Teenaged Siblings with Progressive Neurocognitive Disease

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CASE

Two siblings were referred for workup for progressive neurological deterioration. The elder sibling was a 16-year-old boy who had been asymptomatic until 9 years of age when he developed walking difficulty that progressed to a bed-bound state followed by regression of cognitive function and generalized tonic clonic seizures. The younger sibling was a 14-year-old girl with onset of similar symptoms at the age of 6 years. The siblings were the eldest of 6 children from a family with no history of consanguinity.
Both children principally ate a high-carbohydrate (maize)-based diet with sporadic access to fresh produce and animal protein. They had reached normal developmental milestones until the onset of symptoms. Both children had been treated unsuccessfully with sodium valproate. On examination, they demonstrated minimal communication skills and severe cognitive impairment. They had spastic paralysis of all extremities.

Electroencephalography in the elder sibling revealed generalized, highly potentially epileptogenic foci, and a brain computed tomography scan demonstrated marked cerebral atrophy with minimal white matter. Initial laboratory investigations, including a complete blood count, measurement of electrolytes and urea, and thyroid and liver function tests, were all within reference intervals. Syphilis serology was negative. Screening for inherited metabolic diseases included measurements of plasma amino acids and urine organic acids. Selected laboratory results of the elder boy are provided in Table 1.

Table 1. Selected laboratory results for the elder boy.

Analyte	Result	Reference interval
Plasma creatinine, mg/dL (μmol/L)	0.38 (34)	0.80–1.39 (71–123)
Plasma vitamin B12, pg/mL (pmol/L)	255 (188)	196–863 (145–637)
Red cell folate, ng/mL (nmol/L)	995 (2256)	407–1472 (924–3337)
Plasma homocysteine, μmol/L	>150	2.1–15.7
Plasma methionine, μmol/L	12	16–36
Plasma cystathionine, μmol/L	1.0	0–3
Urine methylmalonic acid, mmol/mol creatinine	0.54	<3.6
Urine 2-methylcitric acid, mmol/mol creatinine	3.2	<8.6

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Questions to Consider
• What is the most common cause of a highly increased (>50 μmol/l) homocyteine?
• Which nutrient deficiencies are associated with increased homocysteine concentrations?
• What are the deleterious effects of increased plasma homocysteine concentrations?

Final Publication and Comments

The final published version with discussion and comments from the experts will appear in the August 2013 issue of *Clinical Chemistry*. To view the case and comments online, go to http://www.clinchem.org/content/vol59/issue8 and follow the link to the Clinical Case Study and Commentaries.

Educational Centers

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