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Vitamin B12 deficiency encephalopaty as a potentially reversible brain injury — case study based on several years of a patient's observation

Encefalopatia z niedoboru witaminy B12 jako potencjalnie odwracalne uszkodzenie mózgu — studium przypadku w oparciu o kilkuletnią obserwację pacjenta

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ABSTRACT

Vitamin B12 is one of the neurotropic vitamins that are key to the proper functioning of the nervous system. It participates in the metabolism of nucleic acids, the synthesis of DNA and biogenic amines, and is also necessary in the transformation of fats resulting, among other things, in an effective process of myelinisation. In severe cases, vitamin B12 deficiency, regardless of the cause, leads to the onset of symptoms from the nervous and hematopoietic systems, as well as to psychiatric symptoms. The most common neurological disorders in infants and small children include: retardation of psychomotor development, progressive weakness, muscle hypotonia, hyporeflexia, tremors, convulsions, ataxia, psychomotor regression.

The following article presents the diagnostic and therapeutic process and long-term results of treatment of an 11-month-old boy with symptoms of encephalopathy caused by vitamin B12 deficiency. The diagnostics of encephalopathy in infants and small children should take into account deficiency-related, potentially reversible causes, due to the possibility of rapid and effective treatment to prevent persistent neurological problems.

Keywords: cobalamin, vitamin B12 deficiency, neurological symptoms, hypotonia, homocysteine, infant

STRESZCZENIE

Witamina B12 jest jedną z witamin neurotropowych czyli kluczowych dla prawidłowego funkcjonowania układu nerwowego. Bierze udział w metabolizmie kwasów nukleinowych, syntezie DNA i amin biogennych, jest także niezbędna w przemianach tłuszczów skutkujących m. in. efektywnym procesem mielinizacji. W ciężkich przypadkach deficyt witaminy B12, niezależnie od przyczyny, prowadzi do wystąpienia objawów ze strony układu nerwowego, krwiotwórczego, a także objawów psychiatrycznych. Do najczęściej występujących zaburzeń neurologicznych u niemowląt i małych dzieci należą: opóźnienie rozwoju psychoruchowego, postępujące osłabienie, hipotonia mięśniowa, hiporefleksja, drżenia, drgawki, niezborność ruchowa, regres psychomotoryczny.

W poniższej pracy zaprezentowano proces diagnostyczno-leczniczy oraz odległe wyniki leczenia 11-miesięcznego chłopca z objawami encefalopatii spowodowanej niedoborem witaminy B12. Diagnostyka encefalopatii u niemowląt i małych dzieci powinna uwzględniać niedoborowe, potencjalnie odwracalne przyczyny ze względu na możliwość szybkiego i efektywnego leczenia zapobiegającemu trwałym deficytom neurologicznym.

Słowa kluczowe: kobalamina, niedobór witaminy B12, objawy neurologiczne, hipotonia, homocysteina, niemowlę

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INTRODUCTION

Vitamin B12, otherwise known as cobalamin, is one of the water-soluble vitamins. Cobalamin has a large variety of biological functions but above all it is essential for haematopoiesis and the development and functioning of the nervous system. It also affects cognitive function. Vitamin B12 is not synthesised in animal and plant organisms, with bacteria being responsible for its production. The only source of vitamin B12 for humans are foods of animal origin [1]. The current guidelines for the recommended daily intake of vitamin B12 for individual groups are shown in Table I. The products richest in cobalamin are liver and kidneys (up to 100 μg/100 g), but crustaceans, fish and meat also provide large amounts of cobalamin. Eggs, cheeses and milk contain relatively little cobalamin (6 μg/L). Vitamin B12 is mainly stored in the liver. The absorption of vitamin B12 from various animal foods varies from 20% to 90%. It is assumed that in healthy adults with normal gastric function, about 50% of this vitamin is absorbed from the diet. Adult hepatic stores of 1–4 mg balance a vitamin B12-devoid diet for several years [2]. In contrast, the foetus stores approx. 0.1–0.2 μg of the vitamin per day. During the first six weeks of life, a significant decrease is seen in the infants' serum cobalamin level. Moreover, infantile vitamin B12 body stores (which usually comprise about 25 μg) may be much lower if the infant's mother is undernourished. Among the causes of cobalamin insufficiency, dietary deficiencies (inadequate dietary vitamin B12 intake, vegetarian diet, vegan diet, malnutrition, alcoholism) are primarily highlighted, as well as absorption disorders caused by gastrointestinal diseases and genetically conditioned disorders of vitamin B12 transportation and metabolism. Gastric causes include Castle's intrinsic factor deficiency, atrophic gastropathy, Zollinger-Ellison syndrome, proton pump inhibitor abuse, total or partial gastrectomy. Intestinal causes include, among others, celiac disease, Crohn's disease, Imerslund-Gräsbeck syndrome and parasitic infestations (broad tapeworm) [3]. In the paediatric population, vitamin B12 deficiency is rare. Its most common cause are food deficits, and the most vulnerable group are infants who are exclusively breastfed by mothers with overt or latent vitamin B12 deficiency [4]. This paper describes the case of an 11-month-old boy with severe vitamin B12 deficiency, exclusively breastfed by a mother who was diagnosed with Addison-Biermer anaemia only during her son's diagnostics. The infant showed clinical symptoms clearly attributable to vitamin B12 deficiency: haematological, neurological and neuropsychiatric abnormalities.

Table I. Recommended daily intake of vitamin B12 for individual groups
Tabela I. Rekomendowane dawki witaminy B12 dla poszczególnych grup

Recommended daily intake of vitamin B12 for individual groups	
Infants	0.4–0.5 μg
Children	0.9–1.8 μg
Adolescents	1.8–2.4 μg
Adults	2.4 μg
Pregnant/breastfeeding mothers	2.6–2.8 μg

CASE DESCRIPTION

The 11-month-old boy was admitted to the Department of Paediatric Neurology in a moderately-severe state due to progressive weakness. On admission, the infant was apathetic, drowsy, did not undertake spontaneous motor activity. He did not make eye contact, did not follow movement visually, froze staring fixedly at one point. He showed a poorly expressed response to sounds, including very loud ones. The boy, who had only been breastfed so far, did not signal hunger, did not want to suck, he choked and vomited at attempts at feeding. The boy G1, P1, normal spontaneous vaginal delivery at 41 weeks of pregnancy, with birth weight of 3,180 g, Apgar score 9, the period of postpartum adjustment was uncomplicated, in the first half-year of life the infant was vaccinated according to the Immunisation Timetable. Until the sixth month of life, the boy was a cheerful, active and curious infant. He had no known muscular tone disorders. His psychomotor development at that time was somewhat delayed: he turned to the sides after 4 months of age, presented rotations around his axis at 6 months of age, in the pronation position he demonstrated a low front support in arms until approx. 6 months of age, then for a brief moment an unstable high front support in arms. The boy did not sit, when settled down he dropped to the front or to a side, did not crawl, did not spring on his legs when supported. In the development of speech there were stages of cooing and babbling. The patient did not pronounce syllables, first words, did not respond to his name, did not present non-verbal gesture communication. Until the age of six months, the boy was breastfed only, after which an attempt was made to extend the diet to include fruit mousse and purée soups. Fed with a spoon, he did not want to eat, he choked even on small portions of food, vomiting. The complete non-acceptance of new foods, their consistency and manner of administration along with behavioural changes were the main reasons for the parents' reporting to the primary care physician at 7–8 months of the boy's life. The most worrying were: decreasing interest in motor activity, surroundings, interaction with the immediate family, initial irritability, progressive weakness, psychomotor regression and finally apathy (during 2–3 weeks prior to admission, the boy slept most of the day, refused to be fed). Initially, a change in the infant's activity was referred for a physician's observation ("will catch up", "still has time"). As the symptoms worsened, diagnostic tests for anaemia were con-

ducted. Although the initial Complete Blood Count results showed no deviations from normal values of the red blood cell system parameters, iron preparations were used in the therapy and the boy was referred to a rehabilitation centre. This process lasting approx. months (8–11 months of age) did not bring the expected results. Not only did the patient make no progress, but he lost his previously acquired motor skills, lost the desire and ability to communicate with his surroundings, did not signal his needs, did not present emotions (cried briefly and quietly, lost social smile, did not babble). With the symptoms of encephalopathy, he was transferred to the Department of Paediatric Neurology. On admission, the following findings were made on physical examination: pale skin, at times rough, discrete symptoms of glossitis. On neurological examination: very poorly expressed reaction to external stimuli, silent cry (whimper); head circumference of 46 cm (10 c.), anterior fontanelle with normal tension, slightly below the skull bone level, e.g. 1×1 cm; it was difficult to make the infants' eyes follow the light source, no deficits were found in the cranial nerves (the boy did not smile), a small degree of generalised joint laxity, poor head control in a traction test — he was able to briefly stabilise, then the head dropped forward or backward, the support was incorrect on the chest, in the supine position the upper limbs were abducted; slightly weakened, deep reflexes were symmetrical. As regards deviations from norm in the primary laboratory studies, the following were found: macrocytic anaemia, leuko- and neutropenia (haemoglobin level 8.3 g/dL, MCV 103.6 fl, WBC $5.33 \times 10^3/\mu$L, granulocte count $0.81 \times 10^3/\mu$L, platelet counts $191 \times 10^3/\mu$L), decreased absolute reticulocyte counts and hypertransaminasemia. The parameters of iron metabolism were normal. Diagnostic tests were extended to include the determination of vitamin B12 level, which was found to be severely deficient — 83 pg/mL (N: 187–883 pg/mL) and folic acid showed a result slightly above the norm. Upon questioning the history in detail, the patient's mother reported to have low serum level of Vitamin B12 at the end of pregnancy. Since the mother's vitamin B12 storage was limited, the mother failed to transfer enough cobalamin during pregnancy and breastfeeding. During the boy's hospitalisation in the course of diagnostic tests the cause of the vitamin B12 deficiency was determined in the mother (atrophic gastropathy of autoimmune aetiology — Addison-Biermer anaemia). The level of biomarkers of active forms of vitamin B12 deficiency was determined in the boy, and significantly elevated levels of homocysteine were found in the plasma as well as a high level of methylmalonic acid in a GC/MS analysis of organic acids in urine. An abdominal ultrasound scan showed that the liver was borderline in size with increased echogenicity. With gastroscopy any evidence of pathology of the upper gastrointestinal

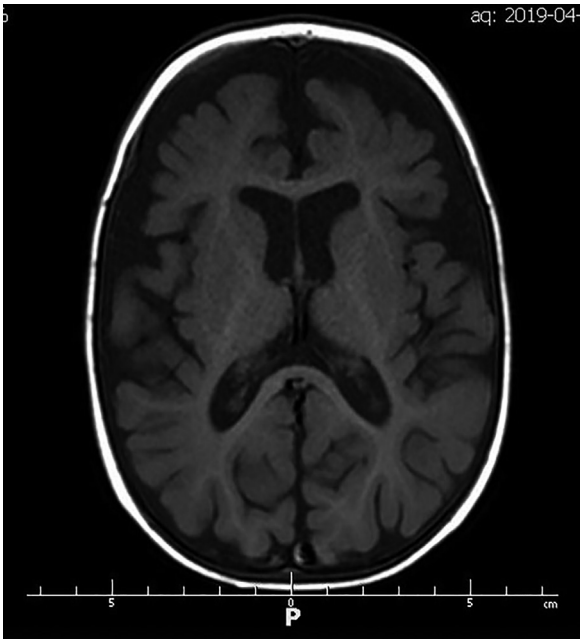

Figure 1. Cerebral atrophy, enlargement of subarachnoid spaces, delayed myelination (magnetic resonance imaging of the central nervous system in axial T1-weighted SE image)

Rycina 1. *Zaniki korowe, poszerzenie przestrzeni płynowych przymózgowych, opóźniona mielinizacja (rezonans magnetyczny ośrodkowego układu nerwowego, przekrój poprzeczny w obrazie T1-zależnym SE)*

tract was ruled out. No antibodies to gastric parietal cells or to the intrinsic factor were found. The faecal occult blood test was negative. On CNS ultrasound: dilated subarachnoid fluid spaces 11–13 mm, atrophic dilation of the lateral ventricles of the brain, the ventricles were 31 mm in width. Under general anaesthesia, a CNS MRI was conducted (Fig. 1.) and the following abnormalities were found: a significantly decreased volume of both hemispheres of the brain, resulting from a decreased volume of the periventricular white matter, mainly, together with the secondary dilation of the subarachnoid fluid spaces, as well as a slight dilation of the supratentorial ventricular system (Evans index approx. 0.33) and the fourth ventricle, the degree of myelination was slightly delayed — corresponding to the age of 9 months, the corpus collosum was slightly thinned, there was a small pineal cyst of 2 mm, the superior recess of the cerebromedullar cistern was dilated. The result of the neuroimaging study was consistent with significant vitamin B12 deficiency. The consulting oncologist supported the view of the deficiency-related cause of the haematological disorders. Due to the presence of cortical atrophy in the CNS MRI in differential diagnosis, lysosomal storage diseases were considered (determination of lysosomal enzymes activity in peripheral blood leukocytes produced a normal result). CLN2 was ruled out with an analysis of enzymatic activity in a dried blood spot. The biotinidase activity in a dried

blood spot was normal. Celiac disease was ruled out. On the basis of serological tests, hepatitis A and C and HIV were excluded. The consulting cardiologist ruled out abnormalities in the circulatory system. The ophthalmologic examination produced normal results. The diagnosis was based on history-taking complemented by the mother's medical history, symptoms and test results. Immediately after the diagnosis, the child's treatment was commenced by an intramuscular administration of vitamin B12 at 200 μg/day for 7 days, obtaining its significant increase in serum levels above the upper limit of normal — 1798 pg/mL (N: 187––883 pg/mL). High reticulocytosis was indicative of haematologic recovery. The patient's clinical condition slowly improved and he became more active. During a break in the boy's treatment, involuntary movements of the right limbs occurred temporarily, more intensely in the upper limbs. A spontaneous sleep EEG test was conducted, with no apparent epilepticform abnormalities in the reading — the patient exhibited normal EEG. These symptoms were considered to be caused by the previously diagnosed vitamin B12 deficiency and decreasing homocysteine levels and accordingly it was decided not to administer antiepileptic treatment. During his stay in the hospital department, the case additionally received a single dose of 1000 μg of vitamin B12 intramuscularly. The treatment resulted in a significant improvement of blood cell counts and transaminases levels going back to normal. Vitamin B12 level was 1345 pg/mL. Clinically, significant improvement in the boy's spontaneous activity was observed, including his interest in the environment, close relatives, the child was playful, has social smile and was babbling. Due to the difficulty in feeding, the boy was tube-fed for 6 weeks, after that period oral feeding was successfully re-introduced and the diet was gradually extended. During the neurological exam conducted on the day of discharge the boy made eye contact, followed movements visually, smiled, his muscle tone improved, deep reflexes were brisk, symmetrical, during a traction test the child stabilised his head and demonstrated high support in the arms when lying prone.

Vitamin B12 treatment was continued on an outpatient basis with monitoring of vitamin B12 levels in blood. Vitamin B12 was administered for the first 3 months intramuscularly at a dose of 1000 μg every 2 weeks. Subsequently, vitamin B12 was administered to the boy for two months orally at a dose of 100 mg/day. For the following year, the patient received the above-mentioned oral dose every other day. The last 6 months of treatment included an administration of oral dose once a week. In total, the treatment lasted 2 years. With his neurologic improvement and normal haematologic values, the cobalamin therapy was discontinued when the child reached 3 years of age. A gradual improvement of boy's neurological condition was observed throughout the treatment.

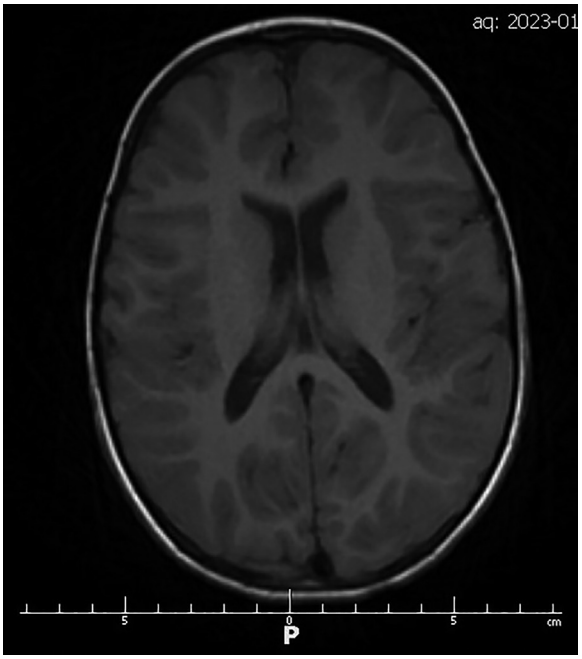

Figure 2. Normal brain image (magnetic resonance imaging of the central nervous system in axial T1-weighted image)

Rycina 2. *Prawidłowy obraz mózgowia (rezonans magnetyczny ośrodkowego układu nerwowego, przekrój poprzeczny w obrazie T1-zależnym)*

There was an increase in his achievement of developmental milestones. At the age of 14 months, he was sitting in a stable position, he started walking when he was 19 months old. He uttered first words at 19 months of age and his further speech development continued harmoniously. The boy was regularly rehabilitated. At 2 years of age, he caught up with the pace of development of healthy peers.

At 4.5 years of age, the boy was re-admitted to the Clinical Department of Paediatric Neurology for a follow-up CNS MRI. The only deviation from the norm in the neurological exam was discretely decreased muscle tone, the child was hyperactive. A vitamin B12 level test result after about one and a half year intake break was normal — 783 pg/mL. A GC/MS analysis of organic acids in urine showed no significant clinical relevance. A follow-up cranial MRI (Fig. 2.) performed 3,5 years after the initiation of therapy demonstrated a recovery of cerebral atrophy, normal width of subarachnoid spaces, and age adequate myelination.

DISCUSSION

Clinical presentations of severe vitamin B12 deficiency are dominated by haematological, neurological and psychiatric symptoms. The classic haematological presentation of vitamin B12 deficiency is megaloblastic anaemia as a result of impaired erythropoiesis [5]. Pancytopenia was detected in a blood test of the boy, with megaloblastic anaemia being a major deviation in a blood test.

As a result of vitamin B12 deficiency, monoamine synthesis is impaired (serotonin, noradrenaline, dopamine) and consequently psychiatric symptoms may develop, such as: chronic fatigue syndrome, memory impairment, mood disorders, slow mentation, apathy, depression, delusional states [6]. Other common findings include: loss of taste, loss of appetite, glossitis, nausea, constipation and diarrhoea [7] . In the case presented the loss of appetite was one of the first symptoms, which alarmed the boy's parents. The neurological manifestation of vitamin B12 deficit varies depending on the patient's age and includes a broad spectrum of symptoms, including: hypotonia, ataxic gait, atactic paraplegia, convulsions, vision loss or vision blurring, polyneuropathy, paraesthesia, loss of cutaneous sensation, impaired sense of vibration, subacute combined neurodegeneration of the spinal cord. The differences in clinical presentations in children and adults are mainly due to the fact that a clinical impairment of a mature nervous system develops slowly in months or even years. In infants and small children, the brain grows and develops rapidly. Vitamin B12 deficiency inhibits these processes and symptoms of this appear as early as several weeks due to the exhaustion of body stores and an inadequate cobalamin supply. As the developing central nervous system seems to be more sensitive to Vitamin B12 deficiency than that of adults, breastfed infants born to undernourished mothers may experience substantial neurological damage with typical neurological symptoms, such as irritability, failure to thrive, poor developmental progression, developmental arrest or delay, psychomotor regression, weakness, hypotonia, encephalopathy. In addition to age, the main factor determining the clinical presentation, including the severity and disease progression rate, is the duration of cobalamin deficiency, and in infants who are exclusively breastfed it is vitamin B12 deficiency, combined with the duration of deficiency. Signs and symptoms usually appear between the ages of 2- and 10-months despite of maternal cause of vitamin B12 deficiency. There is also a relations between the time of diagnosis and the prognosis. The better outcome is reported in children diagnosed and supplemented with cobalamin before the age of 10 months [8].

The present case of vitamin B12 deficiency in an infant, who was exclusively breastfed, was due to its' latent deficiency in the mother with previously undiagnosed pernicious anaemia. It was recognized that cobalamine storage of the mother was limited — the mother's serum vitamine B12 level, taken after the diagnosis of the infant, was 78.9 pg/mL. As as a result of mother's poor vitamine B12 storage she was unable to transfer enough cobalamine during the pregnancy and breastfeeding [9]. The disease was manifested in the boy from his 6 months of age.

In addition to the most common cause of vitamin B12 deficit in infants and small children, i.e. too low supply of the vitamin with the mother's milk/nutrition, one must mention significantly less frequently occurring gastrointestinal diseases causing malabsorption [10], including parasitic infestations and disorders of vitamin B12 transportation and metabolism.

Among the latter, the congenital transcobalamin II deficiency is reported. It is the most common inborn error of metabolism caused by mutation of genes encoding a protein that plays a critical role in the metabolic pathway leading to the formation of succinyl-CoA and methionine. Diagnosis is confirmed by identification of biallelic pathogenic variants in one of the following genes: *MMACHC, MMADHC, MTRR, LMBRD1, MTR, ABCD4, THAP11, ZNF143* or a hemizygous variant in *HCFC1* [11]. Active vitamin B12 absorption, because of its complex structure, is a multi-stage process. It requires involvement of three different transport proteins: the intrinsic factor produced by the gastric parietal cells (IF — Castle Factor), haptocorrin (HC) and transcobalamin II (TCII), which are plasma proteins [12]. Haptocorrin is a unique glycoprotein produced by the salivary glands of the oral cavity in response to food intake. This protein binds to vitamin B12 and protects it from an acidic environment of the stomach. The complex thus formed is resistant to hydrochloric acid and passes through the pylorus into the duodenum. In the initial section of the small intestine, pancreatic proteases release vitamin B12, which binds to the internal factor (IF) in the alkaline environment. The IF-cobalamin complex travels to the final section of the ileum, where it is then attached to the specific receptor — the cubilin, which is situated in the brush border of the intestinal epithelium. The presence of calcium ions and neutral pH are essential for this combination. After being ingested by endocytosis via receptors of the intestinal epithelium, cobalamin is metabolized to catalytically active organometallic cofactors: to methylocobalamin (MeCbl) in the cytoplasm and to adenosylcobalamin (AdoCbl) in the mitochondria. Metabolically active molecules of cobalamins: MeCbl and AdoCbl are the cofactors essential for the function of methionine synthase (MetH) and methylmalonyl-CoA mutase (MMCM), which enzymes are involved, inter alia, in methylation reactions [13]. Methionine synthase converts 5-methyltetrahydrofolate to tetrahydrofolate via remethylation of homocysteine to methionine. Methionine synthase is required for the production of S-adenosylmethionine, which is involved in more than 100 methylation reactions in the body and is an important methyl donor for neurotransmitter synthesis and maintenance of cellular integrity and genomic stability [14, 15]. Transfer of the methyl group is essential for the synthesis of the purines and as a result for the synthesis of DNA required by all rapidly growing cells. The accumulating homocysteine and methylmalonic acid are biomarkers of deficiency of active forms of vitamin B12 — MeCbl and

AdoCbl. They constitute a diagnostic parameter which is relatively easy to assess.

The test results of the case showed a significantly elevated level of homocysteine in plasma and a high level of methylmalonic acid in the GC/MS analysis of organic acids in urine. Tetrahydrofolate and methionine deficiency as well as hyperhomocysteinemia play a pivotal role in abnormal DNA synthesis and in slowing down and even inhibiting cell division, which is best seen in haematopoietic cells. Moreover, an increased plasma homocysteine level in vitamin B12 deficiency is associated with potentially neurotoxic effect and is recognized as a risk factor for seizures and epilepsy [16, 17]. According to literature one half of the infants with vitamine B12 deficit exhibit abnormal movements before the start of treatment with intramuscular cobalamine, which disappear 1 or 2 days after. More rarely, movement disorders appear a few days after treatment, whreas neurological symptoms are improving. The abnormal movements may last for 2 to 6 weeks [18]. As in this case, the infant exhibited involuntary movements of the right limbs, which may have been caused by hyperhomocysteinemia. The vitamin B12-dependent DNA methylation process is also of great importance for cognitive function (explicit memory, selective and sustained attention, learning, inhibitory control). Vitamin B12 deficiency may have a potentially negative effect on cognitive development and ultimately on cognitive functioning. Despite being 11 months old, our case was lethargic, not smiling, presented delayed acquisition of cognitive skills as well as linguistic delay.

Another important process mediated by B12 (in the form of the cofactor AdoCbl) is the reaction catalysed by methylmalonyl-CoA mutase, which converts methylmalonyl-CoA into succinyl-CoA, which enables the production of energy from fats and proteins. MeCbl and AdoCbl also participate in the regulation of protein and lipid metabolic pathways. Their deficiency disturbs, inter alia, the process of proper phospholipid methylation resulting in myelination defect, encephalopathy, myelopathy and nerve transmission disorder [19, 20]. The CNS MRI of the case specifically demonstrated cerebral atrophy and delayed myelination. Vitamin B12 deficiency is a treatable cause of neurological disorders and anaemia in infants exclusively breastfed by vitamin B12-deficient mothers. Recognition of the neurological symptoms enabled early diagnosis and immediate, appropriate treatment. In our case the recovery was observed within the first few weeks of the treatment. Findings from this study suggest that with early awareness infants have favourable neurological outcome.

CONCLUSIONS

Vitamin B12 deficiency in early childhood is a rare cause of neurodevelopmental delay and psychomotor regression. The importance of adequate vitamin B12 status, particularly during early childhood, cannot be overestimated in the light of the role of vitamin B12 in neural myelination and brain development. Maternal vitamin B12 storage is a major factor influencing the severity of its deficiency in infants who are exclusively breastfed. This case illustrates that vitamin B12 deficiency should be considered in the differential diagnosis of lethargy, psychomotor regression, hypotonia, failure to thrive, gait ataxia, developmental delay, convulsions, tremor and cognitive impairment. Vitamin B12 deficiency can be diagnosed through a combination of clinical presentation and laboratory findings such as complete blood count, serum vitamin B12 level, vitamin B12 functional biomarkers. Cranial magnetic resonance imaging should be performed. Infantile vitamin B12 deficiency is treatable. It involves immediate administration of vitamin B12 to the baby and the breastfeeding mother, if necessary. As it corrects metabolic manifestations, accurate treatment prevents further neurological damage and gives a chance to complete recovery. If not treated, vitamine B12 deficiency can cause lasting neurodisability. Therefore, efforts should be directed to prevent deficiency in breast feeding woman and their infants.

ARTICLE INFORMATION AND DECLARATIONS

Conflict of interest

None.

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None.

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