Hereditary Partial Transcobalamin II Deficiency with Neurologic, Mental and Hematologic Abnormalities in Children and Adults

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Key words: transcobalamin, vitamin B₁₂ deficiency, megaloblastic anemia, dyslexia, personality disorders, neuropathy, autosomal dominant transmission

Abstract

Background: Transcobalamin II is a serum transport protein for vitamin B₁₂. Small variations in TC-II affinity were recently linked to a high homocysteine level and increased frequency of neural tube defects. Complete absence of TC-II or total functional abnormality causes tissue vitamin B₁₂ deficiency resulting in a severe disease with megaloblastic anemia and immunologic and intestinal abnormalities in the first months of life. This condition was described in hereditary autosomal-recessive form. Low serum TC-II without any symptoms or clinical significance was noted in relatives of affected homozygotes.

Objectives: To study 23 members of a four-generation family with hereditary vitamin B₁₂ deficiency and neurologic disorders.

Methods: Thorough neurologic, hematologic and family studies were supplemented by transcobalamin studies in 20 family members.

Results: Partial TC-II deficiency was found in 19 subjects. Apo TC-II (free TC-II unbound to vitamin B₁₂) and total unsaturated B₁₂ binding capacity were low in all tested individuals but one, and holo TC-II (TC-II bound by vitamin B₁₂) was low in all family members. The presentation of the disease was chronic rather than acute. Early signs in children and young adults were dyslexia, decreased IQ, vertigo, plantar clonus and personality disorders. Interestingly, affected children and young adults had normal or slightly decreased serum vitamin B₁₂ levels but were not anemic. Low serum B₁₂ levels were measured in early adulthood. In mid-adulthood megaloblastic anemia and subacute combined degeneration of the spinal cord were diagnosed. Treatment with B₁₂ injections resulted in a significant improvement. The pedigree is compatible with an autosomal-dominant transmission. This family study suggests a genetic heterogeneity of TC-II deficiency.

Conclusions: We report the first family with a hereditary transmitted condition of low serum TC-II (partial TC-II deficiency) associated with neurologic and mental manifestations in childhood. Partial TC-II deficiency may decrease the amount of stored cobalamin, resulting in increased susceptibility to impaired intestinal delivery of cobalamin and predisposing to clinically expressed megaloblastic anemia at a later age. Partial TC-II deficiency should be suspected in families with megaloblastic anemia and in individuals with neurologic and mental disturbances – despite normal serum vitamin B₁₂ levels. Low serum UBBC and apo TC-II should confirm the diagnosis. Early vitamin B₁₂ therapy may prevent irreversible neurologic damage.

Cobalamin (vitamin B₁₂) plays a key role in the metabolism and DNA synthesis of proliferating cells [1]. Cobalamin deficiency resulting in neurologic abnormalities and megaloblastic anemia is well-known [1]. In most cases the etiology includes decreased intake and impaired absorption (gastrectomy, pernicious anemia, intestinal factors, pancreatic insufficiency). A similar clinical picture related to dysfunctional or absent cobalamin transport protein (transcobalamin II) is rare.

TC-II ("liver-related") [2] is essential for B₁₂ transportation to cells. The vitamin is absorbed in the terminal ileum and linked to transcobalamins. The cobalamin binding to TC-II forms holo TC-II, which is then transferred to the circulation delivering B₁₂ to every DNA synthesizing cell via interaction with specific surface receptors for holo TC-II [3-5]. Since the plasma half-life of holo TC-II is approximately 6 minutes, almost all measured serum vitamin B₁₂ in the serum is bound to TC-I and III. Thus, patients with TC-II deficiency typically have normal values of serum vitamin B₁₂.

TC-II deficiency has been described as a homozygous form [6-19]. Three mechanisms of TC-II deficiency have been reported: the common type is characterized by the absence of both B₁₂ binding components and immunoreactive TC-II; in the second type there is a lack of B₁₂ binding components but normal immunoreactivity, and in the third type TC-II birds B₁₂ but is non-functional [14].

The classical familial recessive complete TC-II deficiency is characterized by severe megaloblastic anemia, intestinal abnormalities and immunodeficiency, which occur in early infancy. Neurologic dysfunction, including mental retardation, ataxia, pyramidal deficit and seizures, may occur if treatment with cobalamin is delayed [9,11,19].

The relatives of patients with TC-II deficiency have low serum total TC-II levels [7,11,12,17] and were regarded as asymptomatic heterozygous [7]. No clinically significant abnormality that related to partial TC-II deficiency has been reported to date.

We present here a Jewish family of Yemenite origin with neurologic and hematologic manifestations associated with partial TC-II deficiency transmitted in a dominant pattern. This family workup suggests that the heterozygous state of TC-II deficiency may also be of clinical importance.

TC II = transcobalamin II
UBBC = unsaturated B₁₂ binding capacity

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The index patient

A 43 year old Jewish woman of Yemenite origin presented with weakness, paresthesias, confusion and difficulty in walking. Her mother and sister had been known to suffer from megaloblastic anemia and had been on vitamin B₁₂ therapy. On admission she was pale, tachypneic and without organomegaly. The neurologic examination was remarkable for muscular weakness, decreased reflexes, impaired position, vibration sense and ataxia.

Hemoglobin level was 3.6 g/dL, red blood cell count 0.9×10¹²/L, mean corpuscular volume 120 fl, white blood cell 4.6×10⁹/L, platelet count 89×10⁹/L and reticulocytes 1.8%. Routine serum chemistry was normal except for high serum lactate dehydrogenase 600 u/L (normal range 100-225) and bilirubin 3 mg/dL, of which 2 mg/dL was indirect. Serum iron, iron-binding capacity, ferritin, folic acid, thyroid-stimulating hormone, haptoglobin and glucose-6-phosphate dehydrogenases were all within normal limits. Serum vitamin B₁₂ was less than 49 pmol/L (normal range 200–900).

Peripheral blood smear demonstrated marked anisocytosis and macrocytosis. Bone marrow showed a typical picture of severe megaloblastic anemia. The Schilling test was abnormal with and without intrinsic factor (0.1% and 4.4% respectively). Gastroscopy was normal. Neurologic evaluation was consistent with subacute combined system degeneration. Brain computerized tomography, visual evoked potentials, brain stem-evoked responses and somatosensory evoked potentials were all normal.

Treatment with hydroxocobalamin was initiated. Three months later, the patient was asymptomatic with a significant improvement in her neurologic status. Hemoglobin was 12.7 g/dL, RBC 4.47×10⁹/µL and MCV 89.4 fl.

Methods

Blood count, RBC indexes and biochemistry were performed by routine methods. Serum was frozen following centrifugation and thawed for further studies. Cobalamin-binding studies and separation of TC-I and III from TC-II were performed at the Hematology and Nutrition Laboratory, Veterans Affairs Medical Center, New York, using QUSB G-32, a microfine precipitate of silica, as previously described [2]. Vitamin B₁₂ was measured by radioimmunoassay, and vitamin B₁₂ absorption was evaluated by the Schilling test with 1 µg of B₁₂. Parietal cell antibody titer was quantitated by enzyme-linked immunoabsorbent assay. Visual evoked potentials, brain stem-evoked responses and somatosensory evoked potentials were performed by a trained technician in the clinical neurology laboratory.

Results

The presence of familial megaloblastic anemia prompted us to pursue family studies. We located 23 members representing 4 generations of this Jewish Yemenite family and they cooperated with the study. Table 1 summarizes the list of family members tested, their generation (in Roman numerals), age, gender, neurologic manifestations, hemoglobin and MCV. Familial evaluation and the pattern of inheritance is shown in Figure 1.

RBC = red blood cells
MCV = mean corpuscular volume

Figure 1. Pedigree of a Jewish Yemenite family with transcobalamin II deficiency. Examined family members represent four consecutive generations. The proband mother had married twice and TC-II-deficient patients were found among the children and grandchildren from both marriages. The only consanguineous marriage was the index case. Low TC-II levels were found in all four generations, in males as well as females. Both men and women transmitted the disease to their children. Low serum B₁₂ levels, megaloblastic anemia and neurologic abnormalities were found in the second, third and fourth generations. In the fifth generation, neurologic problems were found with normocytic anemia and normal serum B₁₂.

Neurologic evaluation [Table 1]

Our patients suffered from two types of neurologic complications. The first type (with low serum vitamin B₁₂) demonstrated a classical picture of subacute combined system degeneration of the spinal cord, often seen in patients with megaloblastic anemia. The second type developed despite normal serum B₁₂ or hemoglobin and was related exclusively to TC-II deficiency, which probably caused insufficient cobalamin supply to neurologic tissue. The signs of the second type included dyslexia, decreased intelligence, vertigo, plantar sign, personality disorders and neuropathy – a complex of symptoms consistent with the minimal brain dysfunction syndrome. Visual evoked potentials, brain stem-evoked responses and somatosensory evoked potentials (SEP-63) were performed in two patients with megaloblastic anemia and were found to be normal. All evaluated individuals except for one had low serum TC-II levels.

Hematologic evaluation [Table 1]

Low hemoglobin values were recorded in 8 of 20 individuals. Macrocytosis (MCV > 95 fl) was found in only five family members, three of them with anemia and two with normal hemoglobin. Of note, macrocytosis and anemia were diagnosed relatively late. The mean age for diagnosis of megaloblastic anemia was 48 years (range 33-68 years). One patient had normocytic anemia and low serum vitamin B₁₂ (III-5). Three patients had normocytic anemia and normal levels of B₁₂. No patient had hypersegmented neutrophils. Bone marrow examination was performed in two patients and was found to be megaloblastic. Patient III-2 had microcytic anemia and normal vitamin B₁₂ level at the initial evaluation but developed macrocytic vitamin B₁₂-deficient anemia 3 years later (not shown in the table).
Table 1. Clinical and laboratory data, cobalamin and transcobalamins in the described family

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>Neurologic findings</th>
<th>Hb (g/dl)</th>
<th>MCV (fl)</th>
<th>Total B12 (pg/ml)</th>
<th>TCI B12 (pg/ml) (Holotranscobalamin I and II)</th>
<th>TCII UBBC (pg/ml) (Apo TCII)</th>
<th>Total UBBC (pg/ml)</th>
<th>TC4 + III B12 (pg/ml) (Holohaptocorin)</th>
<th>TC-I + III UBBC (pg/ml)</th>
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<tr>
<td>II-8</td>
<td>68</td>
<td>F</td>
<td>Weakness, gait disturbances, SCSD</td>
<td>4.2</td>
<td>128</td>
<td>161* (56)</td>
<td>4</td>
<td>144</td>
<td>396</td>
<td>160</td>
<td>252</td>
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<tr>
<td>II-2</td>
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<td>F</td>
<td>ND</td>
<td>8.6</td>
<td>63</td>
<td>269**</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
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<td>43</td>
<td>F</td>
<td>Weakness, psychiatric disturbances, SCSD</td>
<td>3.6</td>
<td>105</td>
<td>529* (49)</td>
<td>28</td>
<td>509</td>
<td>2200</td>
<td>554</td>
<td>869</td>
</tr>
<tr>
<td>III-5</td>
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<td>M</td>
<td>ND</td>
<td>13</td>
<td>88</td>
<td>147* (168)</td>
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<td>46</td>
<td>409</td>
<td>160</td>
<td>313</td>
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<td>III-7</td>
<td>38</td>
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<td>ND</td>
<td>14</td>
<td>94</td>
<td>129**</td>
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<td>522</td>
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<td>33</td>
<td>F</td>
<td>SCSD, gait disturbances, memory disturbances</td>
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<td>110</td>
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<td>120</td>
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<tr>
<td>III-13</td>
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<td>M</td>
<td>Gait disturbances, memory disturbances</td>
<td>14</td>
<td>90</td>
<td>204* (156)</td>
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<td>116</td>
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<tr>
<td>III-14</td>
<td>24</td>
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<td>15.7</td>
<td>88</td>
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<td>ND</td>
<td>ND</td>
<td>ND</td>
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<td>M</td>
<td>Vertigo, psychiatric disturbances</td>
<td>14.1</td>
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<td>320**</td>
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<td>F</td>
<td>Neuropathy</td>
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<td>88.7</td>
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<td>100</td>
<td>224</td>
<td>350</td>
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<td>IV-5</td>
<td>25</td>
<td>F</td>
<td>Normal</td>
<td>13.3</td>
<td>98</td>
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<td>124</td>
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<td>24</td>
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<td>87</td>
<td>229* (199)</td>
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<td>Learning difficulties, dyslexia</td>
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<td>IV-10</td>
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<td>F</td>
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<td>ND</td>
<td>ND</td>
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<td>20</td>
<td>106</td>
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<td>450</td>
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<tr>
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<td>F</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>716</td>
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<td>ND</td>
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<td>83</td>
<td>299*</td>
<td>9</td>
<td>120</td>
<td>292</td>
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<td>IV-10</td>
<td>17</td>
<td>M</td>
<td>ND</td>
<td>13.3</td>
<td>81</td>
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<td>3</td>
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<td>305</td>
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<tr>
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<td>15</td>
<td>M</td>
<td>ND</td>
<td>13.5</td>
<td>86</td>
<td>443</td>
<td>18</td>
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<td>291</td>
<td>430</td>
<td>170</td>
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<tr>
<td>V-1</td>
<td>8</td>
<td>M</td>
<td>Plantar clonus, brisk reflexes</td>
<td>12.8</td>
<td>90</td>
<td>319</td>
<td>15</td>
<td>66</td>
<td>195</td>
<td>304</td>
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<tr>
<td>V-2</td>
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<td>F</td>
<td>Plantar clonus</td>
<td>15.1</td>
<td>86</td>
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<td>2</td>
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<td>361</td>
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<td>F</td>
<td>Plantar clonus, brisk reflexes</td>
<td>10.9</td>
<td>86</td>
<td>350</td>
<td>8</td>
<td>83</td>
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<td></td>
<td></td>
<td></td>
<td>F 12-16</td>
<td>M 14-18</td>
<td>≤ 95</td>
<td>200-900</td>
<td>&gt; 50</td>
<td>450-1000</td>
<td>&gt; 200</td>
<td>150-400</td>
</tr>
</tbody>
</table>

* Index case

** In four patients (III-2, III-7, III-14, IV-1) vitamin B12 was measured separately

SCSD = subacute combined system degeneration, TC-I + III B12 = saturated transcobalamin I and III (R-binding), UBBC = unsaturated B12 binding capacity.

TC-I + III UBBC = unsaturated TC-I and II, TC-II B12 = saturated transcobalamin II, TC-II UBBC = unsaturated TC-II.

Serum cobalamin and transcobalamins [Table 1]

Low serum B12 levels were found in 11 patients and normal levels in 12 patients. Holo TC-II (TC-II B12) levels were low in all examined family members and undetectable in seven. In all family members except for one (III-4), apo TC-II (free TC-II bound to vitamin B12) and total unsaturated B12 binding capacity levels were low. Patient III-4 had normal level of TC-II, which was possibly false due to B12 therapy. TC-I + III (holohaptocorcin) levels were low in a few tested individuals but not in others. Family members younger than 20 years old had normal serum vitamin B12 and holohaptocorcin (TC-I + III). Four young family members (IV-10, 11, 17, 18) with low TC-II levels were otherwise normal. No patient had folic acid deficiency.

Absorption studies

The Schilling test was performed in six patients with low serum vitamin B12 levels; all except one (patient III-4) also had low TC-II. Absorption was normal in three non-anemic patients (III-7, III-14, III-6). The test was abnormal in three patients with megaloblastic anemia (II-8, III-4, III-11). In two of them (II-8, III-11) the absorption was corrected by intrinsic factor. Parietal cell antibody was positive in titer 1:100 in patient III-4 and III-11 and negative in II-8. Gastric biopsy in patient II-8 showed atrophic gastritis to be the cause of intrinsic factor deficiency.

Discussion

The described family is unique because partial TC-II deficiency was indeed associated with clinically significant neurologic and hematologic complications. The milder degree of TC-II deficiency apparently explains both the lack of symptoms among some affected individuals and the relatively late presentation.

The difference between partial and complete TC-II deficiency may be similar to cystathionine beta-synthase deficiency (hereditary homocysteinuria). In this condition homozygotes have a strong
predisposition to early thrombosis, while in heterozygotes this predilection is much weaker although clinically significant (20).

Recent epidemiologic studies suggest that not only the amount but also the regular functioning of TC-II is important for normal development of the nervous system. Loss of TC-II affinity for vitamin B_{12} in mothers was associated with a three to fivefold increased frequency of neural tube defects in fetuses [21], and homocysteine concentrations in TC-II heterozygotes 299-R/P were significantly higher than in homozygotes 299-R and 299-P [22]. Our data should contribute to a better understanding of the clinical relevance of low TC-II affinity for cobalamin.

In our family, partial TC-II deficiency was the main biochemical abnormality and the most probable cause of the second type of neurologic complications — the complex of symptoms resembling minimal brain dysfunction. MBD affects 5–10% of all school-age children [23]. Approximately one-third of MBD is hereditary [23] although no biochemical or metabolic abnormalities can be detected. Partial TC-II deficiency may account for some of these cases. Given that the vitamin B_{12} serum level is normal, the diagnosis of TC-II deficiency can be established only by measurement of TC-II and UBBC. Establishing a correct diagnosis is crucial, as successful treatment is available.

Unfortunately, we did not examine serum homocysteine levels in the family members. Homocysteine is a useful marker of cobalamin tissue deficiency, and a correlation has been established between the serum holoTC-II and homocysteine [21]. Accordingly, it is likely that we would have found high normal or mildly elevated levels in patients with the second type of neurologic complications (low serum TC-II, but normal B_{12}) and significantly elevated levels in patients with the first type (both low).

The hematologic manifestations in the described family were relatively mild with mainly macrocytosis and megaloblastosis, suggesting that the available amount of TC-II is sufficient for nearly normal hematopoiesis. It is possible that another factor such as dietary vitamin B_{12} deficiency or pernicious anemia is needed for full expression of megaloblastic anemia. For example, patients II-8 and III-1 both had defective absorption of vitamin B_{12}, which was corrected by intrinsic factor. But the presence of antiparietal cell antibody in patient III-1 suggested an autoimmune etiology, whereas in patient II-8 the causative anomaly was atrophic gastritis without antiparietal cell antibody.

Although family clustering of pernicious anemia was previously observed, there is no known genetic basis. According to our findings hereditary partial TC-II deficiency may be responsible; it decreases the amount of stored cobalamin, leading to increased susceptibility to impaired intestinal delivery of cobalamin and predisposing to easily developing megaloblastic anemia. Similarly, heterozygotes with alpha-1-antitrypsin deficiency are predisposed to early smoking-induced emphysema.

In contrast to the previously described autosomal-recessive complete TC-II deficiency, in our family TC-II was present in all the subjects, albeit in a low amount, and bound vitamin B_{12} to form holo TC-II, as demonstrated by the OUSO method. This obviated the need for radioimmunoassay, which is able to detect immunoreactive but non-functional TC-II. In some of our subjects the amount of holoTC-II was very low and close to zero, which is explained by increased tissue metabolism of holoTC-II complex in an environment with cobalamin deficiency.

We observed a trend to overt cobalamin deficiency with increasing age; serum level of vitamin B_{12} was normal in children and tended to become low later in life, probably due to the progressive depletion of B_{12} storage. Vitamin B_{12} absorption was normal in half the family members, suggesting that enough TC-II was present for transferring cobalamin from the intestinal epithelium to the circulation.

The normal level of TC-II found in the proband requires explanation. This patient was given vitamin B_{12} parenteral supplementation of 1,000 µg monthly. Unintentionally, the last dose was injected 2 days before the blood sample was drawn for TC-II measurement. It is known that a high concentration of serum vitamin B_{12} after parenteral injection may interfere with all UBBC measurements. Alternatively, this patient might have had a normal TC-II level, and her vitamin B_{12} deficiency was caused by pernicious anemia. This patient may also have a normal TC-II gene, but her consanguineous husband transmitted the impaired TC-II gene to their offspring. No other patient received a vitamin B_{12} injection during the week before blood testing.

Low levels of holohaptocorrin (TC-I and III) observed in the subjects with low serum vitamin B_{12} reflect depletion of cobalamin stores. The low level of apohaptocorrin found in one individual with normal holohaptocorrin could not be considered pathologic.

In contrast to the autosomal-recessive mode of inheritance in previously described families with TC-II deficiency, in our family the transmission of the disease seems to be autosomal-dominant (Figure 1), although the x-linked dominant type of inheritance could not be excluded. The possibility of a TC regulatory gene abnormality rather than a TC-II genetic defect has not yet been investigated, although such a mutation in this putative gene might explain the clinical picture in some historical cases [8,9]. The concurrent mutations in TC-II and I genes appear to be unlikely since they have been mapped to different chromosomes [24]. Whether this family represents a genetic heterogeneity of TC-II deficiency, i.e., a mutation in a TC-II regulatory gene other than TC-II, or variability in expression among heterozygotes of a mutation in the same TC-II gene remains to be determined. Linkage studies in this family, using polymorphic markers in the TC-II gene locus, will allow us to address this question. Racial differences in the transcobalamin level, as observed in subgroups of the American population [25], may also play a role in the family of Jewish Yemenite origin described here.

The management of TC-II deficiency includes high doses of parenteral (or oral) hydroxycobalamin [11,16]. In our patient population, while only a slight neurologic improvement was noted after vitamin B_{12} treatment, cortical functions such as dyslexia, personality disorders and low IQ persisted, probably due to delay in the proper treatment.

In conclusion, TC-II deficiency should be suspected in families

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MBD = minimal brain dysfunction.
with megaloblastic anemia or neurologic and cognitive deficits. Early detection in infancy or childhood is important, allowing vitamin B₁₂ treatment that may result in normal neurologic development and prevent irreversible disability. Our findings may contribute to a better understanding of TCII-associated pathology.

Acknowledgments. We are in debt to Dr Victor Herbert (Nutrition Research Center, Hematology and Nutrition Laboratory, Veterans Affairs Medical Center, Bronx, New York, USA) for the UBBC studies and valuable discussions. Dr. Herbert died in November 2002. Together with many others in the medical and hematology community, we will miss him.

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Capsule

Protective endocannabinoids

Neurons need to protect themselves from the risk of excessive activity that can lead to neurotoxicity. Protective mechanisms likely exist to provide on-demand defense in the case of unusual high neuronal-spiking activity. Marsico et al. created conditional mouse mutants missing the cannabinoid receptor type 1 (CB₁) in pyramidal cells but not in interneurons of the forebrain. Protection against seizures induced by the excitotoxin kainic acid was exerted via CB₁ receptors in glutamatergic but not in GABAergic neurons. The seizures enhanced production of anandamide—an endogenous cannabinoid—in wild-type but not in mutant mice. Thus, the activation of the endogenous cannabinoid system is an on-demand, early, and necessary step for physiologic protection against excitotoxicity.

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