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Review Articles

Neuropsychiatric Scurvy

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Background: *Scurvy is a disease with well-known peripheral symptoms, such as bleeding and pain.*
Methods: *The clinical and historical evidence for a distinct form of scurvy affecting the central nervous system, called neuropsychiatric scurvy, is reviewed. Pathophysiologic factors are described, as well as its diagnosis and management.*
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INTRODUCTION

Scurvy is an ancient disease that persists and surprises. Its early descriptions can be traced back 3500 years to the Egyptians. Herodotus is often credited with the first formal description of scurvy. He emphasized the hemorrhagic features of the disorder.[1] James Lind's landmark treatise among sailors did much to define the modern clinical image of scurvy as an acute, hemorrhagic, and potentially fulminant nutritional deficiency.[2] This view of scurvy, accurate in what it included, has been replicated and persists to this day.[3–5] Yet hidden within these descriptions, both early and late, are symptoms that do not derive from disturbances of collagen metabolism but rather from the central nervous system (CNS) effects of vitamin C deficiency, such as extrapyramidal symptoms (EPS). This review summarizes what is known about the CNS effects and the clinical presentation of hypovitaminosis C.

THE EVIDENCE FOR NEUROPSYCHIATRIC FINDINGS IN SCURVY

> …the person eats and drinks heartily, and seems in perfect health; except that his countenance and lazy inactive disposition may portend an approaching scurvy.[2]

For centuries, the sentinel findings in scurvy have been neuropsychiatric. Today, the World Health Organization recognizes an early or "latent" form of scurvy characterized in part by "lassitude, weakness, and irritability."[6] Apathy, irritability, and psychomotor retardation have been recognized for centuries as heralding the onset of scurvy. James Lind reported that scurvy began with the development of changes in mood and behavior.[2] Shapter echoed these findings a century later when he reported that "feelings of weakness, of listlessness," "a disinclination to exertion," and a "nervous" state heralded the onset of scurvy.[5] In a study of 38 patients with confirmed scurvy, Fouron and Chicoine found that all of the patients were irritable, and that many more had psychomotor retardation than had hemorrhagic findings.[3] In an elegant study, Hodges et al. monitored the decrease in plasma vitamin C levels, and the emergence of symptoms, in 5 healthy adult men maintained on a diet free of vitamin C. They observed a decrease in plasma vitamin C levels over 30 days. Hemorrhagic findings, beginning with petechiae, emerged at this time.[7] In a companion article, Kinsman and Hood[8] carefully assessed "personality changes" and psychomotor performance in the same subjects. They found

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that "personality changes" developed among the 5 subjects maintained on a diet devoid of vitamin C for 84–97 days. They observed that 4 scales of the Minnesota Multiphasic Personality Inventory increased markedly after day 23 of depletion, and they continued to rise until vitamin C was restored. These scales measured hypochondriasis, hysteria, depression, and social introversion. Each subject tended to become "a depressed and withdrawn individual who is concerned about his physical state." These scales rose before the emergence of hemorrhagic findings, and before there was any decline in psychomotor performance.[8] Recently, disturbances of basal motor nuclei (BMN) function, as a result of vitamin C deficiency, have been described as a late stage of scurvy.

The experience with vitamin C–responsive BMN dysfunction in scurvy is limited but compelling.[9–11] In these cases, a variety of problems referable to the BMN, and responding robustly to intravenous vitamin C administration, were noted. EPS was a universal feature. In these cases, the EPS consisted of a resting tremor with cogwheeling and psychomotor retardation or dyskinesias. In a case in which the intravenous administration of vitamin C was stopped prematurely twice, the patient's dyskinesias quickly resolved each time vitamin C was readministered and gradually returned when the replacement was stopped.[10] These cases were novel because they linked EPS to scurvy. However, an association between vitamin C deficiency and parkinsonism has been previously suggested.[12]

In 1992, Yapa reported that subclinical evidence of vitamin C deficiency, such as the presence of corkscrew hairs, confirmed by serum vitamin C assays, correlated strongly with a diagnosis of Parkinson disease among elderly patients.[13] Logroscino et al. found that a diet rich in non-heme iron is associated with an increased risk of the development of Parkinson disease, and this risk is further increased if the diet is poor in vitamin C.[14] In vascular parkinsonism, serum levels of vitamin C, as well as vitamin E, tend to be lower than in controls.[15] In another interesting study of patients with Parkinson disease, King et al.[16] found that the serum vitamin C level did not differ between patients and healthy young controls. However, the leukocyte vitamin C concentrations, a marker of target-tissue levels of vitamin C, were significantly lower in patients.[16] It seems that dietary intake of vitamin C or serum levels of vitamin C, when considered in isolation, and apart from target-tissue levels of vitamin C, do not always correlate well with the risk of development of Parkinson disease.[17] What does appear to travel with an increased risk of parkinsonism in humans is some evidence of vitamin C deficiency or of increased oxidant stress. Rodent studies have added substantial detail to the link between CNS vitamin C and normal function of the BMN.

In rodents, CNS deficiency of vitamin C clearly disrupts BMN activity. This has long been recognized and repeatedly shown.[18,19] In adult rats severely depleted of striatal vitamin C, psychomotor activity rapidly slows. Novelty seeking and social interactions are similarly reduced.[20] Harrison et al. found that in mice that were unable to synthesize vitamin C, elimination of this vitamin from the diet of pups produced CNS deficits specifically of striatal motor function.[21] These findings were replicated by Chen et al.[22] In another mouse model, the R6/2 transgenic mouse model of Huntington disease, abnormal release of striatal ascorbate is also linked with motor dysfunction.[23] The data for a link between vitamin C deficiency and dysfunction of the BMN in rodents are very strong and complement the data from humans.

In revisiting the cases of vitamin C–responsive EPS, it is also helpful to clarify what they were not. This is especially important as a variety of micronutrient abnormalities are implicated in dysfunction of the BMN. Vitamin E and copper have well-described associations with EPS. Deficiencies of vitamin E may be inherited, or acquired, as after gastric surgery. When inherited, the patient typically has ataxia, although dystonia may also occur.[24] Neuropathy is usually the dominant neurologic finding among acquired cases of vitamin E deficiency.[25] Wilson disease is among the best known of the diseases of metal metabolism that result in abnormalities of BMN function. Excess deposition of copper in these nuclei, or of manganese or iron, can cause movement disorders.[26] Zinc deficiency may also, at least in theory, cause EPS. Basic science data show that zinc is poised to affect neurotransmission in the BMN.[27] And finally, elevated serum levels of homocysteine and methylmalonic acid have been linked with such neurodegenerative disorders as Parkinson disease, progressive supranuclear palsy, and amyotrophic lateral sclerosis.[28] Although all of these potential causes were