Vitamin B12 deficiency

Why refugee patients are at high risk

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Background
Vitamin B12 is one of the most complex vitamins. The measurement of serum levels and the significance of the results are much debated in the literature.

Objective
This article discusses testing for vitamin B12 deficiency, its clinical manifestations and the possible repercussions for Australia's refugee population.

Discussion
Full blood count and blood film, iron studies and haemoglobinopathy studies are routinely performed for newly arrived refugees in Australia. At the Migrant Health Service in Adelaide, South Australia, a young woman was found to have a very unusual blood picture with a normal mean cell volume, despite quite severe iron deficiency and thalassaemia trait. Her vitamin B12 was found to be 75 pmol/L. The following week there arose another case of an 11 month old breastfed baby with a vitamin B12 level of 52 pmol/L, whose mother had a level of 300 pmol/L. Understanding the clinical manifestations of vitamin B12 deficiency and how it is relevant to Australia's refugee population might assist to resolve some of the difficulties that refugees face in Australia.

Keywords: vulnerable populations (health), refugee; diet; vitamin B12

Australia takes about 13 000 refugees per year, about one-third each from Africa, the Middle East and the Asia/Pacific region.[1] The majority have had diets of limited or no animal source foods (ASFs). Vitamin B12 is found in red meat, seafood, dairy products and eggs, and in fortified packaged cereals in developed countries.[2] It is well established that vitamin B12 deficiency is a common problem in most of the developing world.[3–5] Much of the world's population consumes less than 20% of its energy from ASFs compared to wealthier nations where ASF intake comprises about 40% of energy consumption.[5] Literature from countries such as Kenya, where many of Australia's Sudanese refugees lived in refugee camps, confirm the paucity of ASFs in their diets and the low vitamin B12 levels in this population.[3]

Many people of refugee background may continue to have diets deficient in ASFs after arriving in Australia. Contributing factors to this may include a level of poverty due to unemployment, supporting a large family, outstanding debts in the country of origin, or saving to sponsor relatives to migrate. Asylum seekers on bridging visas are at particularly high risk as they have no income from social security and are not allowed to work. Newly arrived refugees are also likely to continue to eat food that is familiar or culturally appropriate and so do not consume packaged foods that may be supplemented with vitamin B12.

Figures from the source countries of Australia's refugees are very similar to those of the Migrant Health Service in Adelaide, South Australia, with 9–50% of patients having vitamin B12 levels <150 pmol/L.[4] Some studies conducted in Africa and Asia have reported that if marginal levels are included, the incidence of deficiency is as high as 80%.[5]

The true prevalence of vitamin B12 deficiency in the general population is unknown, but early detection by screening populations at risk is extremely important because of the possibility of nonspecific but irreversible neurological consequences.[6,7]

Further complicating matters in the newly arrived refugee population is the high prevalence of other factors such as iron deficiency and haemoglobinopathies which are likely to affect the red cell status.[8]

Clinical manifestations

The clinical manifestations of vitamin B12 deficiency include:

- haematologic, such as megaloblastic anaemia and pancytopaenia
- neurologic, such as parasthesia, peripheral neuropathy and subacute combined degeneration of the spinal cord
- psychiatric, such as irritability, personality change,

memory impairment, depression and psychosis
- generalised symptoms such as fatigue, weakness, stomatitis, diarrhoea, constipation, loss of appetite, weight loss and premature birth, and possibly
- cardiovascular (which may be related to increased homocysteine levels), such as an increased risk of myocardial infarction and stroke.[2,4,6,7]

There is also evidence that the babies of mothers with vitamin B12 deficiency, especially if they are exclusively breastfed, are at high risk of severe and permanent neurological damage. They may show movement disorders, irritability, abnormal reflexes, feeding difficulties and eventually permanent developmental disabilities.[2,4] Studies have shown that even subtle increases in vitamin B12 levels can improve cognitive function in children.[3]

Helicobacter pylori and Giardia lamblia

Besides dietary deficiency, the other major risk factor contributing to vitamin B12 deficiency in developing countries is *Helicobacter pylori*, with figures suggesting that as much as 90% of the population is infected.[9] *H. pylori* has been shown to have a direct role in decreasing vitamin B12 levels as well as impeding absorption because of gastric atrophy.[5,9] It has been found in up to 78% of those with severe vitamin B12 deficiency compared with 44% of those with normal levels of vitamin B12.[5,6,9] About 30% of those with *H. pylori* infection will have atrophic gastritis with loss of parietal cell mass which results in an inadequate linking between the consumed vitamin B12 and intrinsic factor. It has been reported that after treatment of *H. pylori*, 40% of patients had their vitamin B12 levels return to normal in less than 2 years.[6,9] *H. pylori* testing is not a routine screening test in refugee patients in Australia and is probably underdiagnosed.[8] *Giardia lamblia* and other intestinal parasites are also very common in patients arriving in Australia as refugees.[8] *G. lamblia* causes chronic diarrhoea and malabsorption, with approximately one-third of the infected population likely to have decreased vitamin B12 levels.[4]

Psychological disorders

There is a high prevalence of psychological problems in refugee patients, with some studies suggesting up to 90% have a mental health diagnosis such as depression or post-traumatic stress disorder (PTSD).[10] There is an acknowledged relationship between depression and low vitamin B12 levels, with up to 30% of severely depressed patients having vitamin B12 levels <150 pmol/L.[11,12] There is also an association of low vitamin B12 levels with other psychiatric disorders such as PTSD, panic disorder and obsessive compulsive disorder.[11] Treatment with medication for psychiatric disorders seems to be less effective in those with low vitamin B12 levels.[11,12] There is a postulated biochemical mechanism related to an impaired synthesis of neurotransmitters and phospholipids that may contribute to increased risk and severity of depression.[12] There are obviously many factors affecting the diagnosis and treatment of mental illness in patients of refugee background. However, vitamin B12 deficiency is readily treated and is likely a contributing factor to the severity of presentation and response to treatment of mental health problems.

Other health complications

There is a higher incidence of cardiovascular disorders in refugee patients and the reasons for this have been much debated.[4,13] It may be that a high homocysteine level, as seen in those with vitamin B12 deficiency, is an emerging risk factor.[14,15] However, despite the fact that elevated homocysteine levels appear to be a marker for vascular disease, and that vitamin therapy normalises these levels, research to date has not shown a reduction in cardiovascular events or mortality with vitamin supplementation.[16]

It has also been found that low serum B12 levels decrease the immune response to pneumococcal vaccine because of impaired humoral immunity.[17] It is possible that there may be similar problems with other vaccines and that low serum B12 levels may also affect investigations such as the Quantiferon Gold test for tuberculosis.

Testing of vitamin B12 levels

As part of the screening of newly arrived refugee patients in Australia, full blood count and blood film, iron studies and haemoglobinopathy studies are routinely performed.

The normal range of the local laboratory in Adelaide is >221 pmol/L. A borderline result with 'vitamin B12 deficiency unlikely' (probability of 1–5%) is 148–241 pmol/L and a low result with 'vitamin B12 deficiency possible' is <148 pmol/L.[18] This level is seen as being consistent with vitamin B12 deficiency (specificity of 95–100%).[19] Vitamin B12 is essential for DNA synthesis, the formation and maintenance of myelin sheaths, the synthesis of neurotransmitters, and erythropoiesis.[6] In combination with folate, vitamin B12 is an essential cofactor in the metabolism of homocysteine and methylmalonic acid (MMA) so when vitamin B12 is truly deficient there is a rise in the levels of these two metabolites.[6] Along with a low holotranscobalamin complex (vitamin B12 plus transcobalamin II), raised MMA and homocysteine levels will indicate whether a low or borderline serum vitamin B12 level signifies a metabolic deficiency.[6]

Most commentators agree that relying solely on the serum vitamin B12 level underestimates those with true deficiency and some suggest that those with borderline results should also have MMA and homocysteine levels checked.[2,3,6,7] However, a raised homocysteine level requires a sensitive test and may occur in other inherited and acquired conditions such as renal impairment.[20] Measurement of MMA is expensive and requires specialised equipment. Homocysteine and holotranscobalamin are measurable in many laboratories but the cost benefit of performing these tests on all those with low or borderline results should be weighed against the low cost of treatment. If patients are symptomatic there should be no question of treating the deficiency and a low vitamin B12 level should never be ignored.

The medical profession has often relied on the presence of megaloblastic anaemia as an indication to check vitamin B12 status. Changes in the blood film with macrocytosis and hypersegmented neutrophils are late manifestations of folate or vitamin B12 deficiency and should not be relied upon as an indication for testing of vitamin B12 levels.[20] In addition, those with a very low vitamin B12 and a normal folate may not have a megaloblastic picture but will still be at risk of developing neuropsychiatric and cardiovascular sequelae.[7]

Serum concentrations of vitamin B12 may be low in the presence of normal tissue levels if there is concomitant folate deficiency, pregnancy, iron deficiency or in certain rare inherited disorders of vitamin B12 metabolism.[20]

Treatment

There is no universal agreement on the recommendations for the treatment of vitamin B12 deficiency in those who do not have pernicious anaemia. All patients with vitamin B12 <220 pmol/L

should have their *H. pylori* status ascertained with serum antibodies (if they have not had previous treatment), breath test or stool antigen, and a discussion about the importance of a diet high in ASFs and the usefulness of fortified cereals.

Certain medications adversely affect vitamin B12 levels, including proton pump inhibitors, H2 antagonists, and metformin.[2,21] Therefore patients using these medications will be unable to build up their stores of vitamin B12 and will remain deficient, even if diet improves and *H. pylori* is treated.

While oral treatment can be effective, its limitation is that with higher doses the ileal receptors for vitamin B12 intrinsic factor complex become saturated. The recommended dietary intake for adults is 2.4 µg/day (higher for pregnant or breastfeeding women) but only about 56% of a 1 µg oral dose will be absorbed.[2,5] Absorption rates fall dramatically as dosage increases; in a >25 µg dose only 1% is absorbed.[5] Even in people with normal absorption only 10 µg of 1000 µg will be absorbed; in those with *H. pylori* or *G. lamblia,* or those on proton pump inhibitors, metformin or H2 antagonists, the absorption rate will be even less.[4]

A Cochrane review found that oral doses of 1000–2000 µg/day, then weekly, then monthly were as effective as intramuscular injection in achieving a clinical response.[22] It is not known whether these preparations would be appropriate for refugee patients who are vitamin B12 deficient.

In the United States of America, patients with vitamin B12 deficiency due to pernicious anaemia are given 1 mg (1000 IU) intramuscularly daily for 1 week, weekly for 1 month, then indefinitely.[6,23] The Danish protocol in pernicious anaemia uses 1 mg weekly for 1 month, then 3 monthly indefinitely.[24] The Migrant Health Service in Adelaide has favoured a protocol between these two, with treatment of patients with vitamin B12 levels <100 pmol/L with 1 mg weekly for 3 weeks, then monthly for 3 months; those with levels of 100–150 pmol/L receive an injection stat then monthly for 3 months, and those with 150–220 pmol/L an injection stat then at 3 months. All patients have their levels reviewed at 4 months and then regularly thereafter.

Conclusion

Vitamin B12 deficiency has largely been overlooked as a cause of some of the symptoms frequently seen in newly arrived refugees but it should not be surprising that vitamin B12 deficiency is a problem when the prevalence and risk factors in countries of origin are taken into account. It may be worth drawing parallels with the high prevalence of vitamin D deficiency seen in refugees, which is now confirmed as a common cause of muscular pain that was previously thought to be either psychological or mechanical.[25]

It may be that many of the issues such as psychological illness, memory impairment and fatigue that make settling into a new country difficult can be partly alleviated with simple vitamin B12 replacement therapy.

It is important to recognise and treat vitamin B12 deficiency early to prevent permanent neurological changes and the potential for increased cardiovascular risk and paediatric developmental difficulties.

There is an urgent need for research in this uncharted area to clarify issues such as the prevalence, clinical significance, prognosis and treatment of vitamin B12 deficiency in newly arrived refugees.

In the meantime, all those who work with newly arrived refugees should be aware of the high risk of vitamin B12 deficiency in this population and institute investigations and treatment accordingly.

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