Vitamin B-12 and neuropathy in the elderly

Dear Editor:

The important study by Brito et al. (1) suggests that a single high dose of vitamin B-12 can improve peripheral sensory nerve function in asymptomatic elderly subjects with vitamin B-12 deficiency and that folate excess may limit the metabolic response to vitamin B-12 therapy in this setting, findings consistent with prior reports (1–3). However, I believe that the results as presented limit understanding of the significance of their findings.

Although it is noted that 10 of the patients studied had sensory action potentials that were detectable only after vitamin B-12 therapy, interpretation of the results is limited in that the data are presented as aggregate means or medians, and neither normal values for the electrophysiologic variables measured nor the degree of change in these variables that was considered to be significant are provided. Thus, it is unclear what proportion of subjects studied had abnormal sensory nerve function before treatment, what proportion of subjects improved significantly after vitamin B-12 therapy, and what proportion of these significant responses involved correction of abnormal values or improvement within the "normal range."

Furthermore, values for the biochemical markers of vitamin B-12 deficiency (total vitamin B-12, holotranscobalamin, methylmalonic acid, and/or homocysteine) were actually normal before vitamin B-12 therapy in 31–47% of subjects, whereas values for these markers were abnormal in 20–39% of subjects 4 mo after vitamin B-12 therapy (reference 1, Table 2). Thus, it cannot be determined from the data presented whether pretreatment-abnormal electrophysiologic findings were truly related to vitamin B-12 deficiency and whether any improvement in electrophysiologic tests after vitamin B-12 therapy was due to correction of vitamin B-12 deficiency or to a nonspecific pharmacologic effect of high-dose vitamin B-12 (4–7). Even when the statistically derived combined indicator of vitamin B-12 status (cB-12) function was used, only 11 of the 51 subjects (22%) were initially felt to have "possible" or "probable" vitamin B-12 deficiency, and "possible" vitamin B-12 deficiency persisted in 4 subjects after treatment.

Although the authors chose to use the cB-12 function to define vitamin B-12 deficiency, this variable originally was derived from 3 prior studies involving apparently healthy volunteers, healthy vegans, and subjects with clinical symptoms which were associated with high methylmalonic acid values but which were not felt to be related to vitamin B-12 deficiency (8). Thus, the cB-12 function has not been validated as a predictor of clinically overt vitamin B-12 deficiency. Because the holotranscobalamin test often is not available in clinical settings and because multiple tests add to cost, it would be helpful to know which, if any, single variable (vitamin B-12, holotranscobalamin, methylmalonic acid, or homocysteine) best predicted for neurologic impairment and/or response. Reanalysis of the data then could indicate what percentage of subjects with any individual metabolite abnormality (or with no metabolite abnormalities) had neurologic impairment before treatment and significant improvement after therapy.

Similarly, the effect of high serum folate concentrations on methylmalonic acid, homocysteine, and holotranscobalamin values before and after vitamin B-12 therapy would be of importance. Moreover, it is not indicated whether or not a high serum folate status was associated with a greater incidence of neurologic abnormalities or with a more limited neurophysiologic response to vitamin B-12 therapy. It is also unclear why the authors define high serum folate values as >45.3 nmol/L in the Methods section and in Table 2 but use the median folate value of 33.9 nmol/L in the analysis of the effect of folate status on the cB-12 response to vitamin B-12 therapy in the Results section.

Finally, as noted, posttreatment analyses occurred 4 mo after a single high dose of vitamin B-12, and markers of vitamin B-12 deficiency were still abnormal in many subjects at this time. Because this treatment regimen is much briefer than those commonly used, it would be of interest to know what proportion of subjects with abnormal metabolic markers before therapy improved during this time and whether any subjects with normal markers initially became abnormal on follow-up (information that cannot be derived from the aggregate means/medians in Table 2). Thus, it is possible that more frequent weekly or monthly doses of vitamin B-12 may have led to greater improvement in both metabolic and neurophysiologic variables.

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