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CASE REPORT
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Novel Homozygous Variant in the SLC19A2 Gene Causing Thiamine Responsive Megaloblastic Anemia Syndrome: A Disease to Be Considered in Diabetes Clinics

ABSTRACT

Thiamine-responsive megaloblastic anemia (TRMA) syndrome is a rare syndrome with an autosomal recessive manner that develops due to a mutation in the SLC19A2gene. SLC19A2 encodes the high-affinity thiamine transport protein 1 (THTR1), which mediates the active transport of thiamine. The classical triad consists of megaloblastic anemia, sensorineural hearing loss, and non-autoimmune diabetes. Apart from this, ophthalmological, cardiological, and neurological findings have also been described. We present a case of thiamine-responsive megaloblastic anemia (TRMA) syndrome diagnosed in an adult with a novel mutation in the SLC19A2 gene. This 38-year-old female patient, a third child from a consanguineous marriage, presented with the classic TRMA triad: sensorineural deafness, megaloblastic anemia, and autoimmune diabetes. Starting thiamine treatment is essential in reducing the development/progression of some complications; it is crucial to increase awareness of the disease and make an early diagnosis.

Keywords: Diabetes mellitus, neonatal diabetes, Rogers' syndrome, megaloblastic anemia, sensorineural deafness, thiamine-responsive megaloblastic anemia syndrome, thiamine

Introduction

Porter et al first described thiamine-dependent megaloblastic anemia (TRMA; OMIM 249270), or Rogers syndrome, in 1969.[1] They hypothesized that the cause of anemia was an abnormality in vitamin B1 metabolism, which was confirmed by the correction of anemia after oral vitamin B1 supplementation. The syndrome is an autosomal recessive inherited disorder characterized by a triad of megaloblastic anemia, sensorineural deafness, and non-type 1 diabetes mellitus. It is caused by a gene mutation in SLC19A2 (solute carrier family 19 member 2) that encodes the thiamine transporter protein.[2] The high-affinity thiamine transporter (THTR-1) is responsible for the transmembrane transport of vitamin B1. Thiamine is an essential cofactor of several enzyme complexes participating in multiple metabolic processes.[3] THTR-1 is the only known thiamine transporter in the bone marrow, pancreatic beta cells, and a subgroup of cochlear cells.[4] Its defect causes extramedullary damage and anemia. Sometimes, the syndrome presents with an atypical clinical picture, and due to its rarity, the lack of understanding of the syndrome may be the reason for the delay in diagnosis and treatment. Most of the publications reporting this syndrome were made in the form of case reports. There are 183 cases from 138 families described in the literature. Although sporadic cases are distributed across 33 countries of origin, most cases were reported from the Middle East, South Asia, and the northern Mediterranean. Of the 50 patients published as case reports, 14 (28%) were Turkish.

Genetic analyses confirmed the diagnosis of TRMA in 155 of 183 patients.[5] Although sporadic cases are distributed across 33 countries of origin, most cases were reported from the Middle East (37.7%), South Asia (21.9%), and the northern Mediterranean (17.0%). In this study, 61.8% of the patients described in the literature were born into consanguineous marriages. Here, we present a 38-year-old Turkish woman with the clinical triad of TRMA with novel compound homozygous variants in SLC19A2.

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Case Report

A 38-year-old female patient, a third child of a consanguineous marriage, applied for the control of her diabetes. There was no pathological feature in the prenatal, natal, or postnatal history. At the time of application, she used insulin glulisine and insulin glargine 300 IU/mL. The patient had a history of multiple hospitalizations for blood glucose regulation because of brittle diabetes. It was learned that bilateral sensorineural hearing loss developed at 11 years old. She had 3 sisters and 1 brother. The patient's 1 sister, 2 uncles, and her grandfather had a similar history of hearing loss at a young age. All her siblings and she had been using glasses since childhood due to myopia. Her sister and 1 uncle died due to myocardial infarction when they were around 18 years old. The patient herself had 3 children. The first child was born prematurely, alive and healthy. The second child died due to hyperglycemia when he was 3 months old. The third child was also being followed up with a diagnosis of neonatal hyperglycemia. Additionally, she had a history of using metoprolol due to an arrhythmia attack. In her blood tests, fasting plasma glucose was 142 mg/dL, HbA1c level was 9.8% (84 mmol/mol), fasting C-peptide level was 1.31 ng/mL, and postprandial plasma glucose was 332 mg/dL. Kidney, liver, and thyroid function tests and urinalysis were normal. The lipid profile was typical. Her examinations revealed concomitant megaloblastic anemia. B12 and folic acid levels were normal. There was normochromic macrocytosis and anisocytosis in her peripheral blood smear. A direct antihuman globulin test was negative. Antiglutamic acid decarboxylase antibody (anti-GAD), islet cell antibody, and anti-insulin antibody levels were measured. Anti-GAD antibody was detected positive at a high titer. A diagnosis of non-proliferative retinopathy was made. Optical coherence tomography angiography (OCT-A) revealed a defect in the outer plexiform layer. Electromyography (EMG) was performed due to diabetic neuropathy symptoms. A diagnosis of bilateral sensorimotor polyneuropathy was made. Alpha lipoic acid treatment was started. The audiogram was suggestive of a profound bilateral sensorineural type of hearing loss. She had no symptoms or signs suggestive of diabetes insipidus. Self-glucose monitoring was not within the target range. Her electrocardiography was in normal sinus rhythm. Due to a previous history of suspected arrhythmia and family history, rhythm Holter and echocardiography were performed. No pathology was detected. Thyroid autoantibodies and ultrasonography were found to be compatible with autoimmune thyroiditis. Given these findings, we consulted the patient with the genetics department.

MAIN POINTS

- The triad of thiamine-dependent megaloblastic anemia or Rogers syndrome consists of megaloblastic anemia, progressive sensorineural deafness, and type 1 diabetes mellitus.
- A new genetic mutation has been identified in the SLC19A2 gene (NM_006996.3), which is responsible for thiamine-responsive megaloblastic anemia syndrome.
- Sensorineural deafness, megaloblastic anemia, and an uncommon diagnosis of autoimmune diabetes are all present in the patient. She demonstrated a partial response to thiamine treatment in terms of glycemic control during the follow-up.

Clinical exome sequencing (CES) identified a novel homozygous variant in the case's SLC19A2 gene (NM_006996.3). CES was performed on an Illumina NextSeq 2000 platform (Illumina Inc., San Diego, California, USA). CES data were analyzed using the Sophia DDM software (Sophia Genetics, Saint-Sulpice, Switzerland). The genomic variants identified were evaluated using Ensembl Genome Browser. Variants were classified in accordance with the American College of Medical Genetics and Genomics (ACMG) guidelines.

The variant was a nucleotide deletion in exon 2 (c.361_369del: p.Leu121_Ala123del). The deletion is not included in the Genome Aggregation Database (gnomAD). The variant changes protein length as a result of an in-frame deletion. Mutation Taster predicts the variant as disease-causing. The phenotype of the patient, who presented with diabetes, hearing loss, megaloblastic anemia, and neurological disorders, was found to be very similar to the disease caused by mutations in the SLCA19A2 gene. According to ACMG Guidelines, we classified the variant as a variant of uncertain significance (VUS) (PM2, PM4, and PP4). However, since the patient's phenotype is particular to the disease, the genomic change may be responsible for the patient's clinical presentation.

With the above clinical data, TRMA syndrome was considered, and the patient was put on 100 mg daily of oral thiamine. The patient was followed closely. The insulin dose requirement decreased during the follow-up period, and the blood glucose level remained regulated. Her hemoglobin level returned to normal, and her peripheral blood smear had normal morphology except for mild anisocytosis. We recommended a specific genetic evaluation, including screening of first-degree family members.

Discussion

This case highlights a 38-year-old Turkish woman diagnosed with TRMA syndrome, featuring a unique presentation that includes autoimmune diabetes alongside the typical symptoms of sensorineural deafness and megaloblastic anemia. Her clinical course was notable for a partial but significant response to thiamine treatment, which stabilized her diabetic condition and normalized her hemoglobin levels. This case underscores the clinical variability of TRMA and the critical need for clinicians to be aware of this diagnosis in similar presentations.

Megaloblastic anemia, progressive sensorineural deafness, and non-type 1 diabetes mellitus are the triad of TRMA syndrome. Anemia usually occurs between infancy and adolescence. A megaloblastic anemia exists in which vitamin B12 and folic acid levels are normal. Examination of the bone marrow reveals megaloblastic changes with ringed sideroblasts. Although anemia improves with thiamine treatment (50-100 mg/day), red cells remain macrocytic. If thiamine treatment is interrupted, anemia develops again. Also, thrombocytopenia or neutropenia may be present.

Progressive sensorineural deafness often occurs in toddlers. Liberman et al showed in their animal study that selective inner hair cell loss in the cochlea could cause hearing loss in TRMA syndrome.[4] It is unclear whether it can be prevented by thiamine treatment; once it develops, it is generally irreversible.[5]

Diabetes mellitus is a non-autoimmune type, with an infancy to adolescence onset age. Onset in adulthood is sporadic. Insulin secretion is present but defective. Diabetes autoantibodies are

negative. Valerio et al presented 2 case reports of TRMA syndrome. Their patients have a normal insulin response to oral glucose, preserved C-peptide secretion, and an excellent response to an oral hypoglycemic agent. Based on this, they emphasized that diabetes mellitus may initiate as a type 2 pattern and progress after several years to an insulin-requiring type, as indicated by the exhaustion of insulin secretory capacity.[6] Oishi et al revealed that intracellular thiamine deficiency disrupts the production and secretion of insulin, which might be the principal mechanism of diabetes.[7] A timely thiamine supplementation can effectively correct the impairment of insulin secretion, as observed in previous cases, so early diagnosis is critical.[6,8,9] Diabetic ketoacidosis was reported in 15.7% of patients with diabetes during the disease in a review.[10] In that review, the incidence of anemia, diabetes, and hearing loss was 95.4%, 92.7%, and 92.7%, respectively. Moreover, 84.1% of patients presented with the triad of the syndrome. Of the triad, hearing loss occurred as the earliest symptom, as in our patient. However, it could typically only be noticed by caregivers, especially in the early life of patients, once the diagnosis of TRMA was established. Unlike the literature, our case had autoimmune diabetes. This may be related to the new pathogenic variant or the presence of accompanying autoimmune diabetes. Diabetes regulation can be achieved after thiamine treatment. It shows the importance for clinicians who follow diabetic patients to be aware of TRMA syndrome in patients with the triad of the syndrome.

Other identified findings include ophthalmological (29.1%), cardiovascular (27.8%), endocrinological (17.9%), neurological, and psychiatric (17.2%) symptoms. Other nonspecific symptoms, such as hepatomegaly, gastroesophageal reflux, and kidney enlargement, were also identified at a rate of 15.9%.[10] (Table 1). In our case, we did not detect any pathology other than autoimmune thyroiditis, myopia, non-proliferative retinopathy, and bilateral sensorineural polyneuropathy.

The diagnosis of TRMA is established in a proband with megaloblastic anemia with normal vitamin B12/folic acid levels, with or without non-autoimmune diabetes or sensorineural deafness, in whom there is a response to oral thiamine. The genetics department should be consulted in patients who meet the triad to examine the pathogenic variant in the SLC19A2 gene. If TRMA is diagnosed, specific genetic evaluation, including screening of first-degree family, is recommended.[11] Although disorders such as Wolfram syndrome, Kearns–Sayre syndrome, and Pearson syndrome, which are included in the differential diagnosis of TRMA, have a similar phenotype, the response of anemia and diabetes to thiamine treatment strongly supports diagnosis in the absence of genetic analysis.[12]

Table 1. Patient's Laboratory Results

Test Result
Fasting plasma glucose: 142 mg/dL
HbA1c level: 9.8% (84 mmol/mol)
Fasting C-peptide level: 1.31 ng/mL
Postprandial plasma glucose: 332 mg/dL
Creatinine: 0.6 mg/dL
ALT: 10 IU/L
AST: 17 IU/L
TSH: 2.1 mIU/L
B12 level: Normal
Folic acid levels: Normal
Peripheral blood smear: Normochromic macrocytosis and anisocytosis
Direct antihuman globulin test: Negative
Anti-GAD antibody: Positive at high titers

Lifelong use of oral thiamine in pharmacological doses (25-100 mg/day) is recommended for affected individuals regardless of age.[6] Standard treatments can be applied for other components, such as diabetes. It should be noted that dose revisions of the treatments given for the existing components may be required after adding thiamine therapy.

In conclusion, we identified a novel compound homozygous variant in SLC19A2 and revealed its accompanying symptoms. The diagnosis of TRMA should be considered in patients with the classic triad of the syndrome, especially in regions where TRMA is common, even at an adult age, and support should be sought from the genetics department to make the diagnosis. It is essential to raise awareness among physicians regarding differential diagnosis, especially since they benefit significantly from thiamine treatment.

Availability of Data and Materials: The data that support the findings of this study are available on request from the corresponding author.

Informed Consent: Written informed consent was obtained from the patient who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – B.C.H.; Design – S.H.; Literature Search – B.C.H.; Writing – B.C.H.; Data Collection and/or Processing – H.S.; Analysis and/or Interpretation – B.C.H., S.H.; Supervision – O.H., E.C.

Declaration of Interests: The authors have no conflict of interest to declare.

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