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Case Report

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Challenge of care in Pyridoxine refractory sideroblastic anaemia with SLC 25A38 mutation: a case report

Abstract

Congenital sideroblastic anaemia (CSA) is a genetic disease linked to several mutational profiles. Mutations in the SLC25A38 gene are responsible for the second most common form of CSA. This form is refractory to pyridoxine and characterised by dependence on blood transfusions. The clinical presentation is non-specific with a variety of iron overload complications. Medical treatment guidelines for CSA remain lacking, and Allogeneic hematopoietic stem cell transplantation (AHSCT) is currently the only proven curative therapy. We report a case of an 18-year-old patient who was diagnosed with pyridoxine-refractory anaemia at the age of two. A homozygous recessive mutation of the SLC 25A38 gene was found. The patient is receiving transfusions and iron chelation therapy. The AHSCT has not been performed for condition requirements.

Keywords: SLC25A38 gene mutation, sideroblastic anemia, transfusion, iron overload, ahsct

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Introduction

The congenital sideroblastic anemias (CSAs) are inherited diseases of mitochondrial dysfunction due to defects in heme biosynthesis, iron-sulfur cluster biogenesis, mitochondrial protein synthesis, or the synthesis of specific mitochondrial proteins involved in oxidative phosphorylation.[1] It's characterized by erythrocyte precursor cells overloaded with iron, inactive erythropoiesis, and elevated tissue iron levels.[2] The characteristic feature required for an initial sideroblastic anemia diagnosis, is the presence of ring sideroblasts in the bone marrow.[3] CSA associated with SLC25A38 mutations is a pyridoxine-refractory form which has very similar clinical course to that of thalassemia major and other red cell aplasia.[4] Conservative therapy includes regular red blood cell transfusion and iron chelation.[1] Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only effective and curative treatment.[5] Here, we report a pyridoxine-refractory sideroblastic anaemia in a patient with a homozygous mutation of the SLC 25A38 gene. Its treatment is based on regular transfusions and iron chelation. He has a haplo-identical HLA related donor and has not benefited from allo-ASCT.

Case report

In this study, we report a 18-year-old boy admitted to a haematological oncology department at the age of two with only severe mucocutaneous pallor. He was born full-term from an uncomplicated pregnancy to a first-degree consanguinity of parents. Birth weight of three kilograms with a height of fifthy centimeters. There was no history of neonatal suffering, ABO incompatibility, neonatal jaundice, or bleeding episodes. Family history was not significant for any hematological or chronic diseases, both parents are healthy and his other two siblings are healthy as well. Initial examination reveals mucocutaneous pallor with no jaundice, or apparent dysmorphic features. Genital examination was unremarkable. He did not have lymphadenopathy or organomegaly.

His laboratory finding at the time of initial diagnosis were as follow; complete blood count Hb 2.1 g/dL (11 -14 g/dL), MCV 61 fL (73-89 fL), MCHC 25 g/dL (32-36.5 g/dL), WBC 11.0x10³/µL (5 -15 x10³/µL), ANC 2.3×10³/µL (1.5 - 8×10³/µL) and platelet count 351×10³/µL (150-400×10³/µL). In peripheral blood smear, red blood cells demonstrate marked anisopoikylocytosis with clear microcytosis and a few ovalocytes. Hypogranulated neutrophils are present with giant forms of platelets. Direct, indirect coombs and antibody screening were negative. Hemoglobin electrophoresis was reported; Hb A1: 97.6% (95-98%), Hb A2: 2.4% (2-3%) and no fetal hemoglobin. Iron study showed; Iron: 36.4 mol/L (8.95 to 31.3 µmol/L), TIBC: 36µmol/L (30.6 to 90.3 µmol/L) and ferritine: 2343 µg/L (30-300 µg/L). Lead level was normal.

Bone marrow aspirates showed 69% erythroblastosis, with signs of dyserythropoiesis. Perl's staining showed 90% of ring sideroblasts. Bone marrow biopsy reveals normal cellularity with maturation disorder mainly of the erythroid lineage without any notable excess of blasts. CD34 negative (Figure 1).

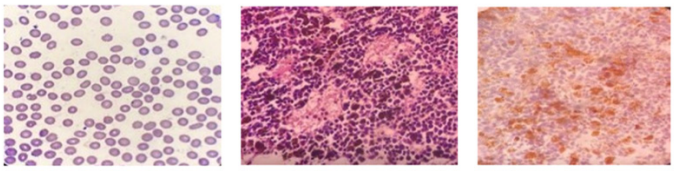

Figure 1 A/a peripheral blood smear (x50) shows dismorphic population of red blood cells as some having marked hypochromia while others are normochromic. B,C/ Bone marrow smear (40%); haemosiderin positive, CD34 negative

The patient was treated with pyridoxine without improvement: a pyridoxine-refractory CSA was confirmed. He continued to require blood transfusion every 2 to 3 weeks with iron chelation therapy. Over this period he developed complications due to iron overload such as hypothyroidism and short stature. On the other side, cardiac and liver assessments, during evolution, have never revealed any abnormalities.

His laboratory finding have been summarized in the following figures:

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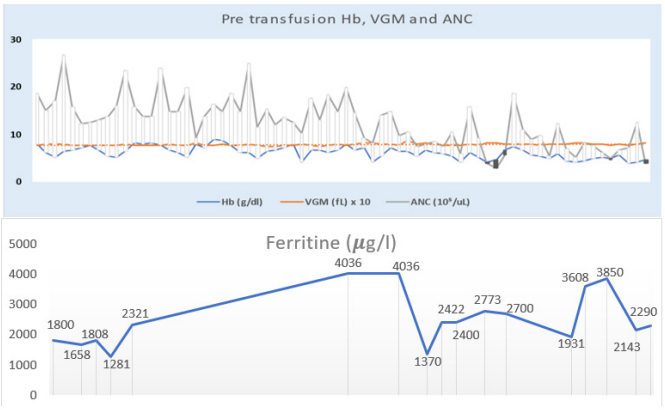

Due to his unusual presentation, his initial diagnosis was challenged and genetic study was carried out. Whole exome sequencing result revealed a homozygous and pathogenic variant in the SLC25A38 gene (p.Arg 278 Gly) and his diagnosis was revised to pyridoxine refractory sideroblastic anemia with SLC 25A38 mutation. The patient has undergone HLA typing revealing a haplo-identical donor and the allo-ASCT has not been carried out. He is currently on a transfusion protocol of one transfusion every three weeks with reinforced iron chelation.

Discussion

CSA is identified by ineffective erythropoiesis, low hepcidin levels, excess iron absorption, and secondary iron overload.[6] It is caused by mutations in genes involved in heme biosynthesis, mitochondrial protein synthesis, iron-sulfur (Fe-S) cluster transport or cluster biogenesis.[2] The most prevalent form of CSA is X-linked sideroblastic anemia (XLSA), caused by mutations in the erythroid-specific δ-aminolevulinate synthase (ALAS2), which is the first enzyme of the heme biosynthesis pathway in erythroid cells.[2] ALAS2 condenses glycine and succinyl-coenzyme A (CoA) to form 5-aminolevulinic acid (ALA) requiring pyridoxal 5′ -phosphate, the active form of vitamin B6.[2] Accordingly, many XLSA patients are responsive to supplementation by pyridoxine with substantial amelioration of anemia.[7] Mutations in the SLC25A38 gene are responsible for the severe type of pyridoxine-refractory CSA.[4] SLC25A38 is located on chromosome 3p22. It's a member of the Mitochondrial Solute Carrier Family 25 (SLC25), family of transporters.[8] SLC 25A38 is highly and selectively expressed in erythroblasts and encodes a mitochondrial carrier protein located in the inner mitochondrial membrane. It acts by exchanging glycine for 5 aminolevulinic acid or importing glycine into mitochondria.[9] Most of the variations reported affect protein levels (nonsense, splice site variations or frameshift) but three missense variations have also been explored (p.Arg187Pro, p.Arg134His, p.Gly130Glu).[10] Patients affected by CSA-SLC25A38 do not respond to folic acid nor to vitamin B6 treatment and glycine.[4] Recently, a relationship of SLC25A38 with purine metabolism was found.[11] In particular, the mitochondrial aspartate–glutamate carrier, together with SLC25A38,[12] are located in proximity to the purinosome to facilitate the channeling of aspartate and glycine, which are needed for purine synthesis.[11]

Risk factors include the presence of biallelic mutations in SLC25A38, profound anemia related to a complete loss-of-function mutation, need for iron chelation therapy, alloimmunization by frequent blood transfusions, and management of potential infections.[13]

The SLC 25A38 CSA phenotype is generally represented by severe microcytic, hypochromic sideroblastic anaemia from the first year after birth, not responding to pyridoxine treatment.[14] Diagnosis of CSA is made by bone marrow aspiration where ring sideroblasts generally constituted >15% of nucleated erythroblasts.[4] A genetic investigation is essential to look for an inherited disease.[15] SLC 25A38 is found and the patient is dependent on blood transfusions as a conservative therapy.[14]

The differential diagnosis are presented by genetic causes of CSA (ALAS2 mutations, XLSA..) and the acquired sideroblastic anemias (Myelodysplastic syndromes, Drug or toxin-induced sideroblastic anemia..).[15] Over the years and following recurrent transfusions, the patient develops multivisceral complications due to iron overload, including the heart (cardiomyopathy), liver (hepatic fibrosis), thyroid, gonads and many other organs. This has a direct impact on morbidity and mortality rate.[16] Patients with SLC 25A38 CSA have an absolute indication for iron chelation such as deferoxamine, deferasirox, and deferiprone, to minimise damage caused by iron overload.[2] Allo-HSCT provides a curative option in SLC25A38 CSA, and may be proposed to young patients with appropriate donors prior to the development of complications of chronic transfusions such as alloimmunization and hemosiderosis.[4] Luspatercept could be an alternative therapy for CSA patients, enhancing iron overload to some extent, reducing transfusion dependence, and even becoming a potential treatment for other diseases related to ineffective erythropoiesis.[17] Luspatercept increased chromatin accessibility of GATA-1, a major regulator of erythropoietic transcription, to promote red lineage maturation.[18]

Patients with SLC 25A38 CSA face a considerable burden throughout their lives, which significantly compromises their quality of life. The combination of severe anaemia, transfusion dependence, and iron overload create profound physical, social and financial challenges. Haematopoietic stem cell transplantation (HSCT) offers a significant improvement in quality of life, but it also carries significant risks.[17] In our case, the interest of this article can be summed up in the following questions: rediscuss allo-ASCT? start Luspatercept despite the lack of randomised studies on its efficacy in SLC 25A38 CSA? keep the transfusion programme and manage the complications of iron overload in time?

Our patient did not receive luspatercept due to a lack of funds and resources. He followed his transfusion programme with iron chelation at an effective and tolerable dose.

Conclusion

Even though it is uncommon and rare desease, SLC25A38 CSA is a clinically distinctive entity associated with transfusion-dependent microcytic, hypochromic sideroblastic anemia from an early age. This phenotype is presently managed in a similar way to other severe anemias, with chronic transfusion and iron chelation. A definitive therapy, HSCT is increasingly indicated and must be preceded by an agressive iron chelation. Characterization of SLC 25A38 CSA and evidence of successful HSCT may leads clinicians to identify affected individuals with CSA and initiate effective treatment on time.

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None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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