REGULAR ARTICLE

B12 deficiency is common in infants and is accompanied by serious neurological symptoms

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ABSTRACT

Aim: Adverse neurological symptoms have been linked to vitamin B12 deficiency in infants. This explorative study described the clinical presentation associated with vitamin B12 deficiency in this age group.

Methods: The study comprised infants who were born between 2004 and 2012 and were tested for vitamin B12 levels after they were admitted to a hospital with neurological symptoms at less than one year of age. Vitamin B12 deficiency was defined as low cobalamin in serum and/or increased homocysteine and/or increased methylmalonate. It was diagnosed according to the applicable International Classification of Diseases, 10th revision, and recorded as vitamin B12 deficiency in the medical records. All information was retrieved from medical records and compared to symptomatic infants with normal levels.

Results: Of the 121 infants tested, 35 had vitamin B12 deficiency and 86 had normal levels. Vitamin B12 deficiency was diagnosed at an average age of 1.7 months and was more common among boys. Seizures and apparent life-threatening events were the most common symptoms among infants with B12 deficiency compared to infants with normal levels.

Conclusion: Vitamin B12 deficiency was more common in infants than we expected and presented with severe symptoms, such as seizures and apparent life-threatening events.

BACKGROUND

Several neurological symptoms have been described in infants with a severe cobalamin deficiency, also referred to as vitamin B12 deficiency. These include irritability, failure to thrive, apathy, anorexia and developmental delay, as well as abnormal electroencephalography and cerebral atrophy on magnetic resonance imaging. The neurological symptoms due to delayed myelination, demyelination, dysmyelination and axonopathy are usually present between the ages of three to nine months (1–4). It can therefore be hypothesised that other neurological symptoms and signs, such as seizures, spasms, apnoea and apparent life-threatening events, can be associated with vitamin B12 deficiency.

Testing for vitamin B12 deficiency is not part of the regular screening process in Sweden when infants present with adverse neurological symptoms and vitamin B12 deficiency have not previously been studied in a defined population in Sweden.

The aim of this explorative study was to describe the first neurological signs and symptoms of infants with vitamin B12 deficiency.

PATIENTS AND METHOD

The study population included all 11 143 children under the age of one, born in Jämtland County between 1 April

2004 and 24 September 2012. We reviewed the medical records for the 121 infants admitted to the only hospital in the county and tested for vitamin B12 and homocysteine in serum and methylmalonate in plasma or serum (Fig. 1).

Infants with no other cause for the symptoms than a vitamin B12 deficiency were described with regard to the first presented symptom. Children with B12 deficiency were defined by low levels of B12 tested by the local laboratory at the hospital (cobalamin <160 pmol/L) and/or increased total homocysteine (>10 µmol/L) and/or increased methylmalonate, together with ICD-10 codes E53.8, E53.9, D51.3

Key notes

- Adverse neurological symptoms have been linked to vitamin B12 deficiency in infants, and this explorative study described the clinical presentation associated with vitamin B12 deficiency in this age group.
- Vitamin B12 deficiency was diagnosed at an average age of 1.7 months and was more common in infants with neurological symptoms (35/121) than we expected.
- The deficiency was presented with severe symptoms such as seizures and apparent life-threatening events.

Figure 1 Number of children included in the study.

D51.8 or D51.9 and stated as vitamin B12 deficiency in medical records. B12, homocysteine and methylmalonate were measured at the same time. The tests were carried out at the local hospital, except for methylmalonate, which was analysed at different laboratories during the time period and was defined as a plasma- or serum level of either $<0.37 \mu\text{mol/L}$ or $<0.4 \mu\text{mol/L}$. Each case was defined according to the normal levels defined by the available laboratory. Infants admitted to the hospital with symptoms typical of a vitamin B12 deficiency, but with normal levels and no obvious cause for the symptoms, were presented for comparison.

Information on symptoms and age in months at diagnosis and treatment was retrieved from medical records. Each infant could present with more than one symptom. An electroencephalography (EEG) was not available for all patients and therefore not included in research data.

All analyses were descriptive in relation to B12 deficiency or normal levels.

This nonintervention study was a medical students' project carried out as part of the medical programme at Umeå University, Sweden, and involved extracting information from medical records at a local hospital. According to the Central Ethical Review Board in Sweden, and the law on ethics in research, ethical approval by the local ethics board was not necessary (5).

RESULTS

We study hospital had tested 121 children who were less than one year of age for vitamin B12 levels during the study period and found that 35 infants had B12 deficiency and 86 had normal levels (Fig. 1, Table 1). B12 deficiency was defined in 10 infants (29%) by low levels of vitamin B12, 26 infants (74%) by increased homocysteine and/or 27 infants (77%) with increased methylmalonate (Table 2). The diagnosis of B12 deficiency was decided by the clinician if only a single abnormal level

Table 1 Study population

	B12 deficiency	Normal levels	Total
Number (M/F)	35 (21/14)	86 (39/47)	121 (60/61)
Symptom (months)	1.7 (0–10 m)	2.7 (0–11 m)	
Diagnose (months)	3 (0–13 m)		
Symptoms (more than one/infant)			
Seizures and spasm	16 (45%)	26 (30%)	42 (35%)
Apnoea	8 (23%)	16 (19%)	24 (20%)
ALTE	5 (14%)	4 (5%)	9 (7%)
Other neurological*	8 (23%)	29 (34%)	37 (31%)
Other†	9 (26%)	30 (35%)	39 (32%)

*Hypo/hypertonia, developmental delay, nystagmus.

†Cyanosis, low saturation, increased screaming, failure to thrive, hypoglycaemia, difficulties in breastfeeding.

Table 2 B12, homocysteine and methylmalonate in the group of children with defined vitamin B12 deficiency

Test	Number		Mean (min–max)
	Total	(M/F)	
B12			
Decreased	10	6/4	136.2 (104–159)
Normal ($>160 \text{ pmol/L}$)	25	15/10	233.7 (165–317)
Homocysteine			
Increased	26	16/10	14.4 (10–29)
Normal ($<10 \mu\text{mol/L}$)	9	5/4	7.1 (4–9)
Methylmalonate			
Increased	27	17/10	
Normal*	3	0/3	
Missing	5	4/1	

*Slight differences of cut-off values from different laboratories.

was found, but the clinical picture was typical: in one infant with a low B12 level, in three infants with increased homocysteine and in seven infants with increased methylmalonate.

B12 deficiency was more common among boys (63%). Infants with B12 deficiency were younger and were tested earlier than infants with normal levels (Table 1). Severe neurological symptoms, such as seizures, apnoea and ALTE, were more common among infants with B12 deficiency, while other neurological or unspecific symptoms were more common among infants with normal levels (Table 1).

All infants, but one, with vitamin B12 deficiency were treated with intramuscular injections of 0.5–1.0 mg vitamin B12. In the other case, a nutritionist advised the parents on improved nutrition for their infant. The majority of the infants (77%) only needed one injection of that dose, but seven (20%) infants needed two injections to increase the level of vitamin B12 to normal. When they were followed up at 12–18 months of age, all infants had normal levels of vitamin B12, with no adverse complications as a result of the treatment and with normal neurological development.

DISCUSSION

We found that vitamin B12 deficiency was much more common than expected and the estimated incidence in this study was at least 35 of 11 143 or 314 of 100 000 and probably higher because only a small fraction of the infants in the population had been tested. This was in line with a recent Norwegian study (6). The incidence of B12 deficiency varies across the world and tends to be high in rural and vegetarian populations (3,7–9). Our findings, along with the Norwegian study (6), indicated that B12 deficiency can be relatively common in other populations as well.

Low levels of vitamin B12 and high levels of homocysteine and methylmalonate are seen between birth and six months of age, suggesting an impairment in cobalamin function (10). Normal mean levels of vitamin B12 of 217–314 pmol/L in the age group of four days to six months have been described (10). In our study, we included levels of vitamin B12, homocysteine, methylmalonate as well as the clinical picture in the definition of infants with B12 deficiency. Our study did not adjust vitamin B12 levels to age, which may have introduced a risk of misclassification. However, our cut-off point (160 pmol/L) was well below the published normal range in this age group of 217–314 pmol/L (10). The level of methylmalonate was analysed at different laboratories, which may have introduced incorrect interpretation of the data, but the differences between the cut-off values were small. Methylmalonate levels are described to be higher in infants compared to older children and adults. Thus, age-specific reference levels are needed. However, age adjustments and different laboratories accounted for infants with B12 deficiency as well as infants with normal levels, and thus, the risk of selection bias was reduced.

Severe vitamin B12 deficiency in infants may produce several neurological symptoms (2,6,11). In our study, severe symptoms, such as seizures and apparent life-threatening events, were more common among infants with B12 deficiency than infants with normal levels (Table 1). The underlying mechanisms of neurological symptoms involve delayed myelination or demyelination of nerves (2). The rapid response to supplements in terms of improvement of neurological symptoms as well as B12 levels in our study was in line with other studies and published case reports (1,6). An early diagnosis and start of treatment are therefore crucial.

The B12-deficient infants were treated with 1–2 intramuscular injections of 0.5–1.0 mg vitamin B12. No adverse reactions were noted, but it may be better to start with smaller doses and increase them over several days (12). An association between neonatal vitamin B12 deficiency following maternal inadequate intake or malabsorption of vitamin B12 has been described in some studies, especially among vegan mothers and children who are exclusively breastfed, while others could not prove this association (13–17). Information on maternal food preference was not included in the medical records and this limited the study. According to a Swedish survey, about 10% of the

population are vegetarians or vegans and this is more common in the larger cities and in the south of Sweden (18). We believe that in Jämtland, in Northern Sweden, the vast majority of women eat meat. Most infants (63%) are exclusively breastfed until the age of six months in Sweden (19). The number of infants exclusively breastfed in the study population was unknown, as there was no information on breastfeeding in the medical records. Therefore, we do not know whether the unexpectedly high number of infants with vitamin B12 deficiency in the county of Jämtland was due to dietary causes.

The low number of cases and the retrospective collection of data limited the study. However, this study was based on all infants admitted to the only hospital in the county, which reduced the risk of selection bias.

Most infants with B12 deficiency in our study presented with symptoms at an earlier age, an average of 1.7 months, compared to other studies that described B12 deficiency at the ages of four to ten months (2,13,14). However, in our study, all infants were tested before the age that infants normally present with the lowest level of vitamin B12 during childhood (10,15). There was no follow-up on biochemical cobalamin function among infants with normal levels and, therefore, it is not known whether these infants presented with lower levels later in life.

This study, as well as other studies, suggests that early diagnosis and treatment are beneficial to infant development (3,6,20). Prolonged low levels of vitamin B12 have been linked to neurological symptoms (1,14,21). The association between vitamin B12 levels and the type of neurological symptom, as well as long-term beneficial effects of early treatment, has not been studied. Our data could stimulate similar studies in larger populations by other research groups and may lead to changes in recommendations for screening and prevention of B12 deficiency and diagnostic evaluation of neurological symptoms in infants.

CONCLUSION

Our study confirmed recent studies that vitamin B12 deficiency was much more common in infants than previously described. Furthermore, severe neurological symptoms, such as seizures and apparent life-threatening events, were common in young infants with a B12 deficiency.

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CONFLICTS OF INTERESTS

The authors declare that they have no competing interests.

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