B12 and Neuropathy

The main causes of vitamin B12 deficiency are insufficient dietary intake of B12, autoimmune gastritis, pancreatic insufficiency, terminal ileum disease, and small intestinal bacterial overgrowth.[1] Deficiency of vitamin B12 is known to result in various neurological complications, including peripheral neuropathy. Vitamin B12 deficiency-associated peripheral neuropathy is characterized by axonal degeneration without evidence of demyelination. It is believed that this subacute combined neuropathy is related to interference with the methylation reactions in the central nervous system.[2] Specifically, inhibition of the B12-dependent enzyme methionine synthase leads to disruption of the ratio between S-adenosylhomocysteine and S-adenosylmethionine, which controls methylation within the central nervous system. The resulting central nervous system hypomethylation is believed to result in B12-associated neuropathy. In the event that B12-associated neuropathy does occur, treatment with vitamin B12 in various forms has been demonstrated to arrest progression of the neuropathy, although residual neurological abnormalities may persist.[3-4]

In addition to the previously listed dietary and pathological causes of vitamin B12 deficiency, diabetes has been associated with elevations in homocysteine[5] and/or low levels of vitamin B12. Furthermore, long-term use of metformin, a very common treatment for type-2 diabetes, has been demonstrated to deplete vitamin B12 stores.[6] Metformin induces vitamin B12 deficiency in about 28% of patients[7-8] and the deficiency may present as peripheral neuropathy, without the expected macrocytic anemia or other hematological abnormalities.[8-9] Vitamin B12 status was inversely correlated with the presence of neuropathy in individuals who were taking metformin.[6] Those on higher doses of metformin and individuals of the male sex were more likely to be deficient in vitamin B12.

Normal or decreased total plasma cobalamin levels may not be a reliable marker of vitamin deficiency;[10] instead, to get a more complete picture of vitamin B12 status and other potential causes of neuropathy, methylmalonic acid, homocysteine, and serum folate should also be evaluated.[1]

In a review that sought to evaluate the efficacy of oral vitamin B12 in the treatment of diabetic neuropathy, one out of the three included randomized controlled trials noted a slight improvement in the B12 group relevant to controls. Overall, the review failed to demonstrate

significant differences in neuropathic pain between individuals treated with oral vitamin B12 and those in the control groups and, again, the majority of studies in the review failed to demonstrate improvements in the nerve conduction velocities or vibration perception threshold in patients with neuropathy.[11] Researchers noted that this was likely because the duration of the studies was not long enough to allow for neurophysiological changes.

An unrelated study demonstrated that decreased serum B12 levels in individuals with type-2 diabetes who were taking metformin can be effectively corrected by either a 3-month course of 1 mg per day sublingual methylcobalamin supplement or a single 1 mg intramuscular hydroxycobalamin injection.[12] Regarding B12 deficiency, a randomized, open label trial demonstrated that 500 µg methylcobalamin intramuscularly three times weekly was more effective at raising cobalamin levels than an intramuscular dose of 1500 µg methylcobalamin once per week,[13] suggesting that intramuscular B12 may be more effective at raising levels when administered in divided doses.

Another study compared outcomes between patients who were given 500 µg by mouth three times per day of methylcobalamin for at least 8 weeks and those who were administered 500 µg per day of methylcobalamin administered intravenously three times per week for 4 weeks followed by oral administration of 500 µg of methylcobalamin three times per day for at least 4 weeks. The study demonstrated a positive overall improvement (e.g. being marked as "improved" or "markedly improved") of 66.6% in the group that was given intravenous and oral B12, whereas only 39.1% of the group that was administered oral B12 alone demonstrated positive overall improvement.[14] Lower extremity vibration perception thresholds were significantly improved in the intravenous and oral group, whereas the oral group did not demonstrate clear improvement. The results of this study demonstrate that intravenous plus oral administration of vitamin B12 is a highly efficacious treatment option for neuropathy and is preferable to oral administration alone for patients who desire more rapid and greater improvement of neurological symptoms.

In an additional study, individuals with immune-mediated or hereditary neuropathy in the chronic progressive or stable phase were administered an ultra-high dose of 25 mg of intravenous methylcobalamin per day for 10 days followed by 25 mg (intravenously) monthly for 5 months.[15]

Researchers concluded that intravenous methylcobalamin is a safe and potentially efficacious therapy for individuals with peripheral neuropathy and chronic axonal degeneration.

Another study demonstrated that 500 μg of intravenous methylcobalamin 3 times per week for 6 months in individuals with uremic and diabetic neuropathy led to decreases in pain or paresthesias and improvements in the ulnar motor and median sensory nerve conduction velocities.[16]

Several researchers suggested that vitamin B12 may be able to improve neuropathies and other neurological conditions, even without a proven deficiency or other B12-responsive metabolic abnormalities,[17-18] and that B12-responsive neuropathy may be a more heterogeneous group of neuropathies than previously described.[19]

One case report in which a three-year-old girl was administered over five times the appropriate weight-adjusted dose of intravenous B12 was unable to attribute any complications directly to intravenous hydroxycobalamin overdose.[20] Overall, the various treatments involving vitamin B12 were safe and effective.[15-16]

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