Vitamin B_{12} Deficiency and Multiple Sclerosis; Is there Any Association?

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ABSTRACT

Background: Vitamin B_{12} (Cobalamin) deficiency can result in some clinical and paraclinical characteristics similar to what is seen in multiple sclerosis (MS) patients. This study aimed to evaluate the controversial association between vitamin B_{12} deficiency and MS.

Methods: We measured serum vitamin B_{12} in 60 patients with MS and 38 healthy controls. Clinical disability was evaluated according to the Extended Disability Status Scale (EDSS). Serum B_{12} concentration was measured with Radioimmunoassay Dual Isotope method. The cutoff value for low serum vitamin B_{12} concentrations was 75 pg/mL. Patients were in remission at the time of blood draw.

Results: There were 13 (21.6%) MS patients and 10 (26.3%) controls with low serum B_{12} concentration with no significant difference between the groups; $P>0.05$. The mean serum vitamin B_{12} concentration in MS patients (108.9±45.3 pg/mL) was not significantly different compared with controls (98.9±44.4 pg/mL); $P=0.284$. Likewise, there was no correlation between the concentration of serum vitamin B_{12} and disease' age of onset, duration, subtypes, or disability status.

Conclusions: In contrast to some previous reports, our findings did not support any association between B_{12} deficiency and MS.

Keywords: Cobalamin, multiple sclerosis, vitamin B_{12}

INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the central nervous system (CNS) with progressive process leading to chronic disability in many cases. Disease onset usually occurs in young adults, more common in females and has a prevalence ranging between 2 and 150 per 100,000.[1] The prevalence of MS in Isfahan-Iran is 43.8 per 100,000.[2] The etiology of MS is complex and multi-factorial involving both genetic and environmental factors, but the main etiology is still unknown.[1]

Vitamin B_{12}, also known as Cobalamin, plays important structural and functional roles in nervous system and its deficiency leads to demyelination, followed by axonal degeneration and eventually irreversible damage due to axonal death. Accordingly, B_{12} deficiency can result in some clinical and paraclinical characteristics similar to what is seen in MS patients.

[3] The association between B_{12} deficiency and MS has been investigated by several studies with different results. Some studies have demonstrated significantly reduced serum B_{12} as well as macrocytosis in MS patients, while others did not show such an association.[3]

The nature of the relation between MS and B_{12} deficiency is unclear and multiple levels of inter-relationship may be suggested. The association could be the result of overlapping autoimmune disorders or it may reflect an increased demand for B_{12} for myelin repair.[3] Anyway, if a subgroup of MS patients should prove to have decreased concentrations of B_{12}, irrespective of the cause, treatment is easy and important to prevent permanent disability. There are reports of MS patients improving with B_{12} therapy.[4]

The only dietary source of cobalamin is animal products (e.g. meat and dairy products) and inadequate intake is one of the main causes of B_{12} deficiency.[5] According to the considerable prevalence of MS and nutritional deficiency in our society,[2,6] we decided to determine the association between MS and B_{12} deficiency in our population. Our objectives were to analyze serum B_{12} of patients with MS and to evaluate if there is any correlation with clinical disability or disease age of onset.

METHODS

This case-control study was conducted from 2007 to 2008 in the city of Isfahan, central Iran. Consecutive MS patients from three neurology clinics were invited to participate. All patients fulfilled the clinical definite criteria for MS.[2] None of the patients had the history of atrophic gastritis or gastrectomy and none of them had anemia or malnutrition on vegetarian diet or chronic alcohol abuse. Control group were recruited from healthy persons that matched for age and sex with case group. They had came for blood donation in the Blood Transfusion Organization of Isfahan. None of the patients or controls had received B_{12} or folate supplementation within the preceding year. The ethics committee of Isfahan University of Medical Sciences approved the study and consent was obtained from participants.

Clinical disability was evaluated according to the Extended Disability Status Scale (EDSS).[7] Serum B_{12} concentration was measured with Radioimmunoassay Dual Isotope method (DiaSorin S.p.A., Italy). The cutoff value for low serum vitamin B_{12} concentrations was 75 pg/mL. Patients were in remission at the time of blood draw.

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 16.0. Comparisons between the two groups were done using Independent Sample *t*-Test. Spearman and Pearson Correlation Coefficients were used to test the relationship of B_{12} concentration with disease age of onset, clinical status, and MS type. A *P* value of less than 0.05 was considered significant.

RESULTS

During the study period, 60 MS patients (54 women and 6 men, age 18-57 years, mean 33±9.8 years) agreed to participate. Age of onset of the disease was 15-39 years, mean 23.42±4.8 years. Duration of disease from first symptom to the present sampling occasion was 1-10 years, mean 4±2 years. Fifteen (15%) patients had remitting-relapsing MS (RR-MS), thirty seven (61.6%) had secondary progressive MS (SP-MS), and eight (13.3%) had primary progressive MS (PP-MS). EDSS scores were 0 to 6 with a mean of 1.7±1.39. Control subjects were thirty three women and five men with the mean age of 31.97±10.2 years (18-51 years).

According to the cut-off value of the diagnostic kit (75 pm/mL), there were 13 (21.6%) MS patients and 10 (26.3%) controls with low serum B_{12} concentration with no significant difference between the groups; $P>0.05$. There was also no significant difference in the mean plasma B_{12} concentration between MS patients and controls ($P>0.05$) Table 1.

Table 1: Comparison of baseline characteristics and B_{12} concentrarion between the two groups

	MS patients *n*=60	**Controls *n*=38**	***P***
Age, year	33±9.8 (18-57)	31.97±10.2 (18-51)	0.623
Female/male	53/7	33/5	0.531
Vitamin B_{12} (pg/mL)	108.9±45.3 (33.5-200.1)	98.9±44.3 (32.0-197.5)	0.282
Low B_{12} consentration	21.6%	26.3%	0.385
Age of onset	23.4±4.8 (15-39)	-	-
EDSS	1.7±1.39 (0-6)	-	-

Data are shown as mean±SD (range) or number (percent)

No correlation was found between concentration of serum vitamin B_{12} and disease age of onset, EDSS scores, or type of the disease; $P>0.05$.

DISCUSSION

The debate concerning the possible role of vitamin B_{12} in MS is long lasting and several studies with different results have been done since 1950s and early 1960s.[3] Although demyelination is a prominent feature of both MS and B_{12} deficiency, these two entities are usually distinguishable based on clinical and pathological characteristics. Neurological presentations of B_{12} deficiency usually occur in middle or late life and a few patients can present before the age 40 years.[8]

The majority of patients with MS do not have detectable B_{12} deficiency. However, there is evidence of an overlap of the two disorders and a subgroup of patients with this association. But our results did not show any association between serum B_{12} concentration and MS, disease age of onset, or clinical disability which is similar to some,[9,10] but in contrast to other reports.[11-14]

Previous studies demonstrated an increased risk of macrocytosis, low serum and/or CSF vitamin B_{12} levels, raised plasma homocysteine, and raised unsaturated R-binder capacity in MS; and they supposed that it seems coincidentally related; they made an impact on searching vitamin B_{12} deficiency in MS and presumed aggravation of MS or impair recovery in B_{12} deficiency.[15] Njist *et al*. [14] reported that B_{12} concentrations in CSF (measured with a radioimmunoassay) and serum of MS patients were lower in control subjects. There was also a significant correlation between serum and CSF vitamin concentrations. Recently, Kocer *et al*. also found a significant relationship between MS and B_{12} deficiency.[13] Another study reported that serum B_{12} concentration in MS patients is related to the age of onset of the disease.[16] According to that report, B_{12} concentration was significantly lower in those who experienced the onset of first neurological symptoms prior to age 18 years compared to patients in whom the disease first manifested after age 18; however, our results did not support that.

The prevalence of low serum B_{12} concentration in our MS patients and controls was about the same as the result of a population study on 1214 people aged 25–64 years in Tehran, Iran.[6] Normal serum B_{12} concentrations in our MS patients, however, cannot rule out B_{12} deficiency. There is evidence that patients with MS may be functionally deficient in vitamin B_{12}, as indicated by elevated levels of homocysteine.[11]

Homocysteine is a potentially neurotoxic metabolite that its concentration raises in the absence of adequate amounts of B_{12}, folic acid, and pyridoxine. If the serum B_{12} concentration is borderline, total plasma homocysteine (tHcy) or methylmalonic acid (MMA) concentrations may be useful guides to functional B_{12} deficiency.[8] Indeed, increased serum MMA and plasma tHcy concentrations indicate an intracellular B_{12} deficiency and are regarded as more sensitive variables than serum B_{12} for the diagnosis of B_{12} deficiency.[10] However, other studies did not show relation between elevated plasma homocysteine and B_{12} in MS patients and further studies are needed in this field.[17,18]

The median intraindividual variation in measured serum Vit B_{12} during two to six weeks was 6-23% in different studies;[19,20] Thus, one measurement may not be accurate enough to draw conclusion about ones vit B_{12} status. This might indeed explain the variation of results in different studies. Also this variation can be attributed to improve nutritional status of MS patients in recent years.

This study had some limitations: We only relied on blood B_{12} concentration, while serum holotranscobalamin, homocysteine, and methylmalonic acid levels may be considered more reliable indicators of B_{12} deficiency than the concentration of B_{12} in blood. Since, patients with low-normal or even normal serum Vit B_{12} values may be deficient for Vit B_{12}, thus measurement of the serum concentrations of the metabolic intermediaries' homocysteine and methylmalonic acid appears to be more sensitive for the diagnosis of these deficiencies than serum vitamin levels. We checked serum vitamin B_{12} in diagnosed patients, who was in remission, and we did not check it in new cases; it can be considered as another limitation of our study.

CONCLUSION

Despite an association between B_{12} deficiency and MS had been reported in some previous

studies, as the same as some other reports we found no relationship between B_{12} deficiency and MS. Accordingly, we do not recommend routine assessment of vitamin B_{12} in patients with known MS. Further studies with more sensitive measures such as total plasma homocysteine or methylmalonic acid concentrations are suggested.

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