ECRONICON OPEN ACCESS

EC PAEDIATRICS
Case Report

Hereditary Folate Malabsorption with a Novel Mutation on SLC46A1

Irum Latif Memon[1]* and Fahad AlManjomi[2]

[1]Former Assistant Consultant/Fellow Pediatric Hematology-Oncology and BMT, Comprehensive Cancer Center, King Fahad Medical City, Riyadh, Saudi Arabia and Clinical Fellow in Pediatric Hematology-Oncology and BMT, Great Ormond Street Hospital for Children NHS Foundation Trust, Great Ormond Street, London, United Kingdom

[2]Consultant Pediatric Hematology-Oncology and BMT, Comprehensive Cancer Center, King Fahad Medical City, Riyadh, Saudi Arabia

***Corresponding Author:** Irum Latif Memon, Former Assistant Consultant/Fellow Pediatric Hematology-Oncology and BMT, Comprehensive Cancer Center, King Fahad Medical City, Riyadh, Saudi Arabia and Clinical Fellow in Pediatric Hematology-Oncology and BMT, Great Ormond Street Hospital for Children NHS Foundation Trust, Great Ormond Street, London, United Kingdom.

Received: November 10, 2022; **Published:** November 20, 2022

Abstract

Hereditary folate malabsorption is an uncommon, autosomal recessive disorder. It occurs due to functional mutation in a proton-coupled folate transporter in the intestine and choroid plexus resulting in impaired absorption and transport of folate. This in turn leads to variable hematological, immunological and neurological manifestations.

Here, we report the case of a Saudi boy who presented with vomiting, fever, and difficulty in breathing at the age of 3 months. On arrival, he was observed to be pale with tachypnea and tachycardia. On examination, no hepatosplenomegaly was found. Laboratory investigations revealed HB of 6.6 g/dl, mean corpuscular volume of 79, white blood cell count of 3.5 x 10^9/L, absolute neutrophils of 0.09 x 10^9/L, lymphocyte count of 2.5 x 10^9/L, platelets of 53 x 10^9/L and low serum folate of 3.4 nmol/L (normal 7 - 46). Molecular genetic analysis revealed a homozygous mutation in the *SLC46A1* gene for a sequence variant designated c.1277del, which is predicted to result in the amino acid deletion p.Phe426Serfs*14.

Keywords: *Hereditary; Folate; Malabsorption; Megaloblastic Anemia; Pancytopenia; Convulsion*

Introduction

Hereditary folate malabsorption (HFM) was first reported in 1961 by Luby., *et al* [1].

It is a rare inborn error of metabolism with only case reports from different ethnic groups reported in the literature [2].

HFM manifestations may not appear until few weeks to months after birth when gestational stores of folate deplete. They are non-specific clinical presentations including Diarrhea, poor weight gain and failure to thrive [3].

Neurologic manifestations including developmental delays, cognitive and behavioral disorders, motor impairment, seizures, and intracranial calcification have been described as associated with a low folate level in cerebrospinal fluid [4].

Laboratory findings include this parameter in addition to pancytopenia and lowered RBC count, and serum levels. In affected individuals, the serum folate level shows minimal or no increase in level after 4 hours, whereas in an unaffected individual, the level increases to at least 100 ng/ml [5-9].

Bone marrow analysis reveals evidence of megaloblastic anemia and dyserythropoiesis [5].

HFM patients may present immunodeficiency due to hypogammaglobinemia and T-cell dysfunction that contribute to unusual infection with an organism such as *Pneumocystis jirovecii* [5].

The mechanism of action of the Proton-Coupled Folate Transporter (PCFT) is to transport folate across the apical brush border membrane of the duodenum, jejunum, and choroid plexus. Functional mutation in the *SLC46A1* gene is the molecular basis of hereditary folate malabsorption.

Early diagnosis requires a high index of suspicion, especially when there is a family history of early childhood death with multisystem manifestations and poor response to oral folate therapy. Treatment of HFM requires lifelong folate replacement therapy in the form of intramuscular leucovorin [2].

Case Report

This 3-month-old boy was referred to our hospital after he presented with pallor and was found to have low hemoglobin of 6 grams/dl. He was born at term as the third child to consanguineous parents of Saudi Arabian descent after an uncomplicated pregnancy and delivery with a birth weight of 3750 grams.

The family history was remarkable for consanguineous parents with the 3-year-old healthy boy. One child had died at the age of 4 months after he was presented to another hospital with unexplained anemia and chest infection. On admission, vital signs included HR: 130; R/R 50 with respiratory distress; B.P 82/52; and temperature 36.6°C. His weight was 5.75 kg (10 - 25th percentile), height 67 cm (Above 97th percentile) and head circumference 40 cm (25th percentile). His general physical examination revealed no splenomegaly and the results of the neurological examination were normal. No dysmorphic features, skeletal anomalies, or skin pigmentation were observed. Hemoglobin was 9.6 g/dL, mean corpuscular volume (MCV) was 79 fL, mean corpuscular hemoglobin (MCH) was 28 pg, white blood cell count (WBC) was 3.9 × 10^9/L, neutrophil count was 0.09 × 10^9/L and platelet count was 21 × 10^9/L. The reticulocyte count was 0.5%. The peripheral blood smear revealed normocytic, hypochromic erythrocytes as well as severe neutropenia with normal WBC morphology.

Serum ferritin level was 700 ng/mL. Bone marrow aspirate was cellular with increased erythropoiesis with some dyserythropoietic and megaloblastic changes, adequate myelopoiesis and markedly reduced megakaryocytes.

Biochemical and endocrinal examination revealed normal liver and renal function, and normal serum electrolytes, calcium, phosphorous, glucose and parathyroid hormone levels. Blood amino acids and acylcarnitine profiles showed no abnormalities and urine organic acid level was unremarkable. Immunological workup revealed normal immunoglobulin G of 12.4 g/L (1.8 - 6), normal immunoglobulin M of 0.31 g/L (0.2 - 1.1) and normal immunoglobulin A of 0.41 g/L (0.05 - 0.80), and normal IgG Subclasses 1-4.

Other observations include lymphopenia, with a normal CD4:CD8 ratio; intact expression of MHC class II antigen on B-lymphocytes and 4% activated T-cells; and intact expression of CD18 and CD11a on granulocytes, monocytes, and lymphocytes.

Serum folate was < 3.4 nmoL/L (normal: 7 - 46.4 nmoL/L); serum vitamin B_{12} was 139 pmoL/L (normal 138 - 652 pmoL/L). The homocysteine level was 141 mcmoL/L and methyl malonic acid level was 0.31 nmol/ml (normal < 0.4).

Treatment began with oral administration of 1 mg/day folic acid. Serum folate and homocysteine levels did not change from previous results. HFM was suspected and molecular genetic analysis revealed a homozygous mutation in the *SLC46A1* gene for a sequence variant designated c.1277del, which was predicted to result in the deletion of the amino acid p.Phe426Serfs*14. Both parents are heterozygous for the same mutation.

Unfortunately, the child fell sick, with spiking high-grade fever and increased respiratory distress and desaturation. He was transferred to the Pediatrics Intensive Care Unit with a diagnosis of septic shock. He required inotropic and mechanical ventilation support. Chest radiograph showed extensive bilateral widespread airspace opacity.

He was treated with a high dose of trimethoprim/sulfamethoxazole but later on, the blood culture grew *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*. Unfortunately, his condition deteriorated rapidly and he died.

During hospitalization, he developed progressive hypotonia and convulsions. Cranial CT scan and magnetic resonance imaging (MRI) revealed no evidence of structural brain abnormality.

Discussion

Folates play a major role in the synthesis of the purine ring. Thus, it is not surprising that folate deficiency is associated with profound multi-systemic defects involving, in particular, hematopoiesis, the development of the central nervous system [6].

Research on their intestinal absorption revealed the mechanism of membrane transport of folates. The reduced folate carrier (RFC, or SLC19A1) has been identified as a major transporter of folates into normal systemic tissues [7].

Treatment aims to prevent hematological, immunologic and neurologic deficits and to optimize the cognitive development of child HFM.

In literature, it has been reported that the safest approach of treatment is intramuscular folate administration to normalize cerebrospinal fluid (CSF) folate levels [2].

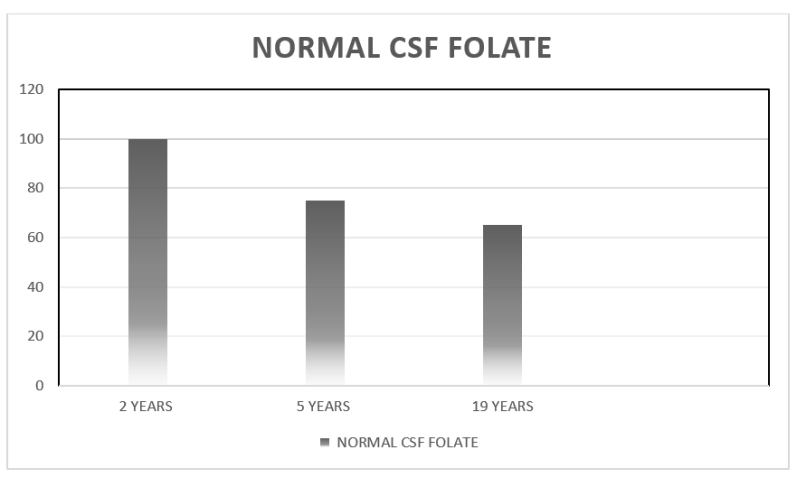
Oral folic acid assists in the complete recovery of anemia and immunological and gastrointestinal symptoms but neurological symptoms are unresponsive to oral folic acid. It's a difficult and challenging task to achieve the reversal of neurological manifestations.

Intramuscular folinic acid (5-methyl-tetra hydro folate) had a normalized CSF level of 5-methyl tetra hydro folate ranging 18 - 46 nmol/L and this level is sufficient to eradicate CNS disease [8].

The parental dose of 1.0 mg/day of 5- formyl THF is adequate to correct anemia, though the final dose will be based on CSF folate level that usually requires much higher doses. Therefore, it is crucial to periodically monitor CSF folate levels [9].

These observations are published in a case report from China. An approximately 18-month-old child who had recurrent convulsion refractory to double antiepileptic medication was cured of these conditions within one month of starting oral folinic acid treatment, but there was little improvement in psychomotor development and it was difficult to achieve normal CSF folate levels even at high oral doses [10].

The aim of this study is to achieve a near-normal CSF folate level that will require lumbar puncture and CSF folate monitoring. Normally, folate CSF levels are higher during infancy: levels are 100 nmol/L at birth to 2 years after birth that reduce to 75 nmol/L by 5 years and 65 nmol/L by 19 years of age [3].



Figure

Conclusion

HFM is a treatable cause of pancytopenia and neurological deterioration in children and should be suspected in any infant presented with non-specific symptoms and megaloblastic anemia.

Early diagnosis and appropriate treatment with 5-methyl tetrahydrofolate may offer life-changing therapy in the patient suffering from HFM. However, how frequent lumbar puncture should be performed and what appropriate dose helps in the prevention of CNS sequelae still need to be determined through research.

Bibliography

1. Luhby L., *et al*. "Relapsing megaloblastic anemia in an infant due to a specific defect in gastrointestinal absorption of folic acid". *American Journal of Diseases of Children* 102.4 (1961): 482.
2. Manea E., *et al*. "Role of intramuscular levofolinate administration in the treatment of hereditary folate malabsorption: report of three cases". *JIMD Reports* 39 (2017): 7-12.
3. Stover PJ., *et al*. "Folate nutrition and blood-brain barrier dysfunction". *Current Opinion in Biotechnology* 44 (2017): 146-152.
4. Zhang Y., *et al*. "Two cases with generalized intracranial calcification due to hereditary folate malabsorption and literature review". *Chinese Journal of Pediatrics* 54.12 (2016): 931-935.
5. Sofer Y., *et al*. "Neurological manifestations of folate transport defect: case report and review of the literature". *Journal of Child Neurology* 22.6 (2007): 783-786.
6. Geller J., *et al*. "Hereditary folate malabsorption: family report and review of the literature". *Medicine* 81.1 (2002): 51-68.
7. Qiu A., *et al*. "Identification of an intestinal folate transporter and the molecular basis for hereditary folate malabsorption". *Cell* 127.5 (2006): 917-928.

8. Pérez-Duenas B., *et al*. "Cerebral folate deficiency syndromes in childhood: clinical, analytical, and etiologic aspects". *Archives of Neurology* 68.5 (2011): 615-621.

9. Jebnoun S., *et al*. "A family study of congenital malabsorption of folate". *Journal of Inherited Metabolic Disease* 24.7 (2001): 749.

10. Tan J., *et al*. "Hereditary folate malabsorption with a novel mutation on *SLC46A1*: A case report". *Medicine* 96.50 (2017): e8712.

Volume 11 Issue 12 December 2022