LETTER TO THE EDITOR
Thiamine Responsive Megaloblastic Anemia With a Novel SLC19A2 Mutation Presenting With Myeloid Maturational Arrest

To the Editor: Thiamine responsive megaloblastic anemia (TRMA) syndrome is caused by the deficiency of thiamine transporter protein is a triad of diabetes mellitus, anemia, and deafness [1]. The only gene known to be associated with TRMA is SLC19A2, which encodes the high-affinity thiamine transporter [2]. A total of 28 mutations in the SLC19A2 gene have been reported in 70 patients [3]. We report a novel in-frame deletion mutation (p. Gly335del).

A 5-year-old female was the daughter of a consanguineous marriage, presented with history of pallor since the age of 2 years. Her first complete blood count (CBC) at 2 years of age showed hemoglobin (Hb) 4 g/dl, total leucocyte count (TLC) 3.9 × 10^9/L with 21% neutrophils, platelet 15 × 10^9/L and mean corpuscular volume 107 fl. Her Hb improved to 11.6 g/dl after therapy with oral iron, vitamin B12, and folic acid. A year later, the Hb again dropped to 4 g/dl after discontinuation of iron and vitamin B12. She was diagnosed with insulin dependent diabetes mellitus, deafness, and decreased visual acuity. There was no family history of similar illnesses. Her weight was 15 kg (<5th percentile for age) and height was 95 cm (<5th percentile for age). On examination, she had pallor, sensineural deafness, and an ejection systolic murmur.

Her bone marrow showed myeloid maturation arrest with a paucity of erythroid cells and megakaryocytes (Fig. 1). The parents refused a repeat marrow examination. Echocardiography showed small patent ductus arteriosus with left to right shunt. Audiometry confirmed bilateral profound hearing loss. Fundi showed pale discs with macular degeneration. With the above constellation of clinical and laboratory findings, a diagnosis of TRMA was made.

Sequence analysis of coding and flanking intronic region of the SLC19A2 gene revealed a homozygous mutation of SLC19A2, showing a deletion of three nucleotides (c.1002_1004delTGG) which results in an in-frame single amino acid deletion (p. Gly335del; Fig. 2). Both parents were heterozygous carriers for this mutation. She was started on thiamine at 75 mg orally daily and her insulin therapy was continued. A month later, her CBC showed Hb 11.1 g/dl, TLC 7.4 × 10^9/L and platelet 225 × 10^9/L. She has been off insulin and on thiamine for the last 24 months and maintains a mean Hb of 11.6 g/dl (11.1–12 g/dl).

The combination of megaloblastic finding and ringed sideroblasts characterizes TRMA. Some patients do show dysplastic changes in bone marrow [4]. We could not stain for ringed sideroblasts due to non-availability of unstained slide. In our case, megaloblastic change was not apparent. However, dysgranulopoiesis was observed in the form of hypogranularity and hypolobation in the granulocytic cells. A similar picture has been described in a murine model after disruption of the SLC19A2 gene [5]. Treatment of TRMA involves lifelong use of thiamine at a dose of 25–75 mg/day. Anemia can recur when thiamine is withdrawn as seen in our case.

The presence of megaloblastic anemia and diabetes mellitus should raise the diagnosis of TRMA. Molecular diagnosis can be definitive when bone marrow findings are not classical. Thiamine is the cornerstone of therapy.

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Fig. 2. Electropherograms showing the p.Gly335del mutation in the SLC19A2 gene. The deletion of three nucleotides (c.1002_1004delTGG) results in the deletion of a Glycine residue at codon 335 (p.Gly335del). Sequence traces for a normal control, the proband, and the unaffected parents are provided. Genomic DNA was extracted from peripheral leukocytes using standard procedures and the six coding exons of SLC19A2 were PCR amplified and sequenced (primers and conditions available upon request). Sequences were compared with the published template (accession no. NM_006996.2) using Mutation Surveyor (version 3.95; SoftGenetics, PA, USA).

REFERENCES


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