

# Thiamine Responsive Megaloblastic Anaemia, Diabetes Mellitus and Sensorineural Hearing Loss in a Child

Ayesha Khurshid<sup>1</sup>, Sarah Fatimah<sup>1</sup>, Chaudhry Altaf<sup>1</sup>, Hamid Saeed Malik<sup>1</sup>,  
Zunera Sajjad<sup>1</sup> and Muhammad Tahir Khadim<sup>2</sup>

## ABSTRACT

Thiamine-responsive megaloblastic anemia (TRMA) syndrome is an autosomal recessive inherited disorder characterised by a triad of megaloblastic anemia, diabetes mellitus, and sensorineural deafness. We report a case of 2-year-old girl whose anemia improved following administration of thiamine. She came with the history of persistent anaemia for the last one year. Anaemia was not responding to iron, vitamin B12, and folate replacement therapy. The bone marrow aspiration revealed hypercellular marrow with megaloblastic changes and more than 15% ring sideroblasts. The hearing assessment revealed sensorineural hearing loss. Blood sugar random and HBA1c was raised. Final diagnosis of TRMA was made. She was started on thiamine 100 mg OD, with normal routine balanced diet. She responded very well to thiamine. Her haemoglobin improved and blood sugar fasting came down in normal range. This case report sensitises the early diagnosis, and treatment with thiamine in children presenting with anemia, diabetes and deafness.

**Key Words:** *Megaloblastic anaemia. Thiamine. Sideroblastic. Congenital. Diabetes mellitus. Sensorineural deafness. SLC19A2 mutation.*

## INTRODUCTION

TRMA is an autosomal recessive disorder, characterised by a triad of anemia, diabetes mellitus and sensorineural deafness.<sup>1</sup> It is caused by mutations in SLC19A2 gene encoding the high-affinity thiamine transporter 1 (h-THTR1), which is the major route of thiamine delivery in a variety of cells lines: pancreatic  $\beta$ -cells, cochlear cells, hemopoietic tissues, and retinal epithelial cells.<sup>2</sup> Deficiency of transport mechanism leads to an inadequate intracellular concentration of thiamine and cell apoptosis. TRMA is exceedingly rare outside of consanguineous pairings or isolated populations and fewer than 80 pedigrees are known world over.<sup>3</sup> Diagnosis of TRMA is confirmed by bone marrow examination with megaloblastic change and >15% ring sideroblasts, deranged glycemic profile and sensorineural deafness on audiometry. Treatment with thiamine is effective to cure anaemia and diabetes mellitus, but sensorineural hearing loss is irreversible.

## CASE REPORT

A 2-year girl child presented with history of persistent anaemia for the last one year. According to her mother, she was in her usual state of health when she developed lethargy, irritability, and progressive pallor. She was taken

to general practitioner, who advised her iron, vitamin B12, and folate replacement therapy. The condition of child worsened with two breath-holding spells, as well. The haemoglobin showed 6 g/dl. She was transfused 200 ml of red cell concentrate (RCC) in March 2017. There was a temporary improvement in condition, but she again started developing pallor. She was referred for haematological consultation. The girl was second daughter of a consanguineous marriage, delivered via lower segment cesarean section at term. She had an immediate cry with an APGAR score of 8. Her elder sister is alive and healthy.

On general physical examination, she was a weak and pale; but no jaundice, cyanosis, clubbing, koilonychia and, lymphadenopathy was present. On systemic examination, there was no hepatomegaly or splenomegaly.

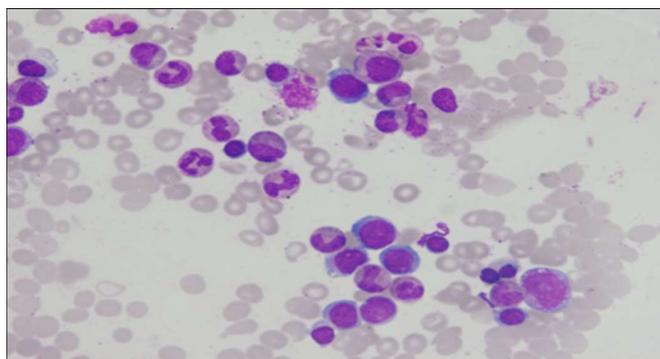
She was investigated for transfusion dependent anaemia. The complete blood count showed haemoglobin 7.0 g/dl, MCV 97.1 fl, MCH 28.8 pg, WBC  $9.8 \times 10^9/L$ , and platelets  $328 \times 10^9/L$ . The blood film showed dimorphic blood picture with tear drop cells and marked macrocytosis. Serum ferritin 384 ng/ml (11-307 ng/mL), TIBC: 43.2  $\mu\text{mol/L}$ , serum vitamin B12: 406 pmol/L (176-686 pmol/L), serum folate 54.4 nmol/L (6.25-45.3nmol/L), and Coomb's test Direct and Indirect were negative. Osmotic fragility was within normal limits with reference to normal controls. The haemoglobin electrophoresis performed by HPLC revealed no haemoglobin disorder with haemoglobin A2 = 2.5% (2.0-3.5), haemoglobin F = 0.8% (<0.9%) and haemoglobin A = 97% (96.0-98.0%). Haemoglobin electrophoresis of both parents were also normal. PCR for beta thalassemia mutations was negative. Bone marrow aspiration revealed hypercellular marrow with megaloblastic changes and

*Department of Haematology<sup>1</sup> / Histopathology<sup>2</sup>, Armed Forces Institute of Pathology (AFIP), Rawalpindi.*

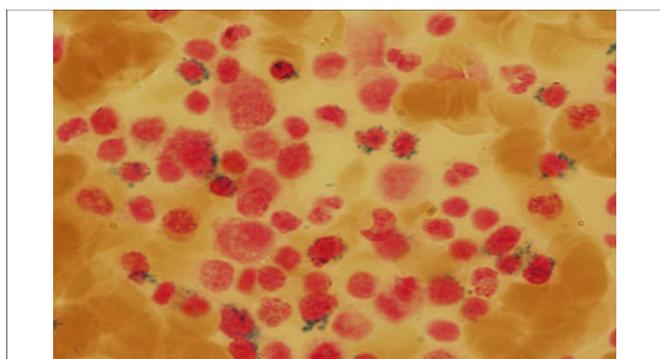
*Correspondence: Dr. Ayesha Khurshid, Consultant Haematologist, Department of Haematology, Armed Forces Institute of Pathology (AFIP), Rawalpindi.*

*E-mail: ayeshafaisal82@yahoo.com*

*Received: December 15, 2017; Accepted: May 14, 2018.*



**Figure 1:** Bone marrow aspirate showing megaloblastic change in erythropoiesis.



**Figure 2:** Perls staining on bone marrow aspirate showing >15% ring sideroblasts.

more than 15% ring sideroblasts on Perl's staining (Figures 1 and 2). Trephine biopsy revealed hypercellular marrow with megaloblastic change and dyserythropoiesis. The hearing assessment from ENT specialist revealed sensorineural hearing loss.

On the basis of history, clinical examination, laboratory investigations, and bone marrow examination, differential diagnoses of TRMA / Rogers syndrome and Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness (DIDMOAD) syndrome were made.

Fasting blood sugar was 10.6 mmol/L (diabetics >7.0 mmol/L), HbA1C was 8.4% (diabetics >6.5%). Random urine osmolality was 450 mOsm/Kg of water (300 - 900 mOsm/Kg of water), which ruled out diabetes insipidus. The examination of eye was unremarkable. So a final diagnosis of TRMA was made. Initial treatment started with vitamin B-6 for treatment of sideroblastic anaemia along with vitamin B-12, folic acid, and multi-vitamin syrup, but conditions did not improve.

The child was started on thiamine (Vit B1) 100 mg OD, with normal routine balanced diet. After one week of treatment, she was re-evaluated. The effect of thiamine therapy was found to be quite remarkable. In just one week, the Hb improved from 6.1g/dl to 9.3 g/dl, TRBC from  $1.8 \times 10^{12}/L$  to  $3.1 \times 10^{12}/L$ . However MCV remained 97.1-101 fl. The blood sugar fasting reduced from 10.6 mmol/L to 4.4 mmol/L. After 1 month, the levels further improved with Hb: 10.8 g/dl, TRBC:  $3.8 \times 10^{12}/L$  and

blood sugar random: 4.8 mmol/L. However, no improvement in sensorineural hearing loss for which she was under consideration for hearing aid/cochlear implant by the ENT specialist.

## DISCUSSION

TRMA is also called Rogers syndrome, named after its discoverer in 1969.<sup>1</sup> It is an autosomal recessive inherited disorder characterised by a triad of megaloblastic anemia, diabetes mellitus, and sensorineural deafness. TRMA is caused by loss of function mutations in the SLC19A2 gene.<sup>1</sup> This gene is located on chromosome 1q24.2 and is responsible for this syndrome. This mutation is identified by molecular genetic testing.<sup>2</sup> TRMA is exceedingly rare outside consanguineous pairings or isolated populations; and fewer than 80 pedigrees are known world over. The reported cases are from populations such as Israeli Arab, Lebanese, Russians, Brazilian, Japanese, Italian, Iranian and Pakistani kindreds.<sup>3</sup>

SLC19A2 gene is widely expressed in human tissues; indeed h-THTR1, which it encodes, is the major route of thiamine delivery in a variety of cells lines, such as pancreatic  $\beta$ -cells, cochlear cells, hemopoietic tissues and retinal pigment epithelial ARPE-19 cells, with the highest expression in skeletal muscle. Deficiency of h-THTR1 results in a defective transport mechanism of the thiamine, which leads to an inadequate intracellular concentration of thiamine and apoptosis. It plays a role in several major metabolic processes, such as carbohydrate metabolism and biosynthesis of cell constituents, including neurotransmitters. Furthermore, it is involved in the production of reducing equivalents in oxidant stress defenses and in the synthesis of pentoses considered as nucleic acid precursors. Normal thiamine homeostasis involves 4 steps: uptake of thiamine from the gut, transport to tissues and into cells, conversion of thiamine into the cofactor and binding of thiamine pyrophosphate to apoenzymes.<sup>4</sup>

The usual age of presentation of megaloblastic anaemia is between infancy and adolescence. The peripheral blood smear shows macrocytosis and the bone marrow reveals megaloblastic changes with ringed sideroblasts (erythroblasts often containing iron-filled mitochondria). The levels of vitamin B12 and folate are within normal limits. The low haemoglobin levels are corrected with pharmacological doses of thiamine (vitamin B1 50-100 mg/day). Even without thiamine supplementation, the serum thiamine concentrations are normal. The red cells, however, remain macrocytic and it is the evidence of persistent erythropoietic abnormality.<sup>5</sup> The anaemia reoccurs whenever thiamine is withdrawn. Some individuals may not have hearing loss, inspite of signs of megaloblastic anaemia and diabetes at early age. Diabetes mellitus in TRMA syndrome is non-autoimmune and is due to impairment of islet cell function caused by

intracellular thiamine deficiency. At puberty, due to increased  $\beta$ -cell apoptosis, insulin may be required in addition to thiamine treatment to control diabetes.<sup>6</sup> Sensorineural deafness is because h-THTR1 is located in the inner hair cells within the cochlea and the loss of SLC19A2 results in selective inner hair cell loss and an auditory neuropathy phenotype.<sup>7</sup> In addition to the triad of clinical features that characterise TRMA, other findings have been observed in different case reports. Optic atrophy in TRMA is due to abnormal appearance of the retina and functional retinal dystrophy.<sup>8</sup> Cardiovascular abnormalities including sudden death, stroke, high-output heart failure, paroxysmal atrial tachycardia, atrial standstill, and congenital heart defects such as atrial or ventricular septal defect have been reported in 27% of individuals with TRMA.<sup>9</sup>

Among acquired anemias, this combination of megaloblastic red cell changes and ringed sideroblasts is mostly suggestive of myelodysplastic syndromes. TRMA should not be confused with myelodysplastic disorders which are having premalignant potential.

There is an overlap between TRMA and DIDMOAD. The features missing in DIDMOAD are megaloblastic anemia and thiamine responsiveness. DIDMOAD is caused by mutation of WFS-1 gene on chromosome 4p16.1.<sup>10</sup>

The differential diagnosis of combination of diabetes mellitus and deafness is mitochondrial disorders (DIDMOAD syndrome, Kearns Sayre syndrome and Pearson syndrome). The mitochondrial disorders do not have macrocytic anemia, bone marrow with megaloblastic changes, and are non-responsiveness to thiamine. The pattern of inheritance in TRMA is autosomal recessive. The pattern of mitochondrial disorders is maternal transmission.<sup>10</sup>

The management of TRMA is lifelong oral administration of thiamine (vitamin B1) at pharmacologic doses (50-100 mg/ day). Early administration of appropriate thiamine supplementation can prevent or significantly delay anemia and diabetes but does not appear to prevent hearing loss in these patients. Transfusion of RCC may be required for treatment of severe anaemia. There is a role of cochlear implants in treatment of sensorineural loss.<sup>11</sup>

It is recommended to monitor the efficacy of the high dose thiamine therapy and progression of disease yearly.

## REFERENCES

- 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.
- Tahir S, Leijssen L, 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.
- Ganie MA, Ali I, Ahangar AG. Thiamine responsive megaloblastic anemia syndrome associated with patent ductus arteriosus: First case report from Kashmir Valley of the Indian subcontinent. *Indian J Endocr Metab* 2012; **16**:646-50.
- Franzese A, Fattorusso V, Mozzillo E. Thiamine-responsive megaloblastic anemia syndrome. In diabetes associated with single gene defects and chromosomal abnormalities. Karger Publishers; 2017; Vol. 25, pp. 49-54.
- 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.
- Ricketts CJ, Minton JA, Samuel J, Ariyawansa I, Wales JK, Lo IF, et al. Thiamine-responsive megaloblastic anaemia syndrome: long-term follow-up and mutation analysis of seven families. *Acta Paediatr* 2006; **95**:99-104.
- Lieberman MC, Tartaglino E, Fleming JC, Neufeld EJ. Deletion of SLC19A2, the high affinity thiamine transporter, causes selective inner hair cell loss and an auditory neuropathy phenotype. *J Assoc Res Otolaryngol* 2006; **7**:211-7.
- Lagarde WH, Underwood LE, Moats-Staats BM, Calikoglu AS. Novel mutation in the SLC19A2 gene in an African-American female with thiamine-responsive megaloblastic anemia syndrome. *Am J Med Genet A* 2004; **125A**:299-305.
- Shaw-Smith C, Flanagan SE, Patch AM, Grulich-Henn J, Habeb AM, Hussain K, et al. Recessive SLC19A2 mutations are a cause of neonatal diabetes mellitus in thiamine-responsive megaloblastic anaemia. *Pediatr Diabetes* 2012; **13**:314-21.
- Fischel-Ghodsian N. Mitochondrial deafness mutations reviewed. *Hum Mutat* 1999; **13**:261-70.
- Hagr AA. Cochlear implant and thiamine-responsive megaloblastic anemia syndrome. *Ann Saudi Med* 2014; **34**:78-80.

