Treating elevated homocysteine improves cognition

Boxer et al. describe a patient with cognitive impairment and elevated serum homocysteine due to a cobalamin metabolic deficit. His cognitive status and white matter disease improved with homocysteine lowering therapy.

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Disorders of cobalamin metabolism

Commentary by John C.M. Brust, MD

The main message of the Boxer et al. case report is that hyperhomocysteinemia can cause potentially reversible cognitive impairment. Of additional interest is that their patient had a rare condition seldom seen by neurologists and other physicians: a hereditary disorder of cobalamin (Cb1) metabolism.[1] Once delivered to cells and internalized, free Cb1 is either methylated within the cytosol to methylcobalamin (MeCb1) or adenosylated within the mitochondrion to adenosylcobalamin (AdoCb1). MeCb1 is a cofactor for methionine synthase, which converts homocysteine to methionine. AdoCb1 is a cofactor for methylmalonyl-CoA mutase, which isomerizes methylmalonyl-CoA to succinyl CoA.

Seven uncommon genetic abnormalities involve intracellular Cb1 metabolism. Three (Cb1C, Cb1D, Cb1F) affect the synthesis of both MeCb1 and AdoCb1 and produce elevations of both homocysteine and methylmalonic acid. Cb1A and Cb1B, by contrast, more selectively affect the synthesis of AdoCb1 and cause elevation only of methylmalonic acid. Cb1E and Cb1G affect the synthesis of MeCb1, resulting in elevated levels of homocysteine. The molecular basis of these intracellular Cb1 processing disorders is diverse. Complementation analysis using cultured fibroblasts distinguishes them as genetically distinct.

The most common of the seven, Cb1C, usually causes failure to thrive, megaloblastic anemia, and developmental delay in the first year of life, but symptoms can be delayed well into adulthood. Serum Cb1 levels are normal, but serum homocysteine and methylmalonic acid levels are elevated. If diagnosis is not delayed, treatment with pharmacologic doses of hydroxycobalamin plus protein restriction and administration of folate, carnitine (which enhances organic acid excretion), and betaine (which donates methyl groups to homocysteine) can improve symptoms. Intracellular Cb1 processing disorders are undoubtedly under-recognized, and clinicians should obtain serum levels of homocysteine and methylmalonic acid in any adult patient with appropriate neurologic symptoms and normal serum Cb1 levels.

Hyperhomocysteinemia is also a risk factor for ischemic stroke, yet in the Vitamin Intervention and Stroke Prevention (VISP) randomized controlled trial lowering serum homocysteine levels with high-dose multivitamin therapy failed to prevent recurrent stroke.[2] That trial, however, was underpowered to detect a reduction in the relative risk of stroke of up to 20%, and further studies of homocysteinemia are currently in progress.[3,4] Whether the effects of hyperhomocysteinemia on cognitive function are related to its effects on cerebral vasculature is unclear. Imaging studies and the improvement in the Boxer et al. patient suggest that they are not.[5]

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John C.M. Brust

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