Infantile-onset thiamine responsive megaloblastic anemia syndrome with SLC19A2 mutation: a case report

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ABSTRACT
Background. Thiamine-responsive megaloblastic anemia syndrome (TRMA), also known as Rogers syndrome, is characterized by megaloblastic anemia, sensorineural hearing loss, and diabetes mellitus. Disturbances of the thiamine transport into the cells results from homozygous or compound heterozygous mutations in the SLC19A2 gene.

Case presentation. We report a girl which presented with sensorineural deafness treated with a hearing prosthesis, insulin requiring diabetes, macrocytic anemia, treated with thiamine (100 mg/day). Hemoglobin level improved to 12.1 g/dl after dose of thiamine therapy increased up to 200 mg/day.

Conclusion. Patients with TRMA must be evaluated for megaloblastic anemia, sensorineural hearing loss, and diabetes mellitus. They must be followed for response of hematologic and diabetic after thiamine therapy. It should be kept in mind that dose of thiamine therapy may be increased according to the clinical response. Genetic counseling should be given.

Key words: diabetes mellitus; hearing loss, sensorineural; anemia, megaloblastic; thiamine, treatment.

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INTRODUCTION
Thiamine-responsive megaloblastic anemia syndrome (TRMA) was first described by Porter et al. in 1969. TRMA, also known as Rogers syndrome, is characterized by three main clinical components: diabetes mellitus, megaloblastic anemia, and sensorineural hearing loss. It is an autosomal recessive disease.1 The disease has been identified in approximately 40 families so far. This syndrome is very rare except in consanguineous marriages and isolated communities.2 The syndrome is due to genetic defect of a thiamine transporter protein in bone marrow, a subset of cochlear cells, and pancreatic beta cells encoded by SLC19A2, located on the long arm of chromosome 1.2,3 SLC19A2 mutations result in thiamine deficiency in pancreatic beta cells and other affected tissues, leading to defects in cellular metabolism, cell stress, and apoptosis.2 As a result, thiamine pyrophosphate level in erythrocytes of cases with TRMA is low. Using mouse models, it has been recently demonstrated that THTR1 along with THTR2 are involved in carrier-mediated thiamine uptake by pancreatic acinar cells.4

It is known that proteins responsible for the intracellular delivery of thiamine are necessary for effective use of thiamine in various tissues. Diabetes mellitus develops when thiamine transfer in pancreatic beta cells is disordered. Diabetes mellitus may appear at any time between infancy and adolescence. Autoantibodies typical of type 1 diabetes are negative and release of insulin is primarily defective. The effect of thiamine treatment on the course of diabetes is controversial. In a few cases, it was reported that insulin requirements decreased with thiamine treatment.2,3,5 It is thought that megaloblastic anemia, another classic sign of the syndrome, occurs as a result of intracellular thiamine deficiency due to a defective nucleic acid synthesis.6 Megaloblastic anemia starts at almost the same age when signs of hyperglycemia occur.2 Anemia improves with pharmacological doses of
thiamine (25-75 mg/day), but mean corpuscular volume is high throughout life. Suspension of treatment results in recurrence of anemia. Furthermore, unresponsiveness to thiamine may develop during treatment. Progressive hearing loss is one of the main findings of the syndrome and is known to be irreversible. However, most of the TRMA cases reported to date have been diagnosed after infancy and the hearing loss was already present in many at the time of diagnosis. In addition to the main components, other findings including thrombocytopenia, pancytopenia, optic atrophy, retinal degeneration, situs inversus, cardiomyopathy, arrhythmias, congenital heart defects, and stroke have been reported in association with TRMA syndrome.

Here, we present an infant with TRMA to describe clinical characteristics of this rare disease and beneficial effects of thiamine on particularly hematologic parameters.

Case presentation
A female patient first presented with pallor at the age of 3 months. She was born at term with a birth weight of 2700 g. The parents were first-degree cousins. On physical examination, weight was 6850 g (97 percentile) and length 55 cm (3-10 percentile). Tachypnea and tachycardia were evident. Ophthalmologic and cardiologic examinations were normal. Hearing loss was detected.

Laboratory results showed macrocytic anemia and neutropenia (hemoglobin 4.2 g/dl, mean corpuscular volume 106 fl, platelets 157 000/mm³, leukocytes 5830/mm³, absolute neutrophil count 190/mm³). Folate and vitamin B12 levels were normal. Bone marrow aspiration was normocellular and megaloblastic changes were observed. The percentage of sideroblasts was 12% and, subsequently, thiamine at a dose of 100 mg/day was started. Simultaneously, hyperglycemia was present (glucose 400 mg/dl, HbA1c 8.4%). Insulin treatment was started. Islet cell, insulin, and glutamic acid decarboxylase autoantibodies were negative. Cochlear implant was used owing to sensorineural hearing loss.

Hemoglobin levels increased to 13 g/dl with 100 mg/day thiamine treatment. However, insulin requirement continued and doses up to 0.6 U/kg/day was needed. During follow-up, the highest level of HbA1c was 8.4%.

Hemoglobin level decreased to 9 g/dl in the fourth year during the therapy of thiamine (100 mg/day). The dose was increased to 200 mg/day. One month later, hemoglobin level improved to 12.1 g/dl. However, no change in the insulin doses was needed.

Sequencing analysis of the SLC19A2 gene identified a known homozygous mutation c.242_243insA (p.Y81*) in exon 2. Because TRMA is an autosomal recessive inherited disorder, our patient’s parents received genetic counseling despite of not having another case relative with same disease.

DISCUSSION
Our case had presented with pallor, tachypnea and tachycardia when she was 3 months old. Megaloblastic anemia with 12% sideroblasts, hyperglycemia and hearing loss was detected and TRMA was considered. While TRMA is a kind of the sideroblastic anemias, it is separated from other sideroblastic anemias due to its megaloblastic nature. Megaloblastic anemia usually begins in early childhood. Megaloblastic changes and the presence of more than 10% sideroblasts in the bone marrow aspiration leads to the diagnosis of TRMA.

Beshlawi et al. reported that response to thiamine was variable, hemoglobin level can reach normal values and insulin dose decreased after one month with thiamine therapy (100 mg/day). Two patients were stopped using insulin after thiamine dose reached 200 mg/day. Alzahrani et al. informed that high dose thiamine therapy in TRMA patients can improve the disease symptoms, correct the anemia and reduce or discontinue the need for exogenous insulin. Our patient was diagnosed non-autoimmune diabetes mellitus at age of 3 months. Diabetes mellitus in TRMA is a non-autoimmune disorder due to a defect of insulin secretion. Although, it has been reported that dose of insulin can be reduced during thiamin treatment; insulin dose of our case did not decline during the 4 year follow-up. Blood glucose of the patient was regulated by 0.4 U/kg/day of insulin dose. Unlike previous reported cases, insulin requirement of our patient did not decrease during this process, notwithstanding dose of thiamine was increased to 200 mg/day.

The patients with TRMA are usually published as a case report, in the literature. Anemia improves with pharmacological doses of thiamine (25-75 mg/day), but mean corpuscular volume is high throughout life. Suspension of treatment results in recurrence of anemia. Furthermore, unresponsiveness to thiamine may develop during treatment.
reported that the clinical condition of a 3-year-old male patient markedly improved several days after the initiation of daily supplementation with thiamine 100 mg.\textsuperscript{13} In our case, anemia initially improved with 100 mg/day thiamine treatment. Hemoglobin level increased to 13 g/dl from 7 g/dl after 100 mg/day thiamine treatment. But anemia worsened in fourth year follow-up by virtue of non-response to the 100 mg/day thiamine treatment. Hemoglobin level decreased to 9 g/dl. Dose of thiamine was increased up to 200 mg/day. After 4 weeks, hemoglobin level increased to 12 g/dl and no side effects of thiamine drug was seen during the 200 mg/day treatment.

Hearing loss was detected at age of 3 months. Cochlear implant was inserted owing to hearing loss despite of thiamine treatment. Although, it is not clear how that sensorineural hearing loss develops in the first stages of life. In experimental animals was found a dysfunction of hair cells in the inner ear. Hearing loss is progressive, irreversible and unresponsive to thiamine treatment.\textsuperscript{14} On the contrary, Önal et al., reported a female case who had not hearing loss at diagnosis and she did not developed hearing loss during follow-up after early thiamine treatment (<2 months).\textsuperscript{15}

TRMA is caused by mutations in \textit{SLC19A2} gene with six exons which reside on chromosome 1q23.3. Although most common mutations are in exon 2, mutations in the exons 1, 3, and 4 are also known.\textsuperscript{16} In our case report, sequencing analysis of the \textit{SLC19A2} gene identified a known homozygous mutation c.242_243insA (p.Y81*) in exon 2.

In conclusion, TRMA is a rare disorder which typically has a clinical triad: megaloblastic anemia, sensorineural hearing loss and diabetes mellitus. Genetic analysis confirms the diagnosis of TRMA. Patients with TRMA must be evaluated for megaloblastic anemia, sensorineural hearing loss, and diabetes mellitus. They must be followed for response of anemia and diabetic after thiamine therapy. Hematologic values are especially improved during thiamine treatment but the dose of thiamine may be increased according to the clinical response. Genetic counseling should be given.

\textbf{REFERENCES}