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Case Report

Hereditary Folate Malabsorption presenting as neutropenic fever in a newborn from the first Palestinian family with the novel SLC46A1-mutation, A-case-report

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ABSTRACT

Introduction and importance: Hereditary Folate Malabsorption (HFM) is an extremely rare autosomal recessive disorder with in the existence of only 30 families world-wide. It presents with hematological, gastrointestinal, and neurological problems.

Case presentation: Three-month-old-boy with a familial history of HFM presented to the clinic due to persistent fatigue, yellowish discoloration, feeding refusal, and pancytopenia. The patient received 3 packs of Red Blood Cells (RBCs). Five days after received 3 packs of RBCs, the patient presented with a fever of 38.3 Celsius with pancytopenia. The patient had low level of all immunoglobulins. He was started on broad-spectrum antibiotics. Testing for the HFM's SLC46A1 gene mutation, was positive. The patient was started on Leucovorin and Respirm.

Clinical discussion: In this case, HFM presented as a neutropenic fever, hypoimmunoglobulinemia, low serum folate, elevated homocysteine, and a positive mutation on the SLC46A1. HFM has a wide-spectrum of presentations which includes hematological, neurological, immunological and gastrointestinal. Treatment involves the administration of folinic acid in either oral or intramuscular injections.

Conclusion: HFM can present as neutropenic fever. High index of suspension is to be maintained when the presenting symptoms of the patients vary over a large number of systems. Genetic counseling is needed for parents when both are carrying an autosomal recessive allele.

1. Introduction

Hereditary Folate Malabsorption (HFM) is a rare autosomal recessive disorder that affects the absorption of folate that is necessary to DNA synthesis [1,2]. The absorption process is mediated via the Protein Coupled Folate Transporter (PCFT) which is defective in HFM [2]. The PCFT is encoded on the SLC46A1 gene, and this gene is mostly affected via either frameshift mutations or stop-codon insertion [3]. Despite its rarity, HFM has a vast array of presentations that includes hematological, gastrointestinal, neurological, and immunological [4,5,and6]].

The severity of this disorder's symptoms makes the diagnosis high-stakes. In this manuscript, we present a case from the first documented Palestinian family with HFM that presented with neutropenic fever and hypoimmunoglobulinemia.

This case is in-line with SCARE 2020 criteria [7].

2. Case presentation

A-Three-month-old male patient presented to a pediatrician office by his family due to persistent fatigue, feeding refusal, and yellow discoloration of the baby that began after his bilateral inguinal hernia surgery at the age of two months and half. His past medical history is unremarkable. Complete Blood Count (CBC) showed a hemoglobin of 4.2 g/dl, platelets count of 61000/μl, and White blood Cells (WBCs) count of 2300 cmm. Physical examination showed a dehydrated, hypoactive and pale patient, with normal facial features, palate and ear positions. His chest has no abnormalities. Two scars at the inguinal region were noted. The rest of the examination was normal. The patient was then referred to

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the hospital. Patient had three units of packed red blood cells transfusion to treat his anemia and was then discharged to follow up at the hematology clinic.

Five days later, the patient presented to the pediatric emergency department with a fever of 38.3 Celsius, CBC showed a hemoglobin level of 6.4 g/dl, platelets count of 56000/μl, and WBCs of 2670 cmm. His Immunoglobulin assay showed the following results (unit of measurement mg/dL): IgA of 10, IgG 109, IgM 11. IV vancomycin and Meropenem were started.

A similar presentation was observed in his cousin, who had Hereditary Folate Malabsorption (HFM). Our patient's folate level (Fig. 2) was 4.49 nmol/l, while his homocysteine level (Fig. 3) was 28.3 mcmol/l. A test for HFM mutation was conducted that showed a homozygous mutation in the SLC46A1 gene c.1244del-(TCTACCC).

The patient was started on leucovorin 4 tabs twice daily and respirim 20mg twice daily, and the folate, homocysteine, CBC started to normalize. The following Figs. 1–5 show the progression of the patient's lab results over a 6-month-period following the diagnosis.

The patient is a product of consanguineous marriage, had 5 siblings, one of them died due to severe anemia at the age of 4 months. Two of the patient's cousins died at a young age from neutropenic fever accompanied by severe anemia. His paternal aunt's two children died from severe anemia as well.

The patient's family was referred to be tested for this mutation, and they were recommended to undergo genetic counseling prior to any future pregnancies.

Currently, the patient is doing well, gaining weight properly, and reaching his age-appropriate milestones. Currently follow ups are maintained monthly at the hematology clinic. Medications that the patient uses are well tolerable as the patient's family mentioned.

3. Clinical discussion

Folate, or vitamin B9, is a water soluble coenzyme that is essential in the synthesis of purines and thymidine, and in the conversion of homocysteine to methionine [1]. Absorption of folate from the apical brush membranes of the gastrointestinal tract as well as from the choroid plexus to the cerebro-spinal fluid is dependent on the presence of (PCFT) [2]. Loss of function mutations on the genes coding the PCFT can lead to a life threatening, yet treatable folate malabsorption. The mode of inheritance for HFM is autosomal recessive [2–4]. The estimated prevalence of HFM is unknown, but 30 families at least have been detected worldwide [5]. Our case is from the first family documented with this mutation in Palestine.

One of the detected mutations is on the SLC46A1 gene, and mostly includes either a frameshift mutation or insertion of the stop codon [3,4]. This gene is located at 17q11.2 [3]. Our case showed a homozygous mutation in the SLC46A1 gene c.1244del (TCTACCC) which led to the malfunctioning PCFT.

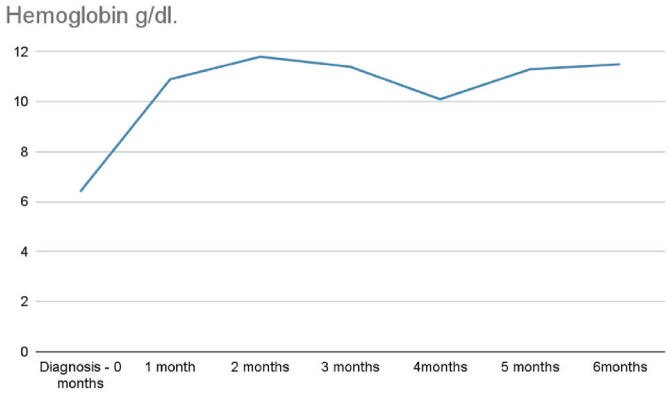

Fig. 1. Shows the patient's hemoglobin levels during a six-month treatment period.

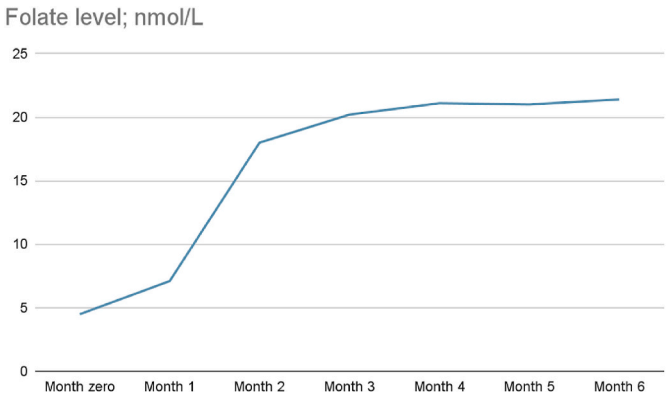

Fig. 2. Shows the patient's folate levels during a six-month treatment period.

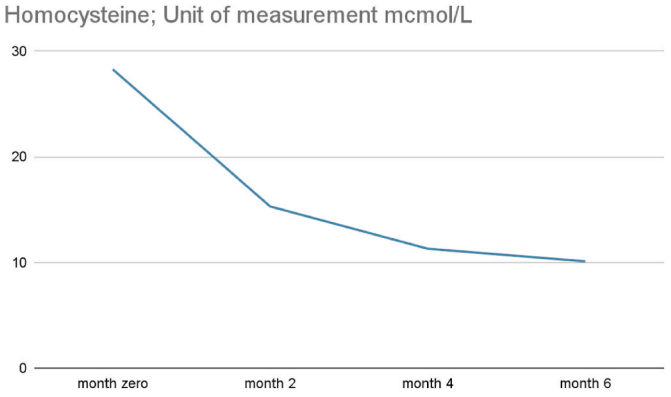

Fig. 3. Shows the patient's homocysteine levels during a six-month treatment period.

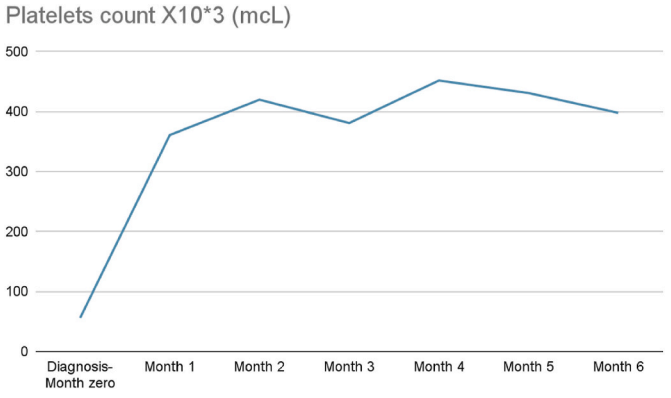

Fig. 4. Shows the patient's platelets levels during a six-month treatment period.

This multisystem disorder causes a wide array of manifestations that includes: failure to thrive, gastrointestinal symptoms in the form of diarrhea and oral ulcer, hematological disorders presenting as megaloblastic anemia, with accompanying thrombocytopenia and leukopenia (pancytopenia if accompanied by the later two), immunologically as hypoimmunoglobulinemia, and/or neurologically as seizures, motor impairment and developmental delay [4,6,8,9]. Our case showed pancytopenia, hypoimmunoglobulinemia, fatigue, feeding refusal and yellowish discoloration.

For patients with neurologically-predominant HFM, computed tomography, and magnetic resonance imaging can detect intracranial

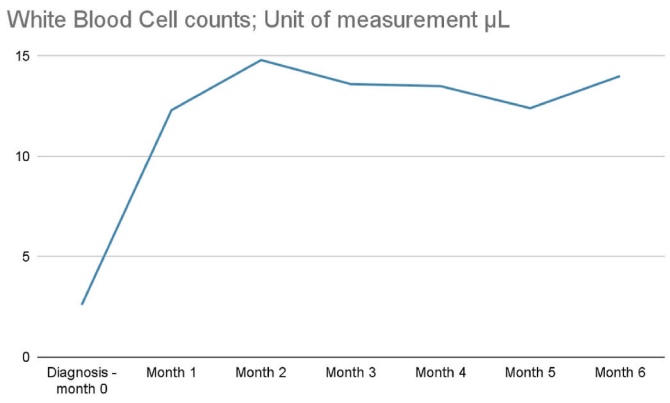

Fig. 5. Shows the patient's WBCs levels during a six-month treatment period.

calcifications [8,9]. Imaging was not done to our patient as no neurological symptoms were found at the presentation.

Diagnosis can be made based on the low serum folate levels, low Cerebro-Spinal Fluid (CSF) folate levels, elevated levels of homocysteine and the SLC46A1 mutation [3,8]. Our case's serum levels of folate were low and measured as 4.49 nmol/l, homocysteine levels were elevated and measured as 28.3 mcmol/l.

The treatment is to restore the normal folate levels in the blood and the CSF [1,9]. Folinic acid, or 5-methyltetrahydrofolate (5-MTHF, and can be administered in either high oral dose or Intramuscular form [11]. Charlotte M.A.Lubout study, demonstrated that the effect of the intramuscular folinic acid shows a better elevation in CSF concentration and thus better alleviation of the neurological symptoms [10].

The total amount of oral folinic acid should be 150–200 mg/day, while Intramuscular injections should be approximately 0.5–1.0 mg/day. Neurological symptoms do take a longer time to be reversed if it was possible [3].

4. Conclusions and take home messages

This case illustrates neutropenic fever as the presenting case HFM. Low folate levels, with elevated homocysteine while maintaining adequate folate intake must raise the index of suspicion for such a rare disorder. High-risk marriages with a family history of early children's death should receive genetic counseling.

The treatment is based on increasing the folate levels in the blood and the cerebrospinal fluid via folinic acid administration.

Ethical approval

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Author contribution

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Consent

Written informed consent was obtained from the patient's family for Publication of this case report and accompanying images. A copy of the informed consent is available for review by the Editor-in-Chief of this journal on request.

Research registration

- Name of the registry: N/A.
- Unique Identifying number or registration ID: N/A
- Hyperlink to your specific registration (must be publicly accessible and will be checked): N/A

Guarantor

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Declaration of competing interest

The authors declare no conflict of interest.

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