CLINICAL VIGNETTE

Relatively Rapid Memory Loss in a Folate Deficient Patient

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Case Report

A 65-year-old male with hypertension, major depression, and anxiety presented with worsening memory. The patient and his wife reported insidious onset and progression of memory problems that began three or four years prior. Short-term memory seemed to be impaired greater than long-term memory. He had to stop working, due to difficulty with the cognitive aspects of his job.

Three months prior to his visit, he developed "seizure-like" events. The episodes were included migraine-type auras, with visual changes with areas of "darkness" in front of both eyes. He passed out on two occasions and awakened without residual symptoms. He was prescribed clonazepam by another provider, which he has taken at the first sign of an impending episode and seemed to prevent loss of consciousness. The patient's wife described him as "out of it" during the episodes, talking about heaven and seeing people who have died. Bladder incontinence occurred once and he denied diarrhea, constipation, abdominal pain, or indigestion.

The patient also reports changes in judgment and difficulty focusing. He continues to perform his activities of daily living independently, including transferring, showering, dressing, eating, and toileting. He acknowledged regular use of alcohol, 2 margaritas per night. He denied depression and has no difficulty walking or balance between episodes and was able to climb and descend stairs without difficulty. He and his wife continue to manage a large ranch.

Current medications include atorvastatin 20 mg, bupropion 75 mg, vitamin-D 5000 unit capsules, clonazepam 1 mg tablets, cyanocobalamin a 1000 mcg tablets, doxepin 50 mg, losartan 100 mg, melatonin, sertraline 50 mg, trazodone 100 mg, and zolpidem 12.5 mg extended release nightly. He has no known drug allergies. ROS was positive for snoring without daytime sleepiness.

His physical exam was essentially normal including MMSE of 30/30. Initial labs were significant for hemoglobin 14.0 g/dL, with increased MCV 102.6 fL, B12 of 458 pg/mL (normal 254-1060 pg/mL), and low folate of 4.5 ng/mL (normal 8.1-30.4 ng/mL). MRI of the brain showed no evidence of acute ischemia or infarction and EEG was normal. He was started on daily oral folic acid. After several weeks of repletion, his memory impairment and personality symptoms totally resolved.

Discussion

Folate deficiency is relatively rare in developed countries. One 2014 study examined nearly 85,000 ambulatory patients and found only 0.06% with true folate deficiency.[1] A major reason for low prevalence is the widespread folate fortification programs that started in the 1990s, including grains, breads, cereals, pasta, and rice. An 2014 study of hospitalized patients concluded the majority of causes of folate deficiency are related to alcohol use, malabsorption, decreased oral intake from psychiatric conditions, and lab errors.[2] Malabsorption causes include post-bariatric surgery, celiac disease, and tropical sprue. Folate deficiency also occurs in patients with rapid cell proliferation which increases requirement for folate.[3] These include pregnancy and lactation, chronic hemolytic anemias, exfoliative skin diseases such as severe eczema and hemodialysis. Finally, certain medications can interfere with folate metabolism. These include methotrexate, certain antibiotics, and certain anti-seizure medications including phenytoin, valproate, and carbamazepine.

Classic symptoms of folate deficiency include macrocytic anemia, jaundice, and various neurological abnormalities. The nonspecific symptoms seen in this patient, including irritability, fatigue, and memory impairment are also common. Folate deficiency can develop rapidly in weeks to months, given limited body stores. This is in contrast to B12 deficiency, which occurs over years. However, because of overlap of these two conditions, both B12 and folate levels should be checked in patients with potential deficiencies.

All patients with folate deficiency should be treated. Patients that have incidental findings of B12 or folate deficiencies can be treated with low doses. However, patients with symptoms need more urgent repletion. Patients with symptomatic anemia or neurological findings, should be repleted parenterally with transition to oral formulations after symptoms have improved.

There is little concern for over-repletion, given that both B12 and folate are water-soluble vitamins that are excreted in the urine when stores are repleted.[4]

One important treatment aspect is folate repletion can partially reverse some of the hematologic abnormalities associated with Vitamin B12 deficiency. However, the neurologic changes associated with low B12 levels are *not* treated by folate repletion, and thus, repletion of folate in a B12 deficient patient can mask the deficiency.[5]

In our patient, the most likely cause of deficiency was excessive alcohol use, which may have been under-reported. The relatively rapid resolution of symptoms with repletion was consistent with an easily reversible cause.

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