>
<td>• Migratory glossitis</td>
<td>&lt;44 pmol/L</td>
<td>Unknown</td>
<td>(B12) 1 mg/day IM for 5 days, followed by 1 mg monthly</td>
<td>27</td>
</tr>
<tr>
<td>25</td>
<td>33 years</td>
<td>Female</td>
<td>• Acute glossitis</td>
<td>&lt;44 pmol/L</td>
<td>Unknown</td>
<td>(B12) 1 mg/day IM for 5 days, followed by 1 mg monthly</td>
<td>27</td>
</tr>
<tr>
<td>26</td>
<td>68 years</td>
<td>Female</td>
<td>• Glossitis</td>
<td>25 pmol/L</td>
<td>Unknown</td>
<td>(B12) 1 mg/day IM for 5 days, followed by 1 mg monthly</td>
<td>27</td>
</tr>
<tr>
<td>27</td>
<td>31 years</td>
<td>Female</td>
<td>• Recurrent aphthous stomatitis (canker sores)</td>
<td>&lt;50 pg/mL</td>
<td>Lack of IF</td>
<td>IM (B12) 1000 µg/day for 1 week, followed by once every two weeks</td>
<td>28</td>
</tr>
<tr>
<td>28</td>
<td>88 years</td>
<td>Female</td>
<td>• Tongue and mouth discomfort • Oral epithelial dysplasia</td>
<td>60 ng/L</td>
<td>Unknown</td>
<td>IM (B12) 1 mg every 3 days</td>
<td>29</td>
</tr>
<tr>
<td>29</td>
<td>25 years</td>
<td>Female</td>
<td>• Blackish discoloration of the skin on knuckles</td>
<td>31.6 pg/mL</td>
<td>Vegetarianism</td>
<td>Oral B12 replacement</td>
<td>30</td>
</tr>
<tr>
<td>30</td>
<td>54 years</td>
<td>Male</td>
<td>• Darkening of hands, feet, and tongue (hyperpigmentation)</td>
<td>35 pg/mL</td>
<td>Malnutrition</td>
<td>IM (B12) 1 mg every week for 2 months, then every month for 3 months</td>
<td>31</td>
</tr>
<tr>
<td>31</td>
<td>43 years</td>
<td>Male</td>
<td>• Increased skin pigmentation • Progressive weakness • Weight loss</td>
<td>34.3 pg/mL</td>
<td>Lack of IF</td>
<td>IM (B12) 100 mg/day for 7 days, then 2x/week for 3 weeks, then 100 mg once a month</td>
<td>32</td>
</tr>
<tr>
<td>Case number</td>
<td>Age</td>
<td>Sex</td>
<td>Symptoms</td>
<td>Serum V B12</td>
<td>Etiology</td>
<td>Treatment</td>
<td>Ref number</td>
</tr>
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<td>-------------</td>
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<td>---------------------------------------------------------------------------</td>
<td>------------</td>
</tr>
</tbody>
</table>
| 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  
• Paresthesias 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. The lowest reported concentration of serum vitamin B12 was that of 5 pg/ml.

When comparing the presented case with data from the literature review we come to the conclusion that our patient was presented with a 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. 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. Patients who are treated for secondary hematological manifestations of vitamin B12 deficiency are resistant to administered therapy, and progression of the disease is possible meanwhile. 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 erythropoiesis in the bone marrow, but at the same time one part of the megaloblasts collapses before it turns into more mature forms and erythrocytes. 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. It happens due to damage of vascular endothelium by homocysteine, causing microangiopathic hemolysis. Vitamin 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-
zymes causes accumulation of homocysteine and methylmalonic acid in the serum. It is believed that homocysteine acts prooxidatively on erythrocytes and vascular endothelium, i.e. as hemolysin. 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. Normal MCV does not exclude anemia caused by vitamin B12 deficiency – with associated iron deficiency, erythrocytes are normocytic. On the other hand, elevated MCV can also be found within another pathology – reticulocytosis within hemolytic anemia, aplastic anemia, megaloblastic syndrome, multiple myeloma, etc. 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.

**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.

**Conflict of interest:** The authors report no conflict of interest.

**REFERENCES**

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