ISSN: 3068-8965
Journal of Pediatric Advance Research

ATHENAEUM SCIENTIFIC PUBLISHERS

Case Report

Brain Involvement in Cobalamin Deficiency: A Case Report

Elvio Della Giustina[1*], Michele Sintini[2]

[1]Division of Pathology, Department of Medical and Surgical Sciences for Children and Adults, University-Hospital of Modena and Reggio Emilia, UNIMORE, Modena, Italy

[2]Casa di Cura "Sol et Salus", Rimini, Italy

***Corresponding author:** Elvio Della Giustina, Division of Pathology, Department of Medical and Surgical Sciences for Children and Adults, University-Hospital of Modena and Reggio Emilia, UNIMORE, Modena, Italy; E-mail: elvio.dellagiustina@gmail.com

Citation: E. Della Giustina, et al. Brain Involvement in Cobalamin Deficiency: A Case Report. J Pediatric Adv Res. 2026;5(2):1-6.

https://doi.org/10.46889/JPAR.2026.5210

Received Date: 29-07-2026

Accepted Date: 17-08-2026

Published Date: 24-08-2026

Abstract

Background: A cobalamin deficiency can harm the brain, especially in infants who are exclusively breastfed. Specifically, it disrupts the mitochondrial citric acid cycle, leading to the accumulation of methylmalonic acid. The main neurological abnormalities are overall developmental delay, hypotonia, muscle weakness, irritability and occasional epileptic seizures. Early cobalamin supplementation can improve the clinical condition.

Methods and Findings: Here, we present the case of an infant whose mother was a vegetarian and who was exclusively breastfed until he was diagnosed at nine months of age. The infant presented with the typical clinical signs of brain involvement. These signs included severe underdevelopment of the supratentorial brain, particularly the corpus callosum, as seen on magnetic resonance imaging. The infant experienced brief, acute episodes of tremors and loss of contact, which were considered seizures due to clear, focal, bitemporal abnormalities observed in electroencephalographic recordings. Cobalamin supplementation only partially improved the infant's condition and rare focal seizures persisted over time. Later neuroimaging revealed nearly complete trophic recovery of the cerebral hemispheres and corpus callosum. However, both hippocampi remained severely hypotrophic, predominantly on the left side.

Conclusion: These long-standing brain abnormalities help explain the persistent focal seizures, as well as the residual mild-to-moderate global developmental delay, behavioral impairment and learning difficulties, particularly in infants who were supplemented with cobalamin late.

Keywords: Vit B12; Cobalamin; MMUT; Mitochodrion; EEG; Epilepsy

Introduction

A vitamin B12 (cobalamin, CBL) deficiency is a common cause of neurological impairment in children. In most cases, the deficiency begins in utero and can interfere with crucial stages of brain development, such as myelination and synaptogenesis. Genetic abnormalities of Intrinsic Factor (IF), produced by gastric parietal cells, are a rare cause of cobalamin deficiency. Most cases result from malabsorption disorders, particularly among exclusively vegan or vegetarian mothers and infants who are exclusively breastfed are most affected. Cobalamin is unique to animal-derived foods. The cobalamin-Intrinsic Factor (IF) complex is absorbed in the final part of the small intestine. Early diagnosis is essential for effective therapy, which must be initiated in the earliest postnatal months. Neurological impairment can be misleading because the initial and often only nonspecific signs and symptoms typically manifest around six to eight months after birth. These symptoms include developmental delay, hypotonia, muscle weakness, irritability and occasional epileptic seizures [1-6]. Defects in crucial developmental processes, such as myelination and synaptogenesis, can occur during fetal life and after birth. Depending on an early diagnosis, appropriate intramuscular and oral doses of cobalamin can replenish its stores and restore many central nervous

system impairments. Here, we present the case of an infant whose mother followed a vegetarian diet during pregnancy and thereafter and who was exclusively breastfed for the first nine months of life. The infant presented with multiple neurodevelopmental impairments, epileptic seizures, muscle tremors, megaloblastic anemia and multiple vitamin deficiencies. The infant also had elevated levels of homocysteine in the plasma and methylmalonic acid in the urine. Brain Magnetic Resonance Imaging (MRI) revealed severe, widespread underdevelopment. Notably, global developmental delay and focal epileptic seizures persisted later in life despite adequate cobalamin supplementation. A follow-up MRI revealed normalization of brain volume. However, signs of atrophy in the hippocampi persisted, which helped explain the infant's neurological sequelae.

Case Presentation

This infant was born at term via C-section due to breech presentation to healthy, unrelated parents. No morphometric or vital function abnormalities were observed at birth or during the first few weeks and months. The mother maintained a vegetarian diet during pregnancy and exclusively breastfed her son for nine months after birth. However, when the infant was six months old, he was examined by a public health service because he appeared apathetic, somnolent and hypotonic. He exhibited clear signs of psychomotor regression and had recently lost his ability to sit up on his own. He was not admitted to our service, however, until he was nine months old. By that time, he had experienced stagnation and regression in his overall development. He also displayed diffuse hypotonia, reduced muscle strength and extreme irritability alternating with somnolence. By that time, he had lost his ability to sit alone, as well as his initial verbal and visual contact and reactivity. He also experienced recurrent, brief episodes of fine tremors in both hands, accompanied by a complete loss of contact. These tremors were considered epileptic seizures because they were associated with multifocal spikes and spike-wave complexes in the fronto-centro-temporal regions on Electroencephalographic (EEG) recordings. He began Antiepileptic Drug (AED) therapy with valproic acid, which was later replaced with other common AEDs. However, the focal seizures were never fully controlled. His seizures persisted over time at a reduced occurrence, still accompanied by rare, slight fronto-temporal abnormalities (Fig.1). From a biological standpoint, the infant presented with megaloblastic anemia and pathologically elevated plasmatic homocysteine and urinary methylmalonic acid levels. These were accompanied by secondary hypometioninemia and hypocystinemia. His serum cobalamin level was 40.1 pg/mL (normal range: 179-1,132 pg/mL). Initially, cobalamin was administered intramuscularly at a dose of 1 mg per day for the first week. Then, the appropriate daily dose was administered orally until the altered biological compounds in the serum and urine normalized. The first brain MRI, performed when the infant was 10 months old and before complete replacement therapy, revealed severe supratentorial brain atrophy, enlarged lateral and third ventricles and an abnormally thin corpus callosum. There were no malformative or lesional aspects (Fig. 2). Two years later, a new MRI revealed that the infant had almost fully recovered from the previous atrophy. The ventricular system and corpus callosum had returned to normal size. However, the subiculum and Ammon's horn of both hippocampi, especially the left one, remained severely hypotrophic. These findings suggested the possibility of permanent hippocampal atrophy or initial sclerosis transformation (Fig. 3).

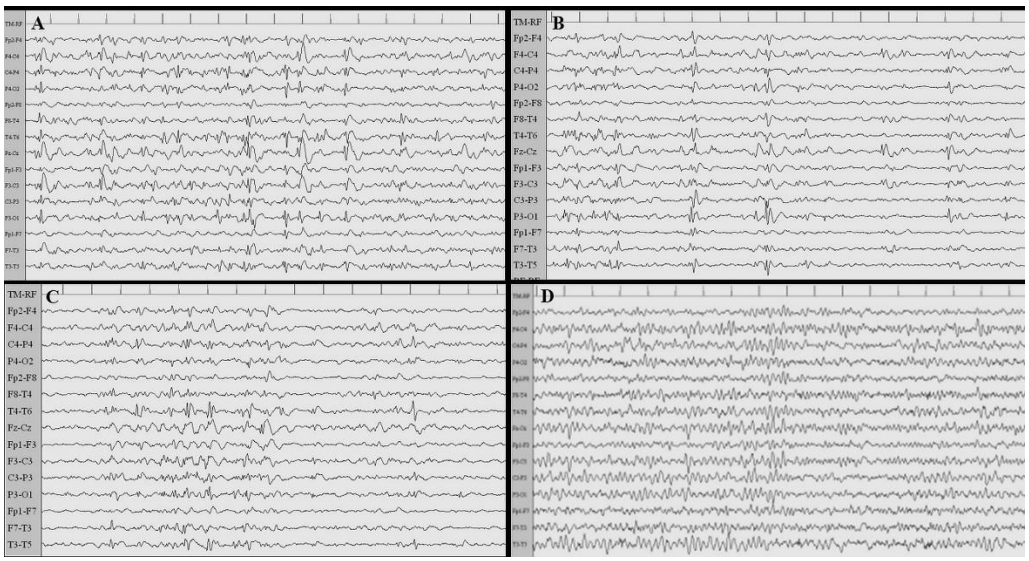

Figure 1: EEG abnormalities before (Panels A, B and C) and after (Panel D) cobalamin supplementation. Note the fronto-centro-temporal epileptogenic focus on both sides before cobalamin supplementation.

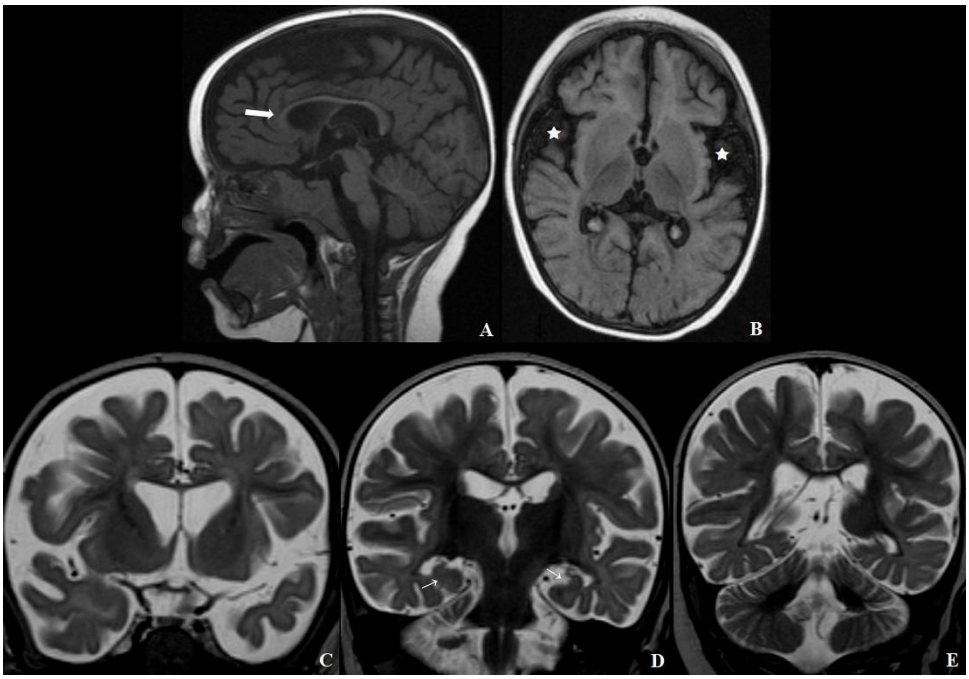

Figure 2: MRI images of the brain before cobalamin supplementation. The supratentorial brain compartments, particularly the temporo-insular regions on both sides (Panel B, axial T1 SE) (white stars), were underdeveloped. The corpus callosum was abnormally thin for the patient's age (Panel A, sagittal T1 SE) (white arrow). The underdevelopment of the supratentorial brain is evident in all Panels (C, D and E, coronal T2 SE) and Ammon's horn is difficult to recognize (thin white arrows).

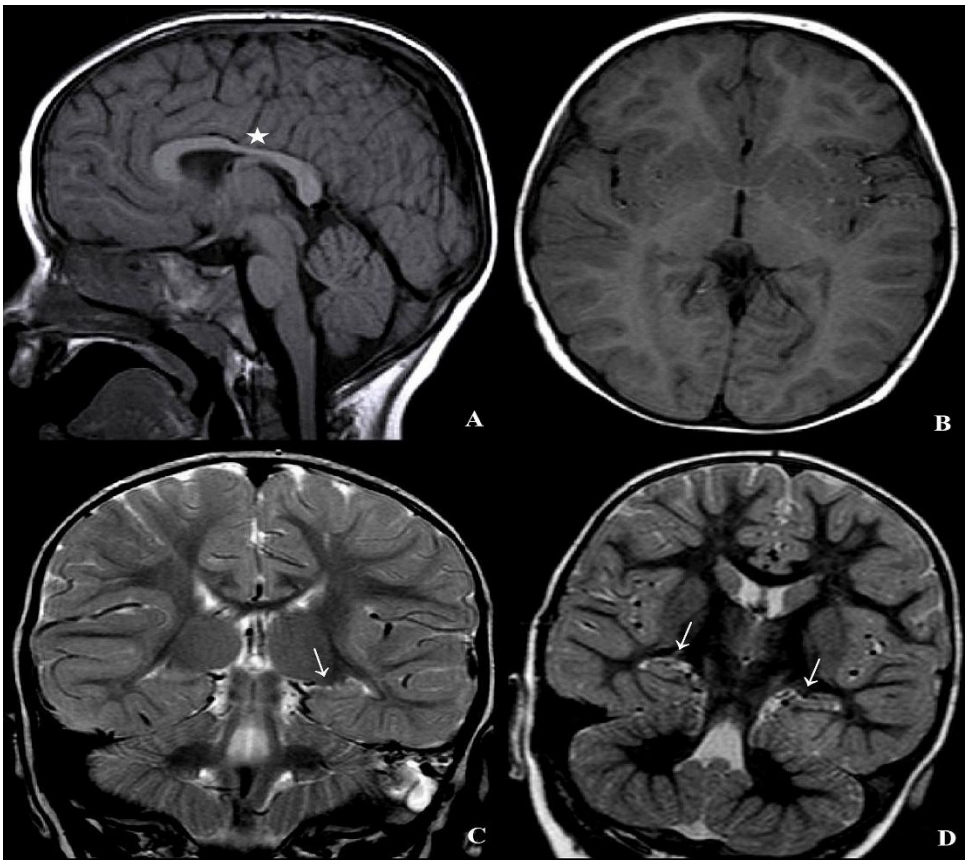

Figure 3: After two years of cobalamin supplementation, MRI images of the brain revealed that the supratentorial brain and corpus callosum (white star) had returned to normal volume (Panel A, sagittal T1 SE; Panel B, axial T1 SE). However, both hippocampi, particularly the left one, showed residual atrophy of the subicular and Ammon's horn regions (thin white arrows) (Panel C, coronal T2 SE; Panel D, coronal inversion recovery).

Discussion

We present the case of an infant with neurological sequelae resulting from cobalamin deficiency during a critical period of brain development. The deficiency was caused by the mother's predominantly vegetarian diet and her decision to exclusively breastfeed. The infant exhibited initial signs of neurological impairment by six months of age, including developmental stagnation and apathetic behavior. Unfortunately, symptoms of cobalamin deficiency typically appear four to eight months after birth, which makes an early neurological diagnosis challenging unless insidious megaloblastic anemia has already been identified [5,7,8]. The most common signs of cobalamin deficiency in infants include delayed psychomotor development, low muscle tone, weak muscles, increased sleepiness alternating with irritability and muscle tremors. They may also have limited verbal and visual interaction. Rare epileptic seizures have been reported in isolated cases [4]. Laboratory investigations play a critical role in diagnosis by revealing megaloblastic anemia and elevated plasmatic homocysteine and urinary methylmalonic acid levels. Secondary hypomethioninemia and hypocystinemia are also present. Cobalamin deficiency can damage many tissues in the body, particularly those with high metabolic rates, such as the brain, heart, kidneys and muscles. This depends on its unique cofactor activity for two enzymes: Mitochondrial Methylmalonyl-CoA mutase (MMUT), which requires adenosylcobalamin and cytosolic methionine synthase, which requires methylcobalamin. In cobalamin deficiency, Methylmalonic Acid (MMA) and homocysteine accumulate [4,9,10]. An increase in homocysteine can also damage cellular metabolism, particularly in the heart [11]. In particular, mitochondrial metabolism is a sensitive target of cobalamin deficiency, which leads to the accumulation of Methylmalonic Acid (MMA), a mitochondrial toxin. Under normal conditions, MMUT converts methylmalonic-CoA into succinyl-CoA, activating the citric acid cycle. Thus, cobalamin deficiency severely impairs mitochondrial oxidative phosphorylation and ATP production. It also increases Reactive Oxygen Species (ROS) production and depletes the mitochondrial antioxidant glutathione defense system. Ultimately, this results in cell death by necrosis or enhanced apoptosis [12-14]. Furthermore, it has been shown that MMA accumulation selectively inhibits complex II of the respiratory chain [15]. Another harmful effect of MMA is its impairment of biogenesis by inhibiting autophagy of damaged mitochondria [16]. MMA also leads to lipid peroxidation and the synthesis of abnormal fatty acids, which alter myelin composition and contribute to central and peripheral neurological impairment [9,10]. Severe MMA accumulation has been reported to cause brain lesions in the basal ganglia, particularly the globus pallidus, as well as in the white matter. Neuropathological evidence of spongiform vacuolization, cellular necrosis and apoptosis has been observed in these lesions [15,17]. One interesting experimental suggestion is that cytokine activity depends directly on cobalamin metabolism, further interconnecting mitochondria and inflammation [18]. The neurological signs and symptoms exhibited by this infant were not significantly different from those described in similar cases. The infant's overall development was impaired and he exhibited tremors that resembled brief, recurrent fine orofacial dyskinesias and trunk oscillations. These cobalamin-responsive, involuntary movements likely depended on mild and transient involvement of the basal ganglia, despite the absence of signal abnormalities on an MRI scan. Evidently, the mother's predominantly vegetarian diet did not severely affect all brain functions. Therefore, outbursts of irritable behavior and global developmental delay improved moderately with cobalamin supplementation.

Conclusion

Epilepsy is often associated with cobalamin deficiency in breastfed infants, yet very few cases have been reported [14]. Our patient experienced apparent ictal events associated with focal, primarily temporal, abnormalities on EEG recordings. Interestingly, we administered several antiepileptic drugs in a progressive manner, beginning with valproic acid. Over time, a combination of levetiracetam and topiramate improved the Electroencephalogram (EEG) despite the persistence of diffuse, monotonous, immature theta activity and reduced recurrence of brief focal clinical seizures. Neuroimaging improved dramatically with cobalamin supplementation, as demonstrated by the follow-up MRI. However, bilateral subiculum and Ammon's horn hypoplasia persisted, affecting the left side more severely. These MRI abnormalities of the brain have not been previously described in patients with this condition. They easily explain the long-standing bitemporal focal irritation on EEGs and the difficulty of controlling epileptogenesis with drugs. Additionally, considering the hippocampus's multiple functions, residual behavioral and cognitive impairment may also be explained.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding Statement

This research did not receive any specific grant from funding agencies in the public, commercial or non-profit sectors.

Acknowledgement
We thank Prof. Luca Reggiani Bonetti for his valuable professional and scientific support.

Data Availability Statement
The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement
This study was conducted in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association. Furthermore, this manuscript of a single case did not need the approval of our institutions.

Informed Consent Statement
The informed consent has been obtained verbally from the parents and the patient anonymity enterely preserved.

Authors' Contributions
Conceptualization: E.D.G. ; Data collection and analysis: E.D.G., M.S.; Data curation: E.D.G.; M.S.; Investigation: E.D.G.; Writing original draft: E.D.G.; Writing-review and editing: E.D.G.; M.S.

References
1. Casella EB, Valente M, de Navarro JM, Kok F. Vitamin B12 deficiency in infancy as a cause of developmental regression. Brain Dev. 2005;27:592-4.
2. Mathey C, Di Marco JN, Poujol A, Cournelle MA, Brevaut V, Livet MO, et al. Stagnation pondérale et régression psychomotrice révèlent une carence en vitamine B12 chez trois nourrissons. Arch Pediatr. 2007;14:467-71.
3. Dror KD, Allen LH. Effect of vitamin B12 deficiency on neurodevelopment in infancy: current knowledge and possible mechanisms. Nutr Rev. 2008;66(5):250-5.
4. Rosas M, Medici C, Lemes A, Cerisola A, Suárez P, Lombardo N, et al. Encefalopatía subaguda adquirida del lactante por deficiencia de vitamina B12 materna. Arch Pediatr Urug. 2020;91(6):348-58.
5. Dubaj C, Czyż K, Furmaga-Jabłońska W. Vitamin B12 deficiency as a cause of severe neurological symptoms in breastfed infant: a case report. Ital J Pediatr. 2020;46:40.
6. Cortés-Albornoz MC, Garcia-Guáqueta DP, Velez-van-Meerbeke A, Talero-Gutiérrez C. Maternal nutrition and neurodevelopment: a scoping review. Nutrients. 2021;13:3530.
7. Zengin E, Sarper N, Caki Kiliç S. Clinical manifestations of infants with nutritional vitamin B12 deficiency due to maternal dietary deficiency. Acta Paediatr. 2009;98:98-102.
8. Honzik T, Adamovicova M, Smolka V, Magner M, Hruba E, Zeman J. Clinical presentation and metabolic consequences in 40 breastfed infants with nutritional vitamin B12 deficiency: what have we learned? Eur J Paediatr Neurol. 2010;14:488-95.
9. Rossi A, Cerone R, Biancheri R, Gatti R, Schiaffino M, Fonda C, et al. Early-onset combined methylmalonic aciduria and homocystinuria: neuroradiologic findings. AJNR Am J Neuroradiol. 2001;22(3):554-63.
10. Frattini D, Fusco C, Ucchino V, Tavazzi B, Della Giustina E. Early onset methylmalonic aciduria and homocystinuria cblC type with demyelinating neuropathy. Pediatr Neurol. 2010;43:135-8.
11. Yao Y, Yao SL, Yao SS, Yao G, Lou W. Prevalence of vitamin B12 deficiency among geriatric outpatients. J Fam Pract. 1992;35:524-8.
12. Okun JG, Hörster L, Farkas M, Feyh P, Hinz A, Sauer S, et al. Neurodegeneration in methylmalonic aciduria involves inhibition of complex II and the tricarboxylic acid cycle and synergically acting excitotoxicity. J Biol Chem. 2002;277:14674-80.
13. Maciel EN, Kowaltowski AJ, Schwalm FD, Rodrigues JM, Souza DO, Vercesi AE, et al. Mitochondrial permeability transition in neuronal damage promoted by Ca2+ and respiratory chain complex II inhibition. J Neurochem. 2004;90:1025-35.
14. Liu Y, Wang SH, Zhang X, Cai H, Liu J, Fang S, et al. The regulation and characterization of mitochondrial-derived methylmalonic acid in mitochondrial dysfunction and oxidative stress: from basic research to clinical practice. Oxid Med Cell Longev. 2022;2022:7043883.
15. Larnaout A, Mongalgi MA, Kaabachi N, Khiari D, Debbabi A, Mebazza A, et al. Methylmalonic acidaemia with bilateral globus pallidus involvement: a neuropathological study. J Inherit Metab Dis. 1998;21:639-44.

16. Luciani A, Schumann A, Berquez M, Chen ZH, Nieri D, Failli M, et al. Impaired mitophagy links mitochondrial disease to epithelial stress in methylmalonyl-CoA mutase deficiency. Nat Commun. 2020;11:970.
17. Brismar J, Ozand PT. CT and MR of the brain in disorders of the propionate and methylmalonate metabolism. AJNR Am J Neuroradiol. 1994;15:1459-73.
18. Scalabrino G, Veber D, Mutti E. Experimental and clinical evidence of the role of cytokines and growth factors in the pathogenesis of acquired cobalamin-deficient leukoneuropathy. Brain Res Rev. 2008;59:42-54.

About the journal

Journal of Pediatric Advance Research is a peer-reviewed, open-access scholarly journal published by Athenaeum Scientific Publishers. The journal publishes original research articles, case reports, reviews, editorials and commentaries within its defined scope, with the aim of supporting scientific research and clinical knowledge in pediatric research.

All manuscripts are evaluated through an independent peer-review process conducted in accordance with the journal's editorial policies and established publication ethics. Editorial decisions are made solely on the basis of academic merit.

Manuscript submission: https://athenaeumpub.com/submit-manuscript/