High prevalence of low serum vitamin B_{12} in a multi-ethnic Israeli population

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Summary. This study ascertained serum vitamin B_{12} levels among patients with Gaucher disease and among healthy Israelis. Serum B_{12} and metabolites’ levels were studied in consecutive adult patients with Gaucher disease not treated with enzyme plus Ashkenazi Jewish neighbour-controls, together with healthy blood-donor volunteers of various ethnicities. Each group showed a high incidence of low serum B_{12} concentrations, with a 22·3% incidence among Ashkenazi Jews and 40% among patients with Gaucher disease. These findings raise questions on the individual and community levels of serum B_{12}. We recommend evaluation of B_{12} levels among geographically contingent peoples.

Keywords: Gaucher disease, vitamin B_{12} deficiency, homocysteine, methylmalonic acid, environmental factors.

Patients and Methods

All adult patients (>18 years) with type I Gaucher disease, who were not treated with enzyme, or with B_{12} supplementation in the previous year, were asked to participate. For each patient, two neighbour-controls were chosen by that patient’s physician from his patient roster. An age- (±5 years) and sex-matched control who was Ashkenazi Jewish but unrelated to the patient was chosen from the names above and below that of the patient. The neighbour-controls were also considered matched with reference to socio-economic factors.

Vitamin B_{12} levels were measured by two different analysers (AxSYM-Abbott Diagnostics, Abbott Park, IL, USA, and Access-Sanofi Pasteur System, France); the correlation was nearly symmetrical. Total run coefficient of variation was ≤10% at levels >200 ng/l, and up to 15% at ≤150 ng/l. A third analysis performed at the UC Davis Medical Center, Sacramento, CA, USA, confirmed the above.

Homocysteine (HCY) and methylmalonic acid (MMA) were determined by standard methods (Jacobsen et al., 1994) using frozen sera. HCY >15 μmol/l and MMA >350 nmol/l were considered outside the normal range.

Blood donor volunteers at various geographical locations of the National Blood Services of Israel were asked to donate an additional sample for this study. Inclusion in an ethnic group was predicated on both parents being of the same ethnicity.
All participants were requested to complete a demographics questionnaire about dietary habits, i.e. being vegetarian, cigarette smoking, use of multivitamins, and food supplements.

All phases of the study were approved by the Shaare Zedek Medical Centre Institutional Review Board (IRB), as well as by the National Blood Services.

Statistical analysis. For continuous variables, the paired t-test and one-sample t-test were applied to test significance of change and the hypothesis that the change was of a given magnitude respectively. The Pearson and Spearman correlation coefficients were calculated to assess the association between continuous variables.

The chi-square test and Fisher’s exact tests were used for comparisons between groups for qualitative variables. To assess a change in qualitative dichotomous variables, the McNemar test was applied.

RESULTS

Among untreated patients, there were 89 patients whose family practitioner provided 122 neighbour-controls (68·5% compliance). There was no statistically significant difference in demographics (data not shown). There was no statistically significant difference with reference to incidence of low serum B12 concentrations, 40% and 31% respectively (Table I).

There was no statistically significant difference when comparing elevated HCY levels (> 15 μmol/l) with vitamin B12 levels (Table I) among untreated patients (28%) and neighbour-controls (24%). MMA assays were performed on 32 samples in each group: 16 samples with B12 levels < 200 ng/l (i.e. presumed low) and 16 samples with B12 levels > 200 ng/l (i.e. presumed normal). Elevated MMA values (> 350 nmol/l) were inversely correlated with B12 levels: 29% in untreated patients and 19% in neighbour-controls, which was not statistically significant. Non-parametric analysis was also not statistically significant.

There were 1512 blood samples drawn from blood donors; in 720 cases, both parents were of the same ethnicity (Table II). All routine haematological parameters were within the normal range, but a > 12% prevalence of low vitamin B12 levels (Table II) was noted in all groups.

DISCUSSION

Many non-specific symptoms of vitamin B12 deficiency are not unique to patients with Gaucher disease; these include subjective complaints such as malaise and fatigue, but also cognitive deficits (memory loss, irritability, and mood swings); gastrointestinal complications; patchy hyperpigmentation; and even reproductive problems, such as infertility (Stabler et al. 1990). The common finding of macrocytosis in Gaucher disease and the presence of symptoms, particularly fatigue unaffected by enzyme replacement therapy, underscored the need for assessment of vitamin B12 levels.

Untreated patients were chosen to minimize the confounding effects of enzyme treatment (although biasing towards milder patients). The incidence of low serum vitamin B12 in untreated patients was surprising, but similar findings among healthy Ashkenazi Jewish control subjects were unexpected.

Methodological bias was theoretically minimal as attested to by excellent correlation of various assays, inverse correlation between vitamin B12 and metabolites, and the fact that paediatric patients with Gaucher disease do not have low serum B12 (data not presented).

Screening of multiethnic healthy blood donors was undertaken to ascertain whether low serum B12 among Ashkenazi Jews reflects a genetic predisposition or an environmental factor in Israel. While racial differences have been previously reported, the prevalence was far lower (Saxena & Carmel, 1987). Moreover, even among patients with dementia/psychosis (Carney & Sheffield, 1978), older adults (Ho et al., 1999), and Kenyan patients with megaloblastic anaemia (Mwanda & Dave, 1999), the incidence of vitamin B12 deficiency was well below 10%.

The results of our studies merit cautious analysis in that all the healthy subjects with low B12 levels were asymptomatic. However, because homocysteinaemia in itself is a well-recognized risk factor for cardiovascular diseases, the results in the healthy cohort merit attention. Issues of

population screening, food fortification (Zeitlin et al., 1997; Czeizel & Merhala, 1998) and serological testing for pernicious anaemia or Schilling tests, as well as (prophylactic) treatment in those with elevated HCY (Sozen et al., 1998), should be addressed.

In conclusion, therefore, more studies are required. To ignore this very real health problem in a multi-ethnic population by re-defining the lower range of normal vitamin B12 values would be inappropriate. Our recommendation is that cooperative efforts be initiated among Mediterranean Basin nations as an environmental modifier may encompass more than the small geographical area that Israel represents and, hence, may exert similar effects in neighbouring countries.

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