Thiamine-responsive megaloblastic anemia: early diagnosis may be effective in preventing deafness

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Thiamine-responsive megaloblastic anemia syndrome is an autosomal recessive disorder characterized by diabetes mellitus, megaloblastic anemia and sensorineural hearing loss. Mutations in the SLC19A2 gene, encoding a high-affinity thiamine transporter protein, THTR-1, are responsible for the clinical features associated with thiamine-responsive megaloblastic anemia syndrome in which treatment with pharmacological doses of thiamine correct the megaloblastic anemia and diabetes mellitus. The anemia can recur when thiamine is withdrawn. Thiamine may be effective in preventing deafness if started before two months. Our patient was found homozygous for a mutation, 242insA, in the nucleic acid sequence of exon B, with insertion of an adenine introducing a stop codon at codon 52 in the high-affinity thiamine transporter gene, SLC19A2, on chromosome 1q23.3.

***Key words:** thiamine-responsive megaloblastic anemia, diabetes mellitus, deafness.*

Thiamine-responsive megaloblastic anemia (TRMA; OMIM 249270) syndrome is an autosomal recessive disorder characterized by diabetes mellitus, megaloblastic anemia, and progressive sensorineural hearing loss. The syndrome was first described by Rogers et al.[1] In addition to the cardinal components, other findings reported in association with TRMA syndrome include congenital heart disease, arrhythmias, cardiomyopathy, retinal degeneration, optic atrophy, situs inversus, aminoaciduria, and stroke[2-4]. Recently, TRMA syndrome locus was localized to a 1.4 cM region on chromosome 1q23.3, and mutations were found in SLC19A2, which encodes for a high-affinity thiamine transporter protein (THTR-1)[5-7]. We report a now 32-month-old female patient with TRMA syndrome who was diagnosed early before development of diabetes mellitus or deafness.

Case Report

A one-month-old female patient presented with vomiting, pallor and petechia. She was born as the third child of a consanguineous family via normal delivery after an uneventful pregnancy. The parents and a female sibling were healthy. An older brother died at three months of age before a well-defined diagnosis, whose laboratory studies revealed a megaloblastic anemia. Our patient's physical examination revealed tachypnea, tachycardia, and hepatomegaly. Laboratory analyses showed bicytopenia with a hemoglobin (Hb) level of 6.2 g/dl, hematocrit (Hct) 19.7%, mean corpuscular volume (MCV) 110 fL, white blood cell count (WBC) 5200/mm^3, absolute neutrophil count 900/mm^3, and platelets 21000/mm^3. The reticulocyte count was 1%. The peripheral blood smear revealed macrocytic cells with no hemolytic findings. The bone marrow aspirate showed a normocellular bone marrow with increased megaloblastic erythropoiesis and megakaryopoiesis. Levels of serum folate and vitamin B_{12} were found as 10 ng/ml (N: 3-17) and 450 pg/ml (N: 180-900), respectively. Serum glucose, creatinine, urea, electrolytes, and transaminases were found to be in normal ranges. Echocardiography confirmed the findings of cardiac failure. Otoacoustic emission test was normal.

The genetic evaluation determined the patient to be homozygous for a mutation, 242insA, in the nucleic acid sequence of exon B, with insertion of an adenine introducing a stop codon at codon 52 in the high-affinity thiamine transporter gene, SLC19A2, on chromosome 1q23.3. The father was heterozygous for the same mutation (performed by Ellis J. Neufeld, Division of Hematology, Children's Hospital, Boston). Mutation analysis of the mother could not be performed.

The patient was transfused with red blood cell and platelet suspensions. Despite transfusions, the patient was still bicytopenic until 100 mg intravenous thiamine was given on the 15th day of hospitalization. After administration of thiamine, the levels of Hb and platelets began to elevate. Three weeks after thiamine therapy, anemia ameliorated completely and Hb concentration increased to 10 g/dl, Hct to 30%, and platelets to 469000/mm^3, and MCV decreased to 91.6 fL. The follow-up of D-dimer level was 50 ng/ml. After one year of oral thiamine supplementation, the Hb concentration was 12.5 g/dl, Hct was 35.9%, platelets were 298000/mm^3, and MCV was 86.2 fL. Otoacoustic emission test, which was repeated at 15 and 30 months of age, was normal. She is now 32 months old and no diabetes mellitus, deafness, or cardiac or eye involvement has been established during the follow-up period to date.

Discussion

The human TRMA gene, SLC19A2, encodes a 497 amino acid protein with 12 putative transmembrane domains that exhibits high-affinity thiamine transport activity. The gene is expressed in a wide range of human tissues including bone marrow, pancreas, brain, retina, heart, skeletal muscle, kidney, liver, lung, small intestine, colon, placenta, lymphocytes, and fibroblasts[6,7]. Thiamine uptake is thought to occur via two pathways: non-linear, active transport by a saturable, high-affinity carrier and passive uptake by a low-affinity carrier[8-10]. Due to mutations in SLC19A2, which have been identified in individuals with TRMA syndrome, a defect in the high affinity thiamine transporter occurs. Thus, at physiological concentrations (food as the only source), thiamine is not transported normally and intracellular thiamine deficiency leads to decreased activity of enzymes associated with thiamine pyrophosphate. Stagg et al.[11] demonstrated that a low thiamine concentration may cause cell death by apoptosis. Oishi et al.[12] showed that targeted disruption of SLC19A2 in mice results in reduced insulin secretion, which was increased with thiamine treatment. Various mutations have been observed in TRMA patients. The mutation identified in this case, 242insA, was previously described[13]. Autosomal recessive inheritance of this disease and widespread consanguinity in the Turkish population can explain the relatively increased frequency of cases in Turkey.

Diabetes mellitus, a component of the triad of TRMA, is due to a non-immune, insulin-deficient mechanism that responds to oral thiamine hydrochloride therapy. However, long-term follow-up of patients shows deterioration, and thiamine supplements become ineffective for the control of diabetes[14-16]. It is thought that the physiological activity of puberty may exceed β-cell capacity, leading to apoptosis of the remaining β-cells[14]. This may explain the requirement of insulin or a hypoglycemic agent at puberty. In contrast to this theory, a paper in the literature mentions reduction of insulin requirement with thiamine therapy during puberty[17]. In our case, thiamine was started before two months of age. During the short follow-up period, no diabetes mellitus or deafness was detected. According to our observations, despite the short follow-up period in our case, early thiamine therapy at two months age could be effective in preventing diabetes mellitus and deafness.

Most of the children with TRMA syndrome can be presented with profound anemia, which occurs between infancy and adolescence. The classical hematological finding is megaloblastic anemia with erythroblasts, which is often complicated with ringed sideroblasts. The megaloblastic and sideroblastic anemia can be explained by the role of thiamine in DNA metabolism and heme synthesis[17,18]. Thrombocytopenia and/or neutropenia sometimes accompany the megaloblastic anemia, as seen in our patient. The anemia is improved with pharmacologic doses of thiamine (25-75 mg/day) and when thiamine is withdrawn, anemia usually relapses.

Progressive sensorineural deafness is irreversible and may not be avoided with thiamine treatment. Patients usually had profound high frequency

sensorineural deafness, and hearing loss was demonstrated during infancy. Liberman et al.[19] demonstrated that deletion of SLC19A2 caused selective inner hair cell loss of the cochlea because of deficiency of the high affinity thiamine transporter. Because of the early diagnosis in our patient, deafness was not detected at the time of diagnosis or in the follow-up period. Otoacoustic emission test, repeated at 15 and 30 months of age, was also normal.

In addition to the characteristic triad, optic atrophy, retinal dystrophy, situs inversus, stroke, and cardiac abnormalities were also described in TRMA patients[20]. Treatment with thiamine therapy provides cardiac improvement, which suggests that SLC19A2 mutation has a role in the pathogenesis of cardiomyopathy.

A sibling of the patient died of an unknown disease manifested with megaloblastic anemia. The presence of megaloblastic anemia and thrombocytopenia but not diabetes mellitus and deafness of the case was attributed to early suspicion of the disease and onset of treatment. The presence of consanguinity and heterozygosity of the father for the mutation helped in reaching the diagnosis.

In conclusion, TRMA is a rare genetic disease that can result in death in a short period if not diagnosed. The possibility of this disease is high in cases that refer with megaloblastic anemia, especially in infancy, and those with a family history. Thiamine may be effective in preventing deafness if started before two months. Whether or not sensorineural deafness will manifest remains a mystery in this child, but this report will help to enlighten the unresolved points regarding the initiation period of thiamine therapy.

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