

Congenital Isolated Folic Acid Malabsorption: Case Report

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Authors' contributions

This work was carried out in collaboration among all authors. Authors NM and RA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors NM and RA managed the analyses of the study. Author NM managed the literature searches. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

We report the case of a female child with congenital isolated malabsorption of folic acid. The patient was referred to our hospital for pancytopenia and a tendency to various infections, but with no neurological disturbances. A bone marrow aspiration demonstrated megaloblastic anemia and serum folic acid was low. An immunodeficiency test was therefore performed, which revealed impairment of both cellular and humoral immunity. The defect persisted after considerable doses of folate were administered orally to the patient. However, parenteral administration of folic acid removed pancytopenia, and restored normal levels of T CD8+, NK, B and immunoglobulins. Our patient, responded only to parenteral folate and her immunologic recovery after parenteral folate repletion was dramatic and provides strong *in vivo* evidence of the importance of folates for lymphocyte function in humans. Our patient's history shows that while it is easy to reverse the systemic consequences of folate deficiency, patients must not stop taking their folate supplementation because they believe that their disorder disappeared.

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1. INTRODUCTION

Folates are a family of B vitamins that play a key role in the synthesis of nucleic acids. The proton-coupled folate transporter (PCFT) is important for normal intestinal folate absorption and normal folate transport into the central nervous system. The SLC46A1 gene provides instructions for making the PCFT protein, and mutations in this gene cause the substitution of one protein building block for another amino acid in the PCFT protein, which results in a PCFT protein that is shorter than normal. The abnormal PCFT protein has little or no activity [1] and the corresponding defect reduces folate levels in serum and cerebrospinal fluid (CSF).

Congenital isolated malabsorption of folate is a rare specific disorder that was first described in 1961 [2]. Thirty cases with clinical diagnosis of this disorder had been reported by 2011 [3]. By 2017, only 38 families had one or more members clinically diagnosed as having the disorder and, of these, the diagnosis was confirmed by molecular genetic testing in 31 families [4,5]. Congenital isolated malabsorption of folate results primarily in megaloblastic anemia but may affect all three hematopoietic lineages [6], resulting in pancytopenia. It also causes cellular and humoral immunodeficiency and has, for two-thirds of the patients, neurologic manifestations [4]. Treatment requires lifelong supplementation of folic acid.

In this report, we describe a child who presented with clinical and biological features related to congenital isolated folic acid malabsorption, but without the neurologic disturbances that often accompany this disorder. We describe how the patient's clinical and biological features improved when parenteral treatment was administered, and how her condition deteriorated when folate supplementation was stopped by her parents.

2. CASE REPORT

Our patient was a 4-month old female infant, born via vaginal delivery after a full term pregnancy, with a weight of 3800 g. She was the third child of healthy parents who were first-cousins. The parents did not report any problems with their two, older, children. The patient was breast-fed since her birth. From the third month

of her life, the patient began to suffer from recurrent infections, especially of upper respiratory tract, lungs and gastrointestinal problems (chronic diarrhea and frequent vomiting). The child was referred for pancytopenia to our pediatrics unit at the Military Teaching Hospital Mohammed V in Rabat, Morocco. On admission, her general condition was very poor; she was very pale and feverish (38.5°C). Her failure to thrive in both weight (5000 g) and height (55 cm) was evident. The infant's blood test revealed anemia (Hemoglobin: 55 gL⁻¹; mean corpuscular volume of 105 fl; mean corpuscular hemoglobin: 30.9 pg); leukopenia (white blood cells: 3.5 10⁹ L⁻¹); and thrombocytopenia (platelets: 62 10⁹ L⁻¹). The peripheral blood smears showed macrocytosis. Biochemical examinations revealed normal renal functions, and normal levels of serum electrolytes, glucose and coagulation function. Further tests showed that there was no biological malabsorption syndrome, as the result of the following assays were in their respective normal ranges: Albumin, ferritin, triglycerides, cholesterol, vitamin B₁₂. Phosphocalcic balance was also normal. Lastly, the negative IgG and IgA anti transglutaminase antibodies, as well as the negative test for HLA-DQ2 and I HLA-DQ8 were not in favor of celiac disease.

The bone marrow aspiration revealed megaloblastosis related to a deficit in folic acid and/or vitamin B₁₂. The deficit in folic acid was confirmed by a subsequent blood test that revealed plasma folate level at 0.5 ng/mL (normal levels are 5-15 ng/mL) [5]. However, Vitamin B₁₂ level of 347 pg/mL was within the normal range (187-883 pg/mL). The low folate and the macrocytic anemia suggested that administration of folate was warranted. The patient was given an oral dose of 5 mg/day of folic acid. Due to the recurrent infections that were not responsive to antibiotics, as well as blood tests that showed persistent low levels of lymphocytes, we suspected immunodeficiency and performed a lymphocyte subtyping test and immunoglobulin quantitation. These tests revealed very low immunoglobulins levels (IgA: 0.02 g L⁻¹; IgG: 2 g L⁻¹; IgM: 0.03 g L⁻¹). There was also a decrease in subpopulation of CD8 lymphocytes, natural killers, and B lymphocytes, without any phenotypic abnormalities. The patient was diagnosed as having a combined severe immunodeficiency. She was, therefore,

prescribed normal human immunoglobulin (Tegeline: 50 mg/mL, at 1 g/kg). However, as the patient's folate levels did not increase despite repeated oral folate administrations, and her macrocytic anemia was persistent, we prescribed a parenteral administration of folates. Two weeks later, tests showed a reversal of previous deficits: serum folate levels were normal (plasma folate: 6 ng/mL); normal blood count; IgA: 0.64 g L⁻¹; IgG: 9.98 g L⁻¹; IgM: 0.81 g L⁻¹) and normal lymphocyte subtyping: lymphocytes T (CD3+ CD8+): 1322 mm⁻³; lymphocytes NK (CD3- CD56+): 661 mm⁻³; lymphocytes B(CD19+): 841 mm⁻³; lymphocytes B (CD20+): 841 mm⁻³. The patient recovered her appetite, had no more diarrheas, and was discharged from the hospital with a prescription of calcium folinate injections every two days (she was 5.5 months old).

After about 10 months, the patient's parents stopped giving their daughter the regular calcium folinate injections because they thought she had fully recovered. Three months later, the parents brought her back to the hospital in poor condition and blood tests revealed low plasma folate: 0.8 ng/mL; Hemoglobin: 8.2 g/L; mean corpuscular volume: 98.5 fl; mean corpuscular hemoglobin: 29.9 pg; white blood cells: 3.2 10⁶ L⁻¹; platelets: 52 10⁶ L⁻¹. We performed a parenteral administration of folates and after two weeks, her condition improved greatly (plasma folate: 18.3 ng/mL; Hemoglobin: 11 g/L; mean corpuscular volume: 86.8 fL; mean corpuscular hemoglobin: 29.7 pg; white blood cells: 10.3 10⁶ L⁻¹; platelets: 358 10⁶ L⁻¹). Once again, the patient recovered her appetite, had no more diarrheas, and was discharged from the hospital with a prescription of calcium folinate injections every two days. Her regular follow-up consultations at our hospital indicate she remained in good health.

3. DISCUSSION

Isolated congenital malabsorption of folic acid is an autosomal recessive disorder characterized by impaired intestinal folate absorption and impaired folate transport across the choroid plexus due to loss of function of the proton-coupled folate transporter (PCFT-SLC46A1) [7,8]. Associated clinical features include poor feeding, failure to thrive, anemia (but may affect all three hematopoietic lineages resulting in pancytopenia), and recurrent infections [4,5,7]. Neurologic disorders, occur in two-thirds of the patients [4], but with large variance in terms of the disorder's time of onset, appearance, severity, and intensity. Typical neurological

manifestations of folate deficiency include progressive psychomotor retardation, cognitive and motor impairment, behavioral disorder and early-onset seizures [9,10,11]. Diagnosis is confirmed by very low baseline serum folate concentrations (often <1.0 ng/mL; normal: 5-15 ng/mL) and little or no increase after an oral loading dose of 5-formyl-tetrahydrofolate. In unaffected individuals, the serum folate concentration increases to at least 100 ng/ mL [10-13].

The immune system appears to be particularly sensitive to folate deficiency. *In vitro* studies have shown that folate deprivation impairs T lymphocyte proliferation, and induces cell cycle arrest in the S-phase and apoptosis [3]. Furthermore, the lymphocyte proliferative defect is reversible, as shown by the fact that lymphocytes cultured without folate for one week resumed proliferation when folate was added to the medium [3]. However, while it is easy to completely reverse the anemia, immune dysfunction and gastrointestinal signs that folate deficiency causes [4,6,14], correcting the neurological consequences is more difficult.

In this case report, we discussed a female child with congenital isolated malabsorption who presented with clinical and immunological features suggestive of severe combined immunodeficiency. Our patient did not exhibit any visible neurological manifestations, and a scan confirmed the absence of lesions on her brain. Individuals affected by this disorder have very low CSF folate concentrations [5] and it is unclear why some individuals have neurologic signs and some do not [4,5]. The patient's parents were informed to look out for any signs of neurological disorders, as they may occur at any time during the child's development. As the CSF folate level necessary to sustain normal brain development has not been established, the CSF folate level may turn out to be low even when the folate blood level is normalized [4]. The neurological elements of this disorder often occur or persist even after effective treatment of the systemic folate deficiency [3]. For these reasons, it is important to monitor folate levels in serum and CSF.

Some studies reported that the isolated congenital malabsorption of folic acid persists after considerable doses of folate were given orally [7,15,16], which is consistent with PCFT dominant role in the body's ability to uptake folates from the gastrointestinal tract. This was

the case with our patient, who responded only to parenteral folate. The patient's immunologic recovery after parenteral folate repletion was so dramatic that it provides strong in vivo evidence of the importance of folates for lymphocyte function in humans [3]. While it is easy to reverse the systemic consequences of folate deficiency using parenteral folate, our patient's history shows the disorder's clinical and biological disorders return if folate supplementation is stopped.

Normal CSF folate levels are lower for adults than for children, which may lead to less frequent parenteral folate administration, but we are not aware of any case report that concludes that folate supplementation is not a lifetime requirement.

The parents are first cousins and the patient's siblings do not have the disorder. No genetic tests were performed on any member of the family, but the parents were counseled of the autosomal recessive nature of this disorder.

4. CONCLUSION

Our patient presented with pancytopenia and infections that could not be treated with antibiotics, leading to the suspicion of severe combined immunodeficiency. However, when the bone marrow assay showed B₉ or B₁₂ deficiency, further tests led to the folic acid malabsorption diagnosis. Therefore, defects of folate uptake need to be considered in the diagnostic work-up of young infants with immunodeficiency and suspected folic acid malabsorption. Folinic acid supplementation can offer life-changing therapy in patients with isolated congenital malabsorption of folic acid, and the earlier a diagnosis is made, the more likely it is to treat the patient before neurological disorders start to appear.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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