

Thiamine-Responsive Megaloblastic Anemia Syndrome: A Case Report

Omkar Patil, Karnam Guruswamy Ravikumar¹, Sundaramoorthy Gopi, Thulasi Raman¹, Venkatesan Radha, Viswanathan Mohan

Madras Diabetes Research Foundation, Affiliated to the University of Madras and Dr. Mohan's Diabetes Specialities Centre, Chennai, Tamil Nadu, India, ¹Kanchi Kamakoti CHILDS Trust Hospital, Chennai, Tamil Nadu, India

Abstract

Thiamine-responsive megaloblastic anemia (TRMA) syndrome is a rare autosomal recessive disorder characterized by a cardinal triad consisting of megaloblastic anemia, sensorineural deafness, and diabetes mellitus. TRMA is caused by mutations in the gene *SLC19A2* encoding a high-affinity thiamine transporter, which disturbs the active thiamine uptake into cells. We report here on a 1-year and 9-month-old female baby with megaloblastic anemia, thrombocytopenia, and diabetes mellitus. Our patient had significant sensorineural hearing loss that was late to appear. Diagnosis was based on clinical features and dramatic response of anemia, thrombocytopenia, and glycemic control to thiamine therapy. In view of the clinical history of the patient, targeted gene sequencing of genes causing monogenic diabetes was performed. The genes selected comprised 40 gene loci and were sequenced by Illumina sequencing platform. We found a novel homozygous deletion mutation of complete exon 2 of the *SLC19A2* gene (*ENST00000236137*), which we believe has not been described to be associated with TRMA. Exon 2 of *SLC19A2* gene includes amino acid from 69 to 269. Thiamine resulted in rapid normalization of the hemoglobin level with improvement in glycemic control. TRMA syndrome should be kept in mind in the differential diagnosis of megaloblastic anemia, deafness, and diabetes mellitus. Early introduction of high-dose thiamine can reverse anemia and allow more glycemic control for diabetes. We conclude that genetic analysis confirms the diagnosis of TRMA. As exogenous thiamine is shown to reverse some of the clinical features of the disease, a genetic diagnosis of TRMA syndrome is extremely important.

Keywords: Diabetes mellitus, *SLC19A2* gene, thiamine-responsive megaloblastic anemia, TRMA

INTRODUCTION

Thiamine-responsive megaloblastic anemia (TRMA) syndrome is a very rare genetic disorder affecting a thiamine transporter. TRMA is characterized by megaloblastic anemia, diabetes mellitus, and hearing loss. It is also known as Rogers syndrome. It is an autosomal recessive disease due to loss of function mutation in the thiamine transport *SLC19A2* gene that resides on chromosome 1q23.2–23 and encodes the high-affinity thiamine transporter 1 (h-THTR1), which is essential for uptake of thiamine by cells.^[1] The *SLC19A2* gene encodes one of the two known high-affinity thiamine transporters (THTR), i.e., THTR-1 encoded by *SLC19A2* and THTR-2 encoded by *SLC19A3*. THTR-1 mediates the active intracellular

thiamine transportation at low extracellular thiamine concentration. This syndrome is very rare and seen in offspring of consanguineous marriages and in isolated communities.^[2] TRMA syndrome has been reported in approximately 40 children. High dose of thiamine results in utilization of another low-affinity pathway.^[3,4]

In patients with the genetic defect, reduced nucleic acid production is the underlying biochemical disturbance that

Address for correspondence: Dr. Viswanathan Mohan, Madras Diabetes Research Foundation and Dr. Mohan's Diabetes Specialities Centre, WHO Collaborating Centre for Noncommunicable Disease Prevention and Control and IDF Centre of Excellence in Diabetes Care, and ICMR Centre for Advanced Research on Diabetes, No. 4, Conran Smith Road, Gopalapuram, Chennai 600 086, Tamil Nadu, India. E-mail: drmohans@diabetes.ind.in

Received: 18-December-2018, **Revised:** 3-May-2019, **Accepted:** 18-May-2019, **Published:** 18-December-2019.

Access this article online

Quick Response Code:



Website:
www.journalofdiabetology.org

DOI:
10.4103/jod.jod_51_18

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Patil O, Ravikumar KG, Gopi S, Raman T, Radha V, Mohan V. Thiamine-responsive megaloblastic anemia syndrome: A case report. *J Diabetol* 2020;11:45-8.

likely induces cell cycle arrest or apoptosis in bone marrow cells and leads to manifestation of TRMA syndrome.^[5,6]

The diagnosis of TRMA is based on the triad of clinical features consisting of megaloblastic anemia, diabetes, and sensorineural deafness. The bone marrow reveals megaloblastic anemia with erythroblasts containing iron-filled mitochondria. We report here a baby with new onset diabetes mellitus who subsequently manifested with megaloblastic anemia and eye abnormalities and with an additional feature—sideroblastic anemia.

CASE DETAILS

A female baby aged 1 year and 9 months presented to a private pediatric hospital at Chennai in South India with new onset diabetes mellitus and mild diabetic ketoacidosis and anemia. The baby was the second born child of a non-consanguineous marriage. She was delivered full term by cesarean section and birth weight was 3.4 kg. Her development was normal. In view of the ketosis, she was started on insulin therapy. There was no history of fever, jaundice, hematemesis, malena, bleeding from any site, or lymphadenopathy. A routine diabetes workup showed the following results: glycosuria, ketonuria, pH 7.29, and HCO₃ 17 mEq/L. The random blood glucose level was 309 mg/dL; serum ketone test was positive. Her Hb was 8.6 g/dL and total white blood cell count was 7380 cells/cumm. The peripheral smear showed leukocytosis with lymphocytosis and monocytosis, and reduced erythrocytes with hypochromic microcytic anemia as well as megaloblastic anemia. Schistocytes were seen in peripheral smear. The reticulocyte count was normal.

She was referred to our center for monogenic diabetes testing. The clinical examination revealed pallor; anthropometry revealed the height as 86.5 cm and weight as 11.7 kg. The glycosylated hemoglobin (HbA1c) was 7.3%. Glutamic acid decarboxylase (GAD 65) antibody was negative; C-peptide showed reduced insulin reserve: fasting 0.3 pmol/mL and stimulated C-peptide 0.7 pmol/mL.

In view of the clinical history of the patient, targeted gene sequencing of the genes causing monogenic diabetes was performed. The genes selected comprised 40 gene loci and were sequenced using the Illumina sequencing platform. We found a novel homozygous deletion mutation of the exon 2 of the *SLC19A2* gene (*ENST00000236137*). This appeared to be a novel mutation for TRMA. The exon 2 of *SLC19A2* gene includes amino acid from 69 to 269 [Figure 1].

Abdominal ultrasound revealed evidence of cystitis and normal pancreas. Echocardiography was suggestive of pulmonary artery hypertension. Repeat hemoglobin level was 6.4 g/dL (reference range for age: 12.5–16.1), mean corpuscular volume (MCV) 92.4 fL (reference range: 78–95), mean corpuscular hemoglobin of 32.7 pg (reference range: 26–32), and mean corpuscular hemoglobin concentration of 33.3 g/dL (reference range: 32–36). Total leukocyte count was normal but the platelet count was 50,000/mL. Erythrocyte sedimentation rate was 10 mm/h in the first hour. Iron profile was as follows: serum iron 174.4 µg/dL (reference range: 30–158), total iron binding capacity 197 µg/dL (reference range 200–400), and ferritin 164.8 ng/mL (reference range 28–300). Hb electrophoresis was normal. Creatinine was 0.26 mg/dL (reference range 0.5–1.1), alanine aminotransferase was 21 (reference range up to 35 IU/L), and aspartate aminotransferase was 26 (reference range up to 35 IU/L). Further investigations for megaloblastic anemia were performed. Serum vitamin B12 level was on the lower side at 253 pg/mL (reference range 220–920) and serum folate level was 23.7 ng/mL (reference range 3–17). The immunoglobulin profile showed IgG 535 mg/dL, IgA 66 mg/dL, IgM 130 mg/dL, and IgE 86 mg/dL.

Bone marrow aspirate revealed dilute aspirate with dyserythropoiesis and ring sideroblasts [Figure 2]. Bone marrow biopsy was performed, which revealed ring sideroblasts that were seen in late normoblast with megaloblastic changes, normal myeloid series, and increased megakaryocytes. Because of the findings

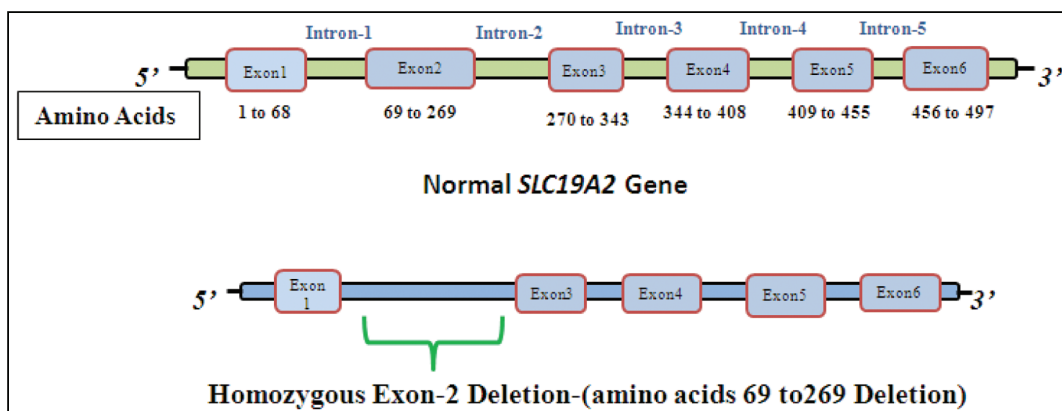


Figure 1: Schematic representation of homozygous novel exon 2 deletion mutation in *SLC19A2* gene

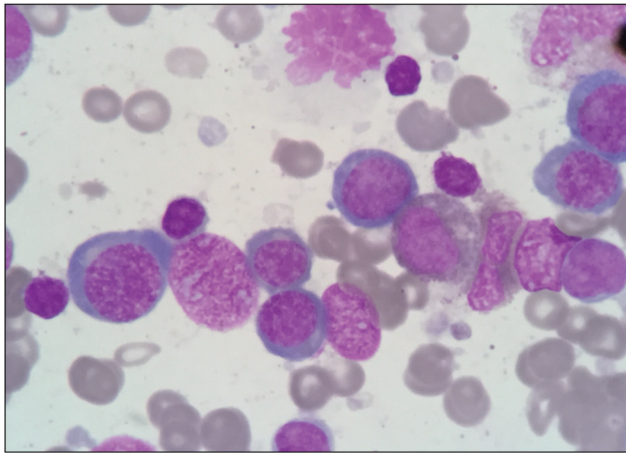


Figure 2: Photomicrograph showing megaloblast in the bone marrow aspirate (Leishman stain, $\times 1000$)

of severe megaloblastic anemia with sideroblasts and diabetes, a diagnosis of TRMA was entertained.

She was initially managed with blood transfusion to correct the severe anemia. After this, her Hb increased from 6.4 to 9.4 g/dL but again after 3 days it started decreasing and it decreased to 6.2 g/dL. The platelet count dropped to 16,000/mL requiring 2 units of platelets transfusion. The white cell count remained normal. Clinically, she became more irritable. A brain-stem auditory evoked potential test later showed bilateral severe sensorineural hearing loss.

After this a trial of oral thiamine (100 mg 3 times a day) therapy and pyridoxine (40 mg) was started. With the aforementioned oral medications, child had a dramatic response within a few hours. The blood sugar levels became normal without insulin injections. Hence, the insulin injection was stopped. Fifteen days after the start of the treatment, the hemoglobin level increased from 7 to 10.7 g/dL but red cells remained macrocytic (MCV was 100 fL). The blood sugar levels dropped, and 20 days after starting the thiamine treatment, it was 97 mg/dL without any diabetic medication. There was no improvement in the hearing loss.

DISCUSSION

TRMA, also known as Rogers syndrome, is an autosomal recessive disorder characterized by megaloblastic anemia, diabetes mellitus, and sensorineural hearing loss.^[1] Fewer than 40 cases have been reported; it is exceedingly rare outside of consanguineous marriages. The reported cases are from Israeli, Arab, Lebanese, Russians, Brazilian, Japanese, Italian, Iranian, and Pakistani kindreds.^[2,5,7]

This child presented with pallor and hyperglycemia. Megaloblastic anemia with sideroblasts and hyperglycemia was detected and hence a diagnosis of TRMA was considered. Although TRMA is a type of sideroblastic anemia, it is distinct 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 lead to the diagnosis of TRMA.^[8] The classic hematological profile in this syndrome is macrocytic anemia with ringed sideroblasts, but a number of different types of blood picture have been reported in TRMA, such as sideroblastic and aplastic anemia, thrombocytopenia, and neutropenia. In this child, thrombocytopenia was present. Bone marrow aspirate revealed dilute aspirate with dyserythropoiesis and ring sideroblasts suggesting a possibility of sideroblastic anemia.

We found a novel homozygous deletion mutation of the whole exon 2 of the *SLC19A2* gene (*ENST00000236137*). This mutation is being described for the first time in association with TRMA. Exon 2 of *SLC19A2* gene includes amino acid from 69 to 269. The *SLC19A2* gene encodes one of the two known high-affinity thiamine transporters (THTR), i.e., THTR-1 encoded by *SLC19A2* and THTR-2 encoded by *SLC19A3*. THTR-1 mediates the active intracellular thiamine transportation at low extracellular thiamine concentration. The normal pancreatic islet structure identified in *SLC19A2* knockout mice indicates that the diabetes caused by *SLC19A2* deficiency was likely to result in damaged insulin synthesis and secretion rather than in a developmental defect in islets.^[9] This also suggests that the patients with *SLC19A2* defect could improve their pancreatic beta cell function after treatment with thiamine.

To date more than 40 different *SLC19A2* mutations has been identified. The majority of them are missense, nonsense, or small indels.^[10-13] Some have been reported to cosegregate with disease in family-based studies.^[14,15] Some of the mutations lead to the production of abnormally short, nonfunctional THTR-1, and others disrupt the proper folding of the protein, preventing it from reaching the cell surface. However, all these mutations prevent THTR-1 from bringing thiamine into the cell.

In this case, we identified a full exon 2 deletion in the patient and to the best of our knowledge this is the first case with full exon 2 deletion in homozygous status. The parental screening was not performed in this study. It is interesting to note that most of the reported common mutations are present in exon 2 of the gene.

Despite improvement in anemia, after introduction of thiamine, macrocytosis persisted. In TRMA syndrome, although megaloblastic anemia is corrected with pharmacologic doses of thiamine, the red cells remain macrocytic, which suggests a persistent erythropoietic abnormality. Treatment of TRMA focuses on lifelong use of pharmacologic doses (25–75 mg/day) of thiamine in affected individuals as early as possible.^[16] This child had severe anemia with megaloblastic picture that reversed dramatically and completely after therapy.

Beshlawi *et al.*^[17] have previously reported a 5224 base pair deletion of the gene in 6 patients belonging to the single family. The deletion involves exon 4, 5, and 6 of the *SLC19A2* gene. They also reported that response to thiamine was variable. Hemoglobin level can reach normal values and insulin dose decreased after 1 month with thiamine therapy (100 mg/day).

Alzahrani *et al.*^[18] also reported that high-dose thiamine therapy in patients with TRMA can improve the disease symptoms and correct the anemia, and may also help to reduce or discontinue the need for exogenous insulin injections.

TRMA syndrome should be kept in mind in the differential diagnosis of megaloblastic anemia, deafness, and diabetes mellitus especially in neonates and children.^[19,20] Early introduction of high-dose thiamine can reverse anemia and achieve euglycemia. Genetic analysis should always be performed to rule out this condition in all suspected cases as therapy with thiamine improves the diabetic control.

Ethical clearance

Written informed consent was obtained from each study participant, and the study was approved by the Madras Diabetes Research Foundation Institutional Ethics Committee. The reported investigations have been carried out in accordance with the principles of the Declaration of Helsinki.

Financial support and sponsorship

VR acknowledges the financial support given by Indian Council for Medical Research, New Delhi, India, for her project “Investigations of Association of Mutations in MODY and NDM by Translational Genomic Research”.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Porter FS, Rogers LE, Sidbury JB Jr. Thiamine-responsive megaloblastic anemia. *J Pediatr* 1969;74:494-504.
- Oishi K, Diaz GA. Thiamine-responsive megaloblastic anemia syndrome. In: Pagon RA, Bird TD, Dolan CR, Stephens K, editors. *Gene Reviews*. Seattle, WA: University of Washington, Seattle; 1993.
- Neufeld EJ, Mandel H, Raz T, Szargel R, Yandava CN, Stagg A, *et al.* Localization of the gene for thiamine-responsive megaloblastic anemia syndrome, on the long arm of chromosome 1, by homozygosity mapping. *Am J Hum Genet* 1997;61:1335-41.
- Diaz GA, Banikazemi M, Oishi K, Desnick RJ, Gelb BD. Mutations in a new gene encoding a thiamine transporter cause thiamine-responsive megaloblastic anaemia syndrome. *Nat Genet* 1999;22:309-12.
- Bergmann AK, Sahai I, Falcone JF, Fleming J, Bagg A, Borgna-Pignati C, *et al.* Thiamine-responsive megaloblastic anaemia: Identification of novel compound heterozygotes and mutation update. *J Pediatr* 2009;155:888-92.
- Bay A, Keskin M, Hizli S, Uygun H, Dai A, Gumruk F. Thiamine-responsive megaloblastic anemia syndrome. *Int J Hematol* 2010;92:524-6.
- Naeem MA, Shabaz A, Shoaib A, Usman M. A rare case of thiamine-responsive megaloblastic anaemia syndrome: A disorder of high-affinity thiamine transport. *J Ayub Med Coll Abbottabad* 2008;20:146-8.
- Bottomley SS, Fleming MD. Sideroblastic anemia: Diagnosis and management. *Hematol Oncol Clin North Am* 2014;28:653-70, v.
- Rathanaswami P, Pourany A, Sundaresan R. Effects of thiamine deficiency on the secretion of insulin and the metabolism of glucose in isolated rat pancreatic islets. *Biochem Int* 1991;25:577-83.
- Manimaran P, Subramanian VS, Karthi S, Gandhimathi K, Varalakshmi P, Ganesh R, *et al.* Novel nonsense mutation (p.Ile411Metfs*12) in the *SLC19A2* gene causing thiamine responsive megaloblastic anemia in an Indian patient. *Clin Chim Acta* 2016;452:44-9.
- Mikstiene V, Songailiene J, Byckova J, Rutkauskienė G, Jasinskiene E, Verkauskienė R, *et al.* Thiamine responsive megaloblastic anemia syndrome: A novel homozygous *SLC19A2* gene mutation identified. *Am J Med Genet A* 2015;167:1605-9.
- Setoodeh A, Haghghi A, Saleh-Gohari N, Ellard S, Haghghi A. Identification of a *SLC19A2* nonsense mutation in Persian families with thiamine-responsive megaloblastic anemia. *Gene* 2013;519:295-7.
- Tahir S, Leijssen LG, Sherif M, Pereira C, Morais A, Hussain K. A novel homozygous *SLC19A2* mutation in a Portuguese patient with diabetes mellitus and thiamine-responsive megaloblastic anaemia. *Int J Pediatr Endocrinol* 2015;2015:6.
- Labay V, Raz T, Baron D, Mandel H, Williams H, Barrett T, *et al.* Mutations in *SLC19A2* cause thiamine-responsive megaloblastic anaemia associated with diabetes mellitus and deafness. *Nat Genet* 1999;22: 300-4.
- Scharfe C, Hauschild M, Klopstock T, Janssen AJ, Heidemann PH, Meitinger T, *et al.* A novel mutation in the responsive megaloblastic anaemia gene *SLC19A2* in a patient with deficiency of respiratory chain complex I. *J Med Genet* 2000;37:669-73.
- Valerio G, Franzese A, Poggi V, Tenore A. Long-term follow-up of diabetes in two patients with thiamine-responsive megaloblastic anemia syndrome. *Diabetes Care* 1998;21:38-41.
- Beshlawi I, Al Zadjali S, Bashir W, Elshinawy M, Alrawas A, Wali Y. Thiamine responsive megaloblastic anemia: The puzzling phenotype. *Pediatr Blood Cancer* 2014;61:528-31.
- Alzahrani AS, Baitei E, Zou M, Shi Y. Thiamine transporter mutation: An example of monogenic diabetes mellitus. *Eur J Endocrinol* 2006;155:787-92.
- Ganesh R, Ezhilarasi S, Vasanthi T, Gowrishankar K, Rajajee S. Thiamine responsive megaloblastic anemia syndrome. *Indian J Pediatr* 2009;76:313-4.
- Ganesh R, Suresh N, Vasanthi T, Ravikumar KG. Neonatal diabetes: A case series. *Indian Pediatr* 2017;54:33-6.