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Karl-Olof Lövblad
Gianpaolo Ramelli
Luca Remonda
Arto C. Nirkko
Christoph Ozdoba
Gerhard Schroth

Retardation of myelination due to dietary vitamin B_{12} deficiency: cranial MRI findings

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K.-O. Lövblad (✉) · L. Remonda · C. Ozdoba · G. Schroth
Department of Neuroradiology, IDR, Inselspital, University of Bern, Freiburgstrasse, CH-3010 Bern, Switzerland

G. Ramelli
Department of Pediatrics, Inselspital, University of Bern, Switzerland

A. C. Nirkko
Department of Neurology, Inselspital, University of Bern, Switzerland

Abstract Vitamin B_{12} deficiency is known to be associated with signs of demyelination, usually in the spinal cord. Lack of vitamin B_{12} in the maternal diet during pregnancy has been shown to cause severe retardation of myelination in the nervous system. We report the case of a $14^1/_2$-month-old child of strictly vegetarian parents who presented with severe psychomotor retardation. This severely hypotonic child had anemia due to insufficient maternal intake of vitamin B_{12} with associated megaloblastic anemia. MRI of the brain revealed severe brain atrophy with signs of retarded myelination, the frontal and temporal lobes being most severely affected. It was concluded that this myelination retardation was due to insufficient intake of vitamin B_{12} and vitamin B_{12} therapy was instituted. The patient responded well with improvement of clinical and imaging abnormalities. We stress the importance of MRI in the diagnosis and follow-up of patients with suspected diseases of myelination.

Introduction

Neurologic disease due to a lack of vitamin B_{12} is a clinical entity known since the turn of the century [1]. Deficiency of vitamin B_{12} affects particularly hematopoietic, epithelial and nervous tissues but the exact role of B_{12} in the metabolism of the nervous system remains unclear. Long-term deficiency of the vitamin cobalamin can cause demyelination of the spinal cord and brain [2–5] but the mechanism of demyelination is also not fully understood [6]. Neurologic symptoms as a sign of dietary deficiency in infancy have rarely been reported [7, 8], and indeed shortage of B_{12} in the diet is today an unusual cause for deficiency. Other causes are a lack of intrinsic factor, the presence of antibodies to B_{12} and intrinsic factor, malabsorption syndromes, ileal disease and inborn errors in metabolism. In previously published series, the administration of vitamin B_{12} has been shown to lead to restoration of neurologic function in many cases. Early diagnosis, therefore is of value.

Case report

This girl was born into a family of vegetarians whose intake of milk and dairy products had been minimal. She was born naturally after an uneventful pregnancy and had a weight at birth of 3300 g. At first postnatal development was normal, but at 6 months of age she presented with lack of progress and would only fixate light for short periods at 14.5 months. She was therefore seen by a pediatric neurologist. On examination she was in poor condition, weighing only 7300 g (below the 3rd percentile). Her skin was markedly pale and the sclera slightly yellow. Neurologic examination revealed generalized hypotonia, few spontaneous movements, a few involuntary movements of the extremities and continuous rolling movements of the tongue. The reflexes were very marked and a positive Babinski's sign was noted on the right side. There was also a positive foot grip reflex on the right. Analysis showed a megaloblastic anemia with hemoglobin (Hb) of 6.0, 1.56×10^{12} erythrocytes, mean corpuscular Hb (MCHb) 39, hematocrit 0.17, MC volume 111, MCHb concentration 35; 2.9×10^9 leukocytes with 89.5 % lymphocytes and 43×10^9 thrombocytes. Blood electrolytes and blood gases were normal. Vitamin B_{12} was low with a level of 92 pmol/l (normal value 180–750) but the B_{12} binding capacity was within normal limits at 1061 pg/ml. Levels of folic acid

(17 nmol/l) and ferritin (48 μg/l) were normal. The electroencephalogram showed generalized slowing of the basal activity compatible with diffuse encephalopathy. Auditory evoked brainstem potentials showed normal bilateral cochlear function.

It was decided to initiate therapy with vitamin B_{12}, consisting of 1000 ng every 2nd day with additional iron, folic acid, trace elements and vitamins. The patient responded well and at 20 months can sit alone, crawl, walk with help and speak simple words. Muscular strength is almost normal. Reflexes are normal and Babinski's sign is no longer present. Laboratory test values have completely returned to normal.

Materials and methods

MRI of the brain and spine was performed on a 1.5-T Magnetom Vision system (Siemens Medical Systems, Erlangen, Germany) using head and surface coils. Sagittal and axial T1-weighted, as well as axial and coronal T2-weighted sequences of the brain were acquired.

Results

MRI revealed marked brain atrophy with widening of both the inner and outer CSF-containing spaces, especially at the level of the frontal and temporal lobes (Figs. 1, 2). There were also signs of retardation of myelination, which was equal to that of a normal 4-month-old child. This retardation was most marked at the level of the temporal and frontal lobes (Fig. 3) where myelination was almost absent. There was also retardation in the brainstem, cerebellum, internal capsule and the posterior parts of the hemispheres. In addition, the corpus callosum was small for the age of the child (Fig. 1). Follow-up MRI 5 months later showed significant regression of the brain atrophy (Fig. 4), with only a few cerebral sulci in the frontal lobes being still too prominent (Figs. 5, 6). Definite signs of progressive myelination were visible and there was further development of the corpus callosum (Fig. 4).

Discussion

This young child of vegetarian parents presented with severe psychomotor retardation, retarded myelination and marked atrophy of the central nervous system due to a dietary lack of vitamin B_{12} with megaloblastic anemia. Neurologic diseases caused by cobalamin deficiency were first described at the turn of the century. In 1900 Russell et al. reported the classic findings in subacute combined degeneration of the spinal cord [1]. Later, Adams and Kubik presented a review of cases also involving the brain in adults [4].

Vitamin B_{12} plays an important part in the metabolism of the nervous system, even though its exact role in normal and pathologic conditions is not fully understood. In infants, the damage is thought to occur in the first 6 months of life, when myelination of the brain is very active. In children the main causes of pathologic myelination associated with vitamin B_{12} deficiency are insufficient oral intake or an inborn error of metabolism. A syndrome consisting of megaloblastic anemia with mucous membrane pallor and hyperpigmentation of the skin associated with neurologic signs such as developmental regression with involuntary movements of the head, trunk and extremities has been reported to occur in infants breast-fed by mothers with B_{12} deficiency. It was first described in infants in southern India and corresponds to the disease reported in this case. Patients responded favorably to the oral administration of vitamin B_{12}.

Until now isolated case reports on MRI of the nervous system in vitamin B_{12} deficiency have centered on subacute combined degeneration or funicular spinal disease [9–13]. Most reports were in adults and MRI showed high signal changes on T2-weighted sequences in the posterior columns of the spinal cord. These lesions consist of demyelination with damage to the myelin sheaths initially and subsequent axonal degeneration. Extensive lesions in the brain itself have only been found in a few cases showing small perivascular areas of demyelination within the white matter. The histologic findings are identical to those of the spinal cord lesions. These lesions have been seen in the white matter on MRI of the brain and spine in the few previously reported cases. One report concerned three cases presenting with demyelination of the nervous system due to sequential inborn errors of the methyl-transfer pathway associated with white matter changes on MRI [14]. Upon treatment all three patients showed imaging findings consistent with improvement, which was also present clinically; one of the patients even presented complete reversal of MRI signs. The improvement upon treatment is thought to be due to improved myelination confirmed by follow-up MRI, which showed less brain atrophy and signs of progression of myelination. In a series of 11 infants, cranial MRI in two showed clear retardation of myelination. Follow-up MRI in one of these patients showed normalization of the imaging findings but the neurologic exam was still abnormal, especially speech [15]. It is unclear to what extent treatment may be beneficial when the lack of vitamin B_{12} has been prolonged during a very critical period for the maturation of oligodendrocytes. Our patient presented with a progression of development of 9–10 months in a period of 6 months. MRI is a non-ionizing imaging method with known multiplanar imaging abilities that has proven to be a sensitive tool in the assessment of myelination in children; it allows both safe diagnosis and monitoring of the disease.

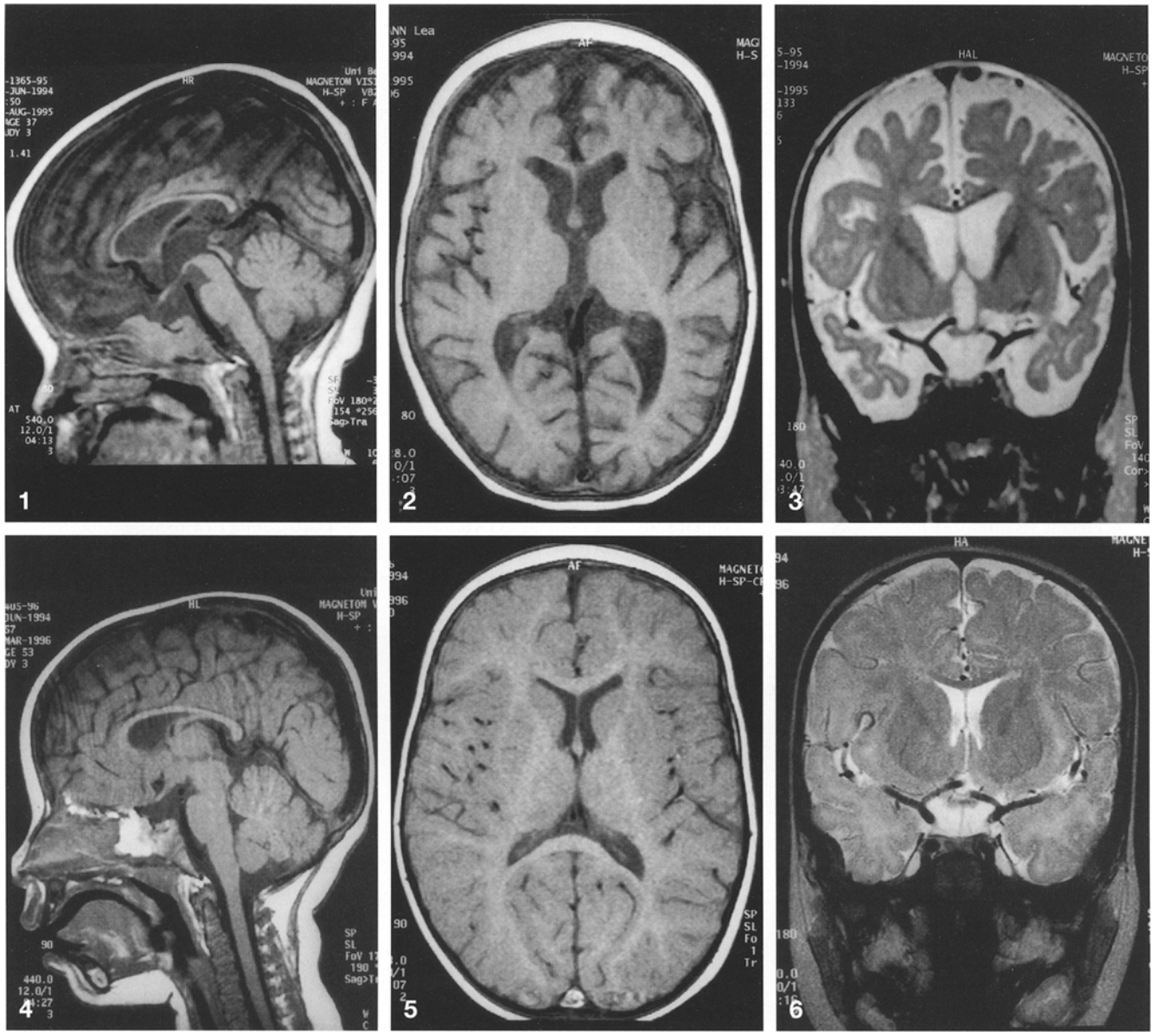

Fig. 1 Sagittal T1-weighted MR image displaying the markedly thin but structurally normal corpus callosum in addition to the prominent frontal cerebrospinal fluid containing spaces

Fig. 2 Axial T1-weighted image of the brain showing marked brain atrophy, most prominent in the frontal and temporal lobes (*AF* anterior frontal)

Fig. 3 Coronal T2-weighted section showing markedly wide cerebral sulci and ventricles. There is also significant brain substance loss in the frontal and temporal lobes

Fig. 4 Sagittal T1-weighted MRI control scan 5 months after therapy showing regression of the brain atrophy. The corpus callosum is also substantially more developed

Fig. 5 Axial T1-weighted image of the brain displaying almost normalized cerebral sulci, only a few frontal sulci being too wide for the age of the patient (*AF* anterior frontal)

Fig. 6 Coronal T2-weighted section displaying the less marked loss of cerebral volume

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