

Numb Hand Syndrome –A Rare Presentation of Vitamin B12 Deficiency In Indian Patient

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I. Introduction

A 40 years female Indian vegetarian patient was admitted with complaints of left hand and face numbness with neck pain and other multiple joint pains,she also had signs of low self esteem,decreased physical activityand occasional excess menstrual bleed .No history of seizures .On examination :Bilateral pedal edema was noticed which the patient said it was present from birth and her mother had the same .Her CVS,LUNGS,ABDOMEN were normal on examination.OnCNS examination: conscious,higher mental functions were normal,no motor deficits(all 4 limbs full motor power and movements),B/L plantars absent and other deep tendon reflexes are normal ,fine and crude touch sensations are diminished in right arm,vibration sense is also diminished in left arm ,no cerebellar signs,no gait changes,rombergs test negative,no bowel and bladder incontinence,no involuntary movements,fundus normal and all cranial nerves intact,GCS score was 15/15.

Peripheral blood smear: RBC are normocytic, normochromic ECG: normal USG abdomen:nohepatosplenomegaly HB:11.3 TLC 7.6 ESR 25 Platelets 315 Total Bilirubin 0.5 Albumin 4,serum uric acid 3.9 serum calcium 9 serum phosphorus 4.9 CRP 0.15 Thyroid tests were normal,serum vitamin B12 was 284 pg/ml,serum vitamin D was 22.7ng/ml ,MRI brain was normal, MRI spine showed mild degenerative changes with diffuse posterior bulge seen at L4-L5,L5-S1 level indenting thecal sac and encroaching lateral recesses.Serumhomocysteinelevels,serummethylmalonic acid level are increased ,NCV studies of all 4 limbs done which showed axonal neuropathy .Patient was consulted by neurosurgeon and orthopedician for MRI spine changes and conservative therapy with physiotherapy was advised.Patient was started on injection vitamin B12 for few weeks and later shifted to oral supplementation and patient showed marked improvement in her sensory and psychiatry symptoms.

II. Discussion

The most common cause of B12 deficiency is pernicious anemia. This autoimmune disorder is characterized by destruction of the gastric mucosa, and the presence of parietal cell and intrinsic factor antibody leading to impaired B12 absorption. The disorder is more common in African-Americans and in patients with Northern European background.Cobalamin deficiency is a common finding. In the elderly the prevalence is 10-20%, but only 5-10% of these are clinicallysymptomatic. Pernicious anaemia is an autoimmune disorder that results in inflammation and damage to the stomach lining, and loss of cells that produce stomach acid (parietal cells), digestive enzymes and mucus. The parietal cells also produce intrinsic factor, a protein needed for absorption of vitamin B12 in the gut.Destruction of parietal cells leads to a lack of intrinsic factor. This syndrome is usually caused by atrophic gastritis, related or unrelated to Helicobacter pylori infection, and long-term ingestion of antacids and biguanides.

Presentations vary greatly among patients.

The symmetric glove-and-stocking paresthesias, or tingling in the distal aspect of the toes, numbness, coldness, a pins-and-needles feeling, and occasional feelings of swelling or constriction, are slowly progressive and insidious. Symptoms progress up the legs,occasionally affect the fingers, and culminate in weakness and spasticity.In late stages, manifestations include moderate muscular wasting, optic atrophy, sphincter dysfunction, and mental disturbances.Examples of these disturbances are mild dementia (which is often the first symptom and clinically indistinguishable from other dementias), disorientation, depression, psychosis, and persecutory delusions.The hematologic manifestation of anemia, if present, can cause weakness, light-

headedness, vertigo, tinnitus, palpitations, angina, heart failure, cardiomegaly, pallor, tachycardia, and hepatosplenomegaly. GI symptoms include a sore, beefy red tongue and anorexia.

If left untreated, the gait becomes ataxic, followed by paraplegia with spasticity and contractures. The subacute combined degeneration that develops results in a severe myelopathy, involving posterior columns and lateral corticospinal tracts, with other manifestations including optic (retrobulbar) neuropathy, sensorimotor polyneuropathy, and dementia.

Whereas vegetarianism is present in all geographic areas, only in the past 50 years it recognized that **vegetarians have consistently lower vitamin B-12 concentrations than do nonvegetarians** and that vegetarians are at greater risk of vitamin B-12 deficiency than are nonvegetarians. Because vitamin B-12 is produced in nature only by vitamin B-12-producing microorganisms, humans must receive vitamin B-12 solely from the diet. Although there are abundant vitamin B-12-producing bacteria that colonize the large bowel, that organ is too distal to allow normal vitamin B-12 absorption. Nonvegetarians obtain most of their vitamin B-12 through eating meat, whereas lactoovo vegetarians obtain most of their vitamin B-12 from milk, dairy products, and eggs. About 80% of all cases are due to pernicious anemia, and another 10% are due to achlorhydria. Exposure to nitrous oxide can suddenly precipitate the deficiency, which should be considered in any patient who develops postoperative paresthesias.

Chronic exposure to nitrous oxide has been associated with subacute combined degeneration. The mechanism by which nitrous oxide induces vitamin B12 deficiency is by inactivation of methyl-cobalamin thereby inhibiting the conversion of homocysteine to methionine and methyltetrahydrofolate (MTHF) and 5-methylene-tetrahydrofolate (THF), which are required for myelin sheath protein and DNA synthesis. The disease predominantly affects the spinal cord; therefore, separating the painful sensory and sensorimotor paresthesias of the peripheral neuropathy from the symptoms of spinal cord involvement is difficult. Histopathological studies have showed breakdown and vacuolization of central nervous system myelin under B12 deficiency states. In contrast to the demyelinating features seen in the spinal cord, axonal neuropathy is seen on nerve biopsies and nerve conduction studies in vitamin B12 polyneuropathy.

Macrocytic anemia is the most common clinical finding, with macrocytosis preceding the anemia by months, but 13% to 27% of patients with PA have little or no anemia, and unrelated microcytosis masks the macrocytosis in 7% of anemic cases. A roughly inverse relationship often exists between hematologic and neurologic deficits. Some medical encounters occur solely because of a known predisposing gastrointestinal disease or, increasingly, an abnormal biochemical finding. Serum cobalamin levels less than 200 ng/L (< 148 pmol/L), or less than 250 ng/L with some assays, are common, especially among the elderly, but approximately 22% to 30% of them are falsely low by both metabolic and clinical criteria, and most of the rest are clinically innocent. Their accidental coexistence with a suspected clinical finding can sometimes be misconstrued. The initial task is to document the clinical and laboratory findings and prove their connection to cobalamin deficiency.

Differentiating vitamin B12 deficiency-related polyneuropathy from cryptogenic sensory polyneuropathy (CSPN) can be difficult on clinical grounds only. Clinical features useful to identify vitamin B12 deficiency related peripheral neuropathy are the acuteness of symptoms onset, and concomitant involvement of upper and lower extremities. Sometimes the sensory symptoms and signs first appear in the upper extremities or the “numb hand syndrome”. When this occurs with other findings of a myeloneuropathy, immediately consider B12 as well as copper deficiency. The myeloneuropathy findings often consist of significant proprioception and vibration, increased tone, weakness in a corticospinal tract distribution, (ex. hip and knee flexors), brisk knee and arm reflexes, Hoffman’s signs in the fingers, and extensor plantar responses in the toes.

The clinical picture is the most important factor in assessing the significance of test results assessing cobalamin status because there is no ‘gold standard’ test to define deficiency.

Direct Tests Of Vitamin B12 Status In Its Various Forms Are Available .

Serum cobalamin currently remains the first-line test, with additional second-line plasma methylmalonic acid to help clarify uncertainties of underlying biochemical/functional deficiencies. Serum holotranscobalamin has the potential as a first-line test, but an indeterminate ‘grey area’ may still exist. Serum holotranscobalamin (holoTC): in serum, vitamin B12 exists in 2 bound forms. It can be bound to haptocorrin to form holohaptocorrin; or bound to transcobalamin to form holoTC. Cells can only take up vitamin B12 in the form of holoTC (Hunt et al. 2014). Therefore, measuring holoTC is more reflective of vitamin B12 status than measuring total vitamin B12 or holohaptocorrin alone. Emerging evidence suggests that a low level of holoTC may be a more reliable marker of vitamin B12 deficiency than a low serum cobalamin level, particularly as an early marker. For nearly 50 years, the diagnostic search began with the Schilling test, which not only identified abnormal IF-related absorption but also distinguished between gastric and intestinal

defects. The underlying diseases themselves (eg, PA) are often asymptomatic and could not be detected otherwise. An abnormal Schilling test result also helps select the optimal final test (eg, intestinal biopsy).

Functional tests for biochemical abnormalities associated with vitamin B12 deficiency, for example methylmalonic acid (MMA) or total homocysteine (Hcy) levels:

MMA is a substance produced when amino acids are metabolised. It is involved in a reaction that uses vitamin B12 (cobalamin) as a cofactor and so can be used as an indicator of vitamin B12 levels. High levels of plasma MMA may indicate cobalamin deficiency. However, levels may not accurately indicate a deficiency in people aged over 65 years with kidney disease, small bowel bacterial overgrowth or reduced fluid content of the blood because these conditions can also cause elevated MMA levels. Total serum Hcy is an indicator of vitamin B12 deficiency because cobalamin is needed for the synthesis of methionine from Hcy, and low levels of vitamin B12 lead to increased total serum Hcy. However, its use as a sole confirmatory test is limited because Hcy levels are also higher in people with folate deficiency, vitamin B6 deficiency, renal failure and hypothyroidism. Both MMA and Hcy are also late indicators of vitamin B12 deficiency.

Plasma homocysteine may be helpful as a second-line test, but is less specific than methylmalonic acid. The availability of these second-line tests is currently limited. Definitive cut-off points to define clinical and subclinical deficiency states are not possible, given the variety of methodologies used and technical issues, and local reference ranges should be established. In the presence of discordance between the test result and strong clinical features of deficiency, treatment should not be delayed to avoid neurological impairment.

The discovery of a treatment for pernicious anemia (PA), a fatal disease until 1926, earned Minot and Murphy a Nobel Prize. With that advance, followed by identification of the defect in intrinsic factor (IF) secretion that defines PA and then synthesis of cyanocobalamin, cobalamin deficiency became relatively easy to diagnose and extremely easy to treat. It remained so until a decade ago. There are no clinical guidelines for the treatment of subclinical vitamin B deficiency (asymptomatic patients with decreased levels of vitamin B and elevated levels of homocysteine and/or methylmalonic acid). Physicians may opt to treat these patients and monitor for improvement of metabolic markers, particularly in populations at high risk of clinical vitamin B deficiency, or observe these patients and periodically reassess their levels of vitamin B, homocysteine, and/or methylmalonic acid. Patients with subclinical vitamin B deficiency will need at least 1 mg of vitamin B daily.

In asymptomatic patients with low-normal levels of vitamin B (200 to 350 pg per mL [147.56 to 258.23 pmol per L]), elevated levels of the precursor compounds homocysteine and methylmalonic acid may prompt a decision to supplement patients with vitamin B. A single injection, whether as an experimental 1- to 2- μ g dose or the more usual 1000- μ g dose, suffices to correct the anemia. The 1000- μ g dose also begins repletion of stores (up to 150 μ g is retained from that injection by most patients)

Mainly oral cobalamin supplementation was used in our study with a significant increase in vitamin B12 levels. An oral cobalamin regimen is proposed for elderly patients with cobalamin deficiency but with no severe neurological signs. While oral cobalamin immediate-release is adequate for many patients, its effectiveness in reversing neurologic abnormalities has yet to be established. Despite an unexplained sense of energy described by some patients in the first 24 hours, hematologic response only begins several days later. The first objective landmark I rely on is the peak reticulocyte count 1 week after starting treatment. Its briskness should be proportional to the severity of the anemia. If reticulocytosis appears blunted, an incorrect diagnosis may be responsible, but I also obtain iron studies because coexisting iron deficiency is frequently obscured before cobalamin is given. The final hematologic landmark is that the blood count, including mean corpuscular volume (MCV), should be completely normal by the eighth week. A failure of homocysteine or MMA to normalize during the first week suggests an incorrect diagnosis, unless renal failure or other causes of metabolite elevation coexist. Cobalamin and holo-transcobalamin II levels are uninformative because they rise with cobalamin influx regardless of therapeutic effectiveness, the extent varying only with the timing in relation to injection.

Neurologic improvement begins within the first week also and is typically complete in 6 weeks to 3 months. Its course is not as predictable as hematologic response, but most studies show little advantage of more intensive cobalamin treatment. Recovery can be slow sometimes, but progression always calls for diagnostic reassessment. Patients with delayed improvement should be offered rehabilitative therapy, particularly for gait, urinary, or bowel dysfunction. Residual disability, estimated to affect 6% of neurologic patients, is the most feared outcome of cobalamin deficiency and is likely to persist if still present after 6 to 12 months of treatment. Irreversibility tends to be associated with more than 6 months of therapeutic delay, but its variability is unexplained. Most attention has focused on high folate status because of possible associations of adverse neurologic outcomes with folate therapy, but no consistent findings have emerged. While almost all patients respond hematologically, only half of the patients with neurological signs, and a small minority of psychiatric patients respond to treatment.

Moreover, cobalamin resistance may occur in diabetes, renal insufficiency and advanced age leading to functional cobalamin deficiency despite adequate cobalamin. Folate and B12 should always be assessed together

due to the close relationship of metabolism and overlap of clinical symptoms deficiency causes. There has been a great deal of interest in the link between elevated levels of homocysteine, a direct consequence of vitamin B deficiency, and cardiovascular disease. No studies have directly evaluated the cardiovascular effects of correcting vitamin B deficiency in patients with known cardiovascular disease, although numerous studies have failed to demonstrate that correction of hyperhomocysteinemia itself reduces cardiovascular mortality or cardiovascular complications. The routine use of vitamin B to lower levels of serum homocysteine in patients at high risk of cardiovascular events is not recommended.

III. Conclusions

In strict vegetarians, vitamin B12 supplementation should be advised irrespective of normal serum vit b12 levels when patients are having clinical symptoms to prevent severe neuropathy and subacute combined degeneration of spinal cord. Pregnant vegetarians who plan to exclusively breastfeed need supplementation; their babies are at much greater risk for severe deficiency than the mothers. The key management principle is the importance of follow-up, which also requires knowing how the deficiency occurred.

Acknowledgments

List of abbreviations:

Pa-pernicious anemia
Mma-methyl malonic acid
Holotc-Serum holotranscobalamin
Hcy-homocysteine
Mthf-methyltetrahydrofolate
Thf-5-methylene-tetrahydrofolate
Cspn-cryptogenic sensory polyneuropathy
If-intrinsic factor
VIT-vitamin

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