

# A Thiamine Responsive Megaloblastic Anemia Presented with Hypertriglyceridemia and Auto-immune Diabetes

**One Sentence Summary:** Thiamine therapy might be an alternative in patients presenting with diabetes and anemia.

## Authors

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## Key words

- thiamine responsive megaloblastic anemia
- diabetes mellitus
- hypertriglyceridemia

## Abstract

**Background:** Thiamine responsive megaloblastic anemia syndrome (TRMA) is an autosomal recessive disorder characterized by non type 1 diabetes mellitus (DM), sensorineural hearing loss and megaloblastic anemia and caused by mutations in *SLC19A2* gene, encoding a thiamine transporter protein.

**Case:** A 3-month-old male infant presented with megaloblastic anemia, DM, patent ductus arteriosus and hypertriglyceridemia. His auto-

immune markers for DM were positive but with the additional finding of sensorineural deafness he was diagnosed with TRMA and thiamine therapy was started. His anemia was improved and insulin needs decreased and his genetic studies revealed a homozygous frameshift mutation, c.641del within coding region of *SLC19A2* gene.

**Conclusion:** Clinical presentation of TRMA could be highly variable and some co-existence could perplex physicians, but this diagnosis should be considered in all patients with DM and anemia and further assessment should be done.

## Introduction

Thiamine-responsive megaloblastic anemia syndrome (TRMA) or Rogers' syndrome (OMIM 249270) is an autosomal recessive disorder whereby active thiamine uptake into cells is disturbed and is characterized by the triad of anemia, non type 1 diabetes mellitus (DM) and sensorineural deafness. In addition, optic atrophy, retinal involvement [1], congenital heart defects [2], stroke [3], pancytopenia and severe psychosis [4] have also been described in patients with TRMA. Although the syndrome was first described by Rogers in 1969 [5], *SLC19A2*, the gene encoding a high-affinity thiamine transporter protein (THTR-1), was identified in 1999 [6]. This 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 [7].

Hypertriglyceridemia in children is rarely seen and maybe hereditary or secondary to DM [8]. Monogenic disorders usually result from loss of function mutations in the genes lipoprotein lipase (LPL) or apolipoprotein C2 (APOC2) [9]. Anemia during childhood is not rare and nearly 20% of American children have anemia during

their childhood [10]. Evaluation of anemia is usually based on mean corpuscular volume and severe anemia warrants further investigations [11].

Here, we report a 3-month-old male infant who presented with anemia, autoantibody positive DM and hypertriglyceridemia and was diagnosed with TRMA by indicating *SLC19A2* gene mutation.

## Case Report

A 3-month-old male infant presented to our outpatient clinic with weakness and pallor. He was born as the first child of healthy first degree consanguineous parents at term, after an uneventful pregnancy with normal birth weight. His physical examination revealed tachycardia, grade 2/6 continuous murmur and a palpable hepatomegaly of 2 cm below the right subcostal margin. His weight was 5270 g (-1.27 SDS), height was 59 cm (-0.85 SDS), and head circumference was 38.2 cm (-2.14 SDS). Laboratory analyses showed severe anemia with a hemoglobin level of 6.9 g/dL, hematocrit 16.9%, mean corpuscular volume 89 fL, white blood cell count 9900/mm<sup>3</sup>, and platelets 251 000/mm<sup>3</sup>. The reticulocyte

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count was 0.1%. The peripheral blood smear revealed poikilocytosis, polychromasia, microcytic hypochromic erythrocytes without atypical cells. Ferritin, folic acid and vitamin B12 were all in normal limits. Viral serology was negative. Red blood cell transfusion was done. Examination of his bone marrow aspirate demonstrated increased megaloblastic erythropoiesis and megakaryopoiesis.

At his first presentation his blood samples, drawn for the laboratory analysis were white colored and serum biochemistry revealed hypertriglyceridemia (triglyceride 951 mg/dL). His total cholesterol level was 140 mg/dL at that time and after 1 week HDL cholesterol 16 mg/dL and LDL cholesterol 78 mg/dL while triglyceride was 257 mg/dL. For differential diagnosis of hypertriglyceridemia, fresh frozen plasma was given to infant and patient was accepted as responsive due to the decrease of triglyceride level (416 mg/dL). Therefore, condition was accepted as APOC2 deficiency and special formula and medium-chain fatty acids were ordered. With those therapies his triglyceride levels were improved gradually and after 6 months his diet therapy was stopped. His parent's lipid profiles were normal.

In addition to his anemia and hypertriglyceridemia, his serum glucose level was very high (glucose 404 mg/dL) at initial presentation. Blood gas analysis and other biochemistry were normal. HbA1c was high (7.2%), insulin and C-peptide levels were low with respect to his very high blood glucose level (3.0  $\mu$ U/mL and 1.14 ng/mL, respectively). But C-peptide level with glukagon stimulation was normal (glucose 124 mg/dL, C-peptide 2.36 ng/mL). Subcutaneous insulin therapy was started because of the high glucose levels at the follow-up. His glutamic acid decarboxylase antibody (Anti-GAD) was found to be negative [0.22 U/mL (normal: <1)], but anti insulin antibody (AIA) and islet cell antibody were positive [2.47 U/mL (normal: <0.4) and 39 JDFu (normal: <10), respectively].

His echocardiography revealed small patent ductus arteriosus (PDA). Abdominal ultrasonography showed grade 1 hepatosteatosis. Bilateral sensorineural hearing loss was detected and the patient was referred to an otolaryngologist for evaluation for hearing device implantation. His ophthalmologic examination revealed macular scars of retina, but his optic nerves were normal.

The findings of macrocytic anemia, sensorineural hearing loss and DM led us to consider a presumptive diagnosis of TRMA, and oral thiamine therapy with a dose of 100 mg/day was started. Hemoglobin level increased gradually and was 12.3 mg/dL at the end of second week on thiamine therapy. Insulin doses could be reduced but insulin therapy could not be ceased totally. The diagnosis of TRMA was confirmed by sequence analysis of coding and flanking intronic regions of the *SLC18A2* gene, which showed a homozygous frameshift mutation, c.641del in exon 2. This mutation was a deletion of a G nucleotide at position 641 (c.641delG) which was predicted to result in premature termination at codon 227 (p.S214fsX14). His father and mother were heterozygous for this mutation. (Peninsula Medical School, Exeter, United Kingdom).

At the last follow-up visit he was 4 years and 8 months old and his height was 116.7 cm (1.88 SDS), his weight was 20.7 kg (0.99 SDS). He was on multiple dose daily insulin (0.7 U/kg/day) and thiamine (100 mg/day) therapy. His HbA1c was 7.4% and his lipid profile was normal. PDA was closed spontaneously but first degree atrioventricular block was detected on his routine cardiological evaluation. Hepatic steatosis resolved completely, as estimated by ultrasonography.

## Discussion



DM in infancy is very rare and usually caused by single gene mutations [12,13]. DM in TRMA is due to a non-autoimmune mechanism and is most likely secondary to impairment of islet cell function caused by intracellular thiamine deficiency [14]. Thiamine and TMP/TPP transporters may have abnormal expression in diabetes. Increased THTR1 levels were found in red blood cells (RBCs) and mononuclear leucocytes of patients with diabetes [15]. There might be different responses of THTR1 expression in different cell types in diabetes: RBC precursors and leucocytes appeared to upregulate THTR1 expression in response to decreased thiamine availability, whereas renal tubular epithelial cells have decreased expression [16].

DM usually develops in early childhood in TRMA and the response to thiamine supplementation is variable [17]. Insulin could be stopped at the beginning of thiamine therapy, but required in addition to thiamine supplementation after puberty in most of the patients [18]. The classical hematological finding of TRMA is megaloblastic anemia and can be explained by the role of thiamine in DNA metabolism and heme synthesis. In a study with 13 TRMA patients, Ricketts et al [18] has shown that the anemia and DM responded to oral thiamine hydrochloride, but during puberty thiamine supplements became ineffective, and almost all patients require insulin therapy and regular blood transfusions in adulthood. All patients that Ricketts et al. reported were homozygous for mutations in the *SLC19A2* gene. Although our patient did not need any red blood cell transfusion after thiamine supplementation, his insulin requirement continued. Because of the positive autoantibodies an additional autoimmune process is suspected, but his young age at the time of autoantibody investigation make the results unreliable and so it is not clear whether this finding is due to the type of his mutation or to an additional autoimmune process.

Crouzet-Ozenda Luci et al. [19] were first to show a co-existence of metabolic disease with TRMA. They reported an infant followed with the diagnosis of congenital galactosemia since the age of 8 days, diagnosed with TRMA at the age of 10 months. In our patient, severe hypertriglyceridemia was detected at admission. For the differential diagnosis, fresh frozen plasma was given and with the good response to this treatment he was accepted as APO C2 enzyme deficient and special treatment ordered. In his follow-up, triglyceride levels decreased dramatically and at the end of 6 months, special formula was ceased and breastfeeding continued. His hypertriglyceridemia was considered as a consequence of his DM. Marked elevations in the levels of triglycerides can be seen in poorly controlled type 1 DM because of a reduction in the activity of LPL. LPL is an insulin regulated enzyme, synthesized in adipose tissue and muscle, and hydrolyzes triglycerides in the core of chylomicrons and VLDL [20].

In conclusion, clinical presentation of TRMA could be highly variable and some co-existence could perplex physicians, but this diagnosis should be considered in all patients with DM and anemia. In patients with the diagnosis of TRMA cardiovascular evaluation should be done at the follow-up period in addition to hematology, endocrinology, otolaryngology, ophthalmology assessments, even if they did not have any cardiac manifestations before the thiamine therapy.

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▼  
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**Conflict of interest:** None.

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