Case in Point

Parkinsonism and Vitamin C Deficiency

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Patients with vitamin C deficiencies and parkinsonism can show rapid improvement with vitamin C replacement therapy.

Vitamin C (ascorbic acid) deficiency is known to affect brain function and is associated with parkinsonism.[1] In 1752, James Lind, MD, described emotional and behavioral changes that herald the onset of scurvy and precede hemorrhagic findings.[2] The World Health Organization (WHO) today refers to this stage as latent scurvy.[3] The 2 case studies that follow present examples of patients with vitamin C deficiencies whose parkinsonism responded robustly to vitamin C replacement. These cases suggest that vitamin C deficiency may be a treatable cause of parkinsonism.

CASE 1

Mr. A, a 60-year-old white male, was admitted to the Medicine Service for alcohol detoxification. The patient had a history of alcohol dependence, alcohol withdrawal seizures, tobacco dependence, and hyperlipidemia. He took no medications as an outpatient. On admission Mr. A's body mass index (BMI) was 27.2. An initial examination revealed a marked resting tremor of the patient's right hand with cogwheeling, which had not been present in examinations conducted in the previous 3 years. Mr. A had no prior history of a tremor. He had no cerebellar findings and no evidence of asterixis or of tremulousness associated with high-output cardiac states, such as de Musset sign.

Mr. A reported he had experienced the tremor for a month and that it had been worsening. He also was having difficulty using his dominant right hand, for routine daily activities. Mr. A was oriented, and his short-term memory was intact. He was ill-appearing, irritable with psychomotor slowing, and did not wish to rise from his bed. He had no gingival or periungual bleeding and did not bruise easily. He had no corkscrew hairs. The patient was started on no medications known to cause extrapyramidal symptoms (EPS).

In the hospital, the tremor persisted unabated for 2 days. On the third day, Mr. A was started on 1,000 mg vitamin C IV twice daily. He received a total of 2,000 mg IV that day, but the IV fell out, and he refused its replacement. Several hours later, Mr. A stated that he felt much better, got out of bed, and asked to go outside to smoke. The author noted complete resolution of the right hand tremor and cogwheeling 20 hours after starting the vitamin C IV. Mr. A refused a repeat serum vitamin C assay.

Laboratory studies initially revealed that Mr. A had hyponatremia with a serum sodium of 121 mmol/L (normal range: 133 to 145 mmol/L) as well as hypokalemia with a serum potassium of 3.2 mmol/L (normal range: 3.5 to 5.0 mmol/L). He was hypoosmolar, with a serum osmolality of 276 mOsm/kg (normal range: 278 to 305 mOsm/kg). His vitamin C level was low at 0.2 mg/dL (normal range: 0.4 to 2.0 mg/dL). Mr. A also had a serum vitamin C level drawn 2 years prior that showed no symptoms of EPS, and at that time, the reading was 0.7 mg/dL. At admission to Medicine Services, Mr. A had a serum alcohol level of 211 mg/dL. Neuroimaging revealed diffuse cerebral and cerebellar volume loss.

Normal laboratory results included serum levels of vitamin B12, red cell folate, homocysteine, methylmalonic acid, free and total carnitine, alkaline phosphatase, manganese, and zinc. A urine drug screen was negative.

CASE 2

Mr. B, a 69-year-old black male, was admitted to the hospital for

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depression complicated by alcohol dependence. He also had tobacco dependence, type 2 diabetes mellitus, hypertension, and gout. The patient's BMI at admission was 16.1. Mr. B appeared ill, was worried about his health, and remained recumbent unless asked to move. He reported that his right hand had begun to shake at rest in the month prior to admission. The tremor made it difficult for him to drink. He pointed out stains on his hospital gurney from an attempt to drink orange juice prior to being assessed.

A physical examination revealed a distinct resting tremor with cogwheeling of the right hand; there was no other evidence of EPS, nor was there evidence of cognitive, cerebellar, or skin abnormalities, such as hemorrhages or corkscrew hairs. Asterixis was absent as was evidence of a high-output cardiac state that might produce a tremor, such as de Musset sign. A serum vitamin C level was obtained and returned at 0.0 mg/dL. A head computed tomography scan obtained the next day revealed mild cerebellar volume loss. A serum alkaline phosphatase level was elevated slightly at 136 U/L (normal range: 42 to 113 U/L). Normal serum values were returned for zinc, vitamins B12 and folate, rapid plasma reagin, sodium, and serum osmolality. A urine drug screen was negative, and serum alcohol level was < 5.0 mg/dL.

Mr. B took no medications expected to cause EPS. He received no micronutrient replacement until the day after admission when he began receiving oral vitamin C 1,000 mg twice a day. After receiving 3 doses, Mr. B's resting tremor and cogwheeling completely resolved. He noticed he had stopped shaking and could now drink without spilling fluids. He also got out of bed and began interacting with others. Mr. B said he felt he was "doing well." A repeat serum vitamin C level was 0.2 mg/dL on that day. The improvement was sustained over 3 days, and Mr. B was discharged to home.

Table 1. Proposed Criteria for a Diagnosis of Neuropsychiatric Scurvy

For a diagnosis of neuropsychiatric scurvy, the patient must satisfy each of the following 3 criteria:

1. The patient has either a or b:
   a. Psychomotor retardation **plus** evidence of an affective disturbance (**either** apathy, anxiety, **or** irritability);
   b. Extrapyramidal findings.
2. The patient has some systemic evidence of hypovitaminosis C as manifested by either:
   a. Some disturbance of collagen metabolism, such as classic hemorrhagic findings **or** corkscrew hairs;
   or
   b. Biochemical evidence of deficiency, such as a low serum vitamin C level.
3. The above findings respond to replacement of vitamin C.

DISCUSSION

Both Mr. A and Mr. B presented with a typical picture of latent scurvy and the additional finding of parkinsonism. These cases are important for 2 reasons. First, the swift and full response of these patients' parkinsonism to vitamin C replacement underscores the importance of considering a vitamin C deficiency when confronted with EPS. And second, both patients lacked signs of bleeding or of impaired collagen synthesis. This differs from the classic presentation of scurvy as a disorder primarily of collagen metabolism.[4]

Lind described the onset of scurvy as one in which striking emotional and behavior changes developed and later were followed by abnormal bleeding and even death.[2] These early changes also were recognized by Shapter in 1847.[5] Furthermore, the evidence that exists about the time-course of scurvy's development suggests that neuropsychiatric findings precede the hemorrhagic.[6] Indeed, classic skin findings, such as petechiae or corkscrew hairs, may develop years after the onset of neuropsychiatric changes.[7,8]

Despite WHO characterizing it as latent scurvy, the distinct syndromal presentation of hypovitaminosis C with parkinsonism along with the rapid response to vitamin C replacement argues for its recognition as a distinct clinical entity and not just a prelude to the hemorrhagic state. To assist in recognizing neuropsychiatric scurvy, the author suggests the operationalized approach described in Table 1.[9]

Pathophysiology

Vitamin C has an intimate role in the normal functioning of the basal ganglia. It is involved in the synthesis of catechecholamines, the regulation of the release and postsynaptic activities of various neurotransmitters, and managing the oxyradical toxicity of aerobic metabolism. Table 2 outlines some of the normal brain functions of vitamin C and the potential consequences of inadequate central vitamin C.[9,10] Risk factors for vitamin C

Table 2. Suspected Pathophysiologic Factors in Neuropsychiatric Scurvy

Vitamin C Actions	Result of Reduced Vitamin C Availability
Cofactor in catecholamine synthesis	Reduced production of catecholamines
Inhibits acetycholine release in rabbit caudate nucleus	Potential to disinhibit acetylcholine release and promote EPS
Regulates postsynaptic actions of GABA and glutamate	Loss of this regulatory factor may tend to promote EPS
Antioxidant	Loss of antioxidant activity may replicate the pathophysiology of Parkinson disease

Abbreviations: EPS, extrapyramidal symptoms; GABA, gamma-aminobutyric acid.

deficiency include those affecting the uptake, response to, and elimination of this vitamin (Table 3).[11-14]

The potential role of alcohol use by both patients also warrants mention. Current data suggest a nonlinear relationship between alcohol use and neurotoxicity. Epidemiologic data show that moderate alcohol consumption protects against the development of such neurodegenerative processes as Parkinson disease and Alzheimer disease.[15,16] But the cases here reflect excessive use of alcohol. In this situation, a variety of progressive insults, such as those caused by oxyradical toxicity as well as malnutrition may foster the development of basal ganglia dysfunction.[17]

Measuring Deficiency

A deficiency of vitamin C may be determined in several ways. The most frequently used laboratory measure of vitamin C status is the serum vitamin C level. This level is included in the WHO's recommendations for diagnosis.[3] However, this assay is limited because when facing total body depletion, the kidneys may restrict the elimination of vitamin C and tend to maintain serum vitamin C levels even as target tissue levels fall. An interesting example of this is the 0.2 mg/dL value that each patient registered. In Mr. A's case, this reflected a systemic deficit of vitamin C, while in Mr. B's case it correlated with the onset of effective repletion of body's stores.

A fall in urinary output of vitamin C is another marker of hypovitaminosis C. When available, this laboratory test can be used with the serum level to assess total body stores of vitamin C. Lymphocytes, neutrophils, and platelets also store vitamin C. These target tissues tend to saturate when the oral intake ranges between 100 mg to 200 mg a day. This is the same point at which serum vitamin C levels peak and level off in normal, healthy adults.[18,19] Once again, the limited availability of target-tissue assays puts these studies out of reach for most clinicians.

No evaluation is complete without some assurance of what the disease is not. Deficiencies of biotin, zinc, folate, and B12 all may affect the function of the basal ganglia.[20] The biotin deficiencies literature is particularly robust. Biotin deficiencies affecting basal ganglia function are best known as inherited disorders of metabolism.[21] Manganese intoxication also may present as a movement disorder.[22]

Treatment

Treatment of neuropsychiatric scurvy has relied on IV administration of vitamin C. Although the bioavailability of oral vitamin C among healthy adult volunteers is nearly complete up to about 200 mg a day, a patient with neuropsychiatric scurvy may need substantially more than that amount to accommodate total body deficiencies and increased demands.[23] The IV route allows serum vitamin C levels up to 100 times higher than by the oral route.[24] Mr. B is, in fact, the first person reported in the literature with neuropsychiatric scurvy to respond to oral vitamin C replacement alone. Once repletion of vitamin C is complete, it is useful to consider a maintenance replacement dose based on a patient's risk factors and needs.

A healthy adult should ingest about 120 mg of vitamin C daily. Smokers and pregnant women may require more, but this recommendation was intended to address their needs as well.[25] Many commercial multivitamins use the old recommended daily allowance of 60 mg, so it may be safest to recommend specifically a vitamin C tablet with at least 120 mg when ordering vitamin C replacement.

Tight control of the serum vitamin C concentration means that little additional vitamin C will be taken up by the gut beyond 200 mg orally a day, which helps minimize any concerns about long-term toxicity. It takes several weeks to deplete vitamin C from the human body when vitamin C is removed from the diet, so a patient with a previously treated deficiency of vitamin C should wait a month

Table 3. Patient-Specific Risk Factors for Vitamin C Deficiency

Factors That Decrease Availability or Uptake	Factors That Cause Tissue Resistance or Increase Demand	Factors That Accelerate Elimination
• Anorexia or starvation • Gut disease, including Crohn disease and celiac disease • Severe psychiatric illness affecting food intake • Hypotestosteronemia: a cause of anorexia • Alcoholism or substance abuse • Food allergies and related disorders (eg, atopic dermatitis) • Processed foods	• Hypoosmolar state • Hyponatremia • Acidosis • Insulin resistance or deficiency • Stress or catabolic states (eg, wound healing, burns, pregnancy, surgery, infection) • Inflammatory states (eg, infection, peripheral arterial disease) • Oxidizing medications (eg, benzocaine, dapsone, lidocaine, haloperidol, metoclopramide) • Hypotestosteronemia Promotes catabolism Promotes insulin resistance • Genetic variation in vitamin C uptake and use	• Smoking: may double the normal rate of vitamin C consumption • Diuretics: enhance renal elimination of water-soluble vitamins • Alcohol: speeds elimination of vitamin C • Oral contraceptives: reduce serum vitamin C levels • Renal insufficiency: can markedly reduce the ability to recapture water-soluble vitamins • Hemodialysis: removes water-soluble vitamins

before a repeat serum vitamin C level measurement.

The half life of vitamin C is normally ≤ 2 hours. When renal function is intact, vitamin C in excess of immediate need is lost through renal filtration. Toxicity is rare under these conditions.[26] When vitamin C toxicity has been reported, it has occurred in the setting of prolonged supplementation, usually when a patient already experienced a renal injury. The main toxicities attributed to vitamin C are oxalate crystal formation with subsequent renal injury and exacerbation of glucose 6-phosphate dehydrogenase deficiency (G6PD).[24]

Oxalate formation due to vitamin C replacement is uncommon, but patients with preexisting calcium oxalate stones may be at risk for further stone formation when they receive additional vitamin C.[27] This is most likely to occur when treatment with parenteral vitamin C is prolonged, which is not typical for patients with neuropsychiatric scurvy who tend to respond rapidly to vitamin C replenishment. Reports of acute hemolytic episodes among patient with G6PD deficiency receiving vitamin C exist, although these cases are rare.[28] Furthermore, some authors advocate for the use of ascorbic acid to treat methemoglobinemia associated with G6PD deficiency, when methylene blue is not available.[29] It may be reasonable to begin treatment with oral vitamin C for patients with NPS and G6PD deficiency. This is equivalent to a low-dose form of vitamin C replacement and may help avoid the theoretically pro-oxidant effects of larger, IV doses of vitamin C.[30]

CONCLUSION

The recent discovery of movement disorders in scurvy has enlarged the picture of vitamin C deficiency. The cases here demonstrate how hypovitaminosis C with central nervous system manifestations may be identified and treated. This relationship fits well within the established basic science and clinical framework for scurvy, and the clinical implications for scurvy remain in many ways unchanged. First, malnutrition must be considered even when a patient's habitus suggests he is well fed. Also, it is more likely to see scurvy without all of the classic findings than an end-stage case of the disease.[31] In the right clinical setting, it is reasonable to think of a vitamin C deficiency before the patient develops bleeding gums and corkscrew hairs. And as is typical of vitamin deficiencies, the treatment of a vitamin C deficiency usually results in swift improvement. Finally, for those who treat movement disorders or who prescribe agents such as antipsychotics that may cause movement disorders, it is important to recognize vitamin C deficiency as another potential explanation for EPS. ●

Author disclosures

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