An Adolescent with Increased Plasma Methylmalonic Acid and Total Homocysteine

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CASE DESCRIPTION

An 18-year-old male patient was transferred to our hospital for evaluation of recent-onset generalized weakness, difficulty walking, and a 3-week history of progressive numbness in his fingertips and distal extremities. The patient's mother reported that she had experienced 4 similar episodes of lower-body weakness at the age of 16 years that had self-resolved. In addition, the patient's brother was hospitalized for a similar episode of lower-body weakness that had also self-resolved.

The patient's neurologic exam was notable for difficulty walking, with an unsteady, wide-based gait. He could not walk on toes or heels without assistance; otherwise he had full strength on manual muscle testing. Sensory exam revealed decreased appreciation of sensation to touch, temperature, vibration and proprioception (position sense) from feet proximally to knees and fingertips to palms.

Laboratory findings were as follows: plasma methylmalonic acid (MMA)[5] was highly increased: 17.4 μmol/L (reference interval: 0–0.29 μmol/L); total homocysteine was highly increased: 125 μmol/L (reference interval: <12.5 μmol/L); vitamin B_{12} was low: 188 pg/mL (200–1100 pg/mL); and liver enzymes were slightly increased: alanine transaminase (ALT): 54 U/L (reference interval: 3–35 U/L); aspartate transaminase (AST): 48 U/L (reference interval: 15–46 U/L). All other blood test results were within reference intervals except for a slightly increased red cell distribution width (RDW)-CV, 18.0% (reference interval: 11.5%–14.5%) and very slightly decreased hematocrit (HCT), 38.4% (reference interval: 39%–53%). There was no laboratory evidence of megaloblastic anemia.

The patient was treated with 1 intramuscular injection of cyanocobalamin and referred to an adolescent clinic for psychosocial evaluation, but he then left the hospital against medical advice before further treatment.

Eight months later, he presented with similar findings with loss of lower-extremity proprioception and vibratory sense, spastic diplegia with foot drop, and widebased ataxic gait. He was admitted to the hospital again due to worsening gait progressing to a nonambulatory status. His laboratory

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findings were as follows: MMA was highly increased, 8.6 µmol/L (reference interval: 0–0.29 µmol/L); total homocysteine was highly increased: 116 µmol/L (reference interval <12.5 µmol/L); vitamin B_{12} was low: 149 pg/mL (reference interval: 200–1100 pg/ mL); folate >24.0 ng/mL (reference interval: 2–20 ng/ mL). His RDW-CV was very slightly increased, 14.8% (reference interval: 11.5%–14.5%). All other blood tests were essentially within reference intervals. MRI of brain and spine did not show specific findings. Electromyography (EMG) was consistent with mixed axonal demyelinating polyneuropathy.

QUESTIONS TO CONSIDER
• Describe the metabolites that are increased in inherited intracellular vitamin B12 (cobalamin) defects.
• Explain the clinical and biochemical findings in vitamin B12 deficiency.
• List potential causes of vitamin B12 deficiency.

Final Publication and Comments

The final published version with discussion and comments from the experts will appear in the June 2017 issue of *Clinical Chemistry*. To view the case and comments online, go to http://www.clinchem.org/content/vol63/issue6 and follow the link to the Clinical Case Study and Commentaries.

Educational Centers

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