10 Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, *et al*. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007;**48:**124–31.
11 De Gottardi J, Montani M, Angelillo-Scherrer A, Rovo A, Berzigotti A. Hepatic sinusoidal hemophagocytosis with and without hemophagocytic lymphohistiocytosis. *PLoS One* 2019;**14:**e0226899.
12 Ost A, Nilsson-Ardnor S, Henter JI. Autopsy findings in 27 children with haemophagocytic lymphohistiocytosis. *Histopathology* 1998;**32:**310–16.
13 Abughanimeh O, Qasrawi A, Abu Ghanimeh M. Hemophagocytic lymphohistiocytosis complicating systemic sarcoidosis. *Cureus* 2018;**10:**e2838.
14 Wahbi A, Graveleau J, Néel A, Joubert M, Masseau A, Joly GM, *et al*. Macrovesicular hepatic steatosis revealing pregnancy hemophagocytic lymphohistiocytosis. *Rev Med Interne* 2015;**36:**555–7.
15 Padhi S, Sarangi R, Patra S, Chandra Samal S. Hepatic involvement in hemophagocytic lymphohistiocytosis. In: *Hepatitis A and other associated hepatobiliary diseases.* London, UK:IntechOpen; 2019.

Thiamine-responsive megaloblastic anaemia

VIMAL MAVILA VEETIL, DIVYA PACHAT, K. NIKITHA, JESHEERA MOHAMMED KUTTY

ABSTRACT

We report a 26-year-old girl who was diagnosed with diabetes mellitus in her childhood and was treated with insulin. With a history of visual disturbances during her childhood and anaemia, which was partially evaluated; the possibility of syndromic diabetes was considered. Genetic analysis was done and revealed a mutation in the *SLC19A2* gene, confirming the diagnosis of thiamine-responsive megaloblastic anaemia. She was supplemented with thiamine, which dramatically improved her haemoglobin levels and glucose control. However, her vision could not be salvaged as the rod-cone dystrophy is a permanent damage.

Natl Med J India 2023;36:314–15

INTRODUCTION

Thiamine-responsive megaloblastic anaemia (TRMA) is a syndrome characterized by megaloblastic anaemia, sensorineural hearing loss and diabetes mellitus. It is an autosomal recessive disease, caused by a mutation in the *SLC19A2* gene. Other associated clinical features include optic atrophy or cardiovascular and neurological abnormalities. We report a young girl who was genetically diagnosed as TRMA with clinical features of megaloblastic anaemia, young-onset diabetes and rod-cone dystrophy.

THE CASE

A 26-year-old girl with history of diabetes detected at the age of 9 years, on insulin thereafter, presented with complaints of osmotic symptoms. She was born as a full-term normal baby. There was no history of consanguinity. She was immunized up to age and had normal developmental milestones. However, the parents noticed visual disturbances at about 3 years of age, which gradually progressed to visual impairment. She was intellectually average with no other sensory system impairment. She was evaluated at another hospital for anaemia, at the age of 7 years, the details of which are not available. A bone marrow study was done and it was reported as dimorphic anaemia. At the age of 9 years, she was diagnosed with diabetes mellitus and started on insulin for control of blood sugar. She attained menarche at the age of 13 years and had regular cycles. There was no history of seizures, arthritis or other cardiorespiratory symptoms.

On examination, she was short-statured with a height of 145 cm and moderately nourished, with a body mass index of 22.7. She had pallor and was clinically euthyroid. She had no acanthosis nigricans or skin tags. There were no dysmorphic features. Ophthalmological evaluation was done, which was suggestive of rod-cone dystrophy. Echocardiogram and ultrasonogram of the abdomen ruled out concerned organ pathologies. Blood investigations showed poor glycaemic control with an HbA1c of 10%. Her haemoglobin level was 9.2 g/dl and peripheral smear showed dimorphic anaemia.

As her clinical profile was suggestive of a syndromic diabetes, a detailed genetic evaluation was done. Based on her multisystem involvement, anaemia, diabetes and visual impairment, one of the main possibility considered was mitochondrial cytopathies. However, serum electrolytes, creatinine phosphokinase, lactate and pyruvate were within normal limits. Apart from diabetes, there was no evidence of other endocrinopathies, myopathy, hearing loss, central nervous system (CNS) or cardiac manifestations. Hence, her samples were sent for clinical exome as well as whole mitochondrial genomic sequencing. The latter did not show any variations. Clinical exome revealed her as a compound heterozygote for *SLC19A2* gene, associated with the autosomal recessive disorder TRMA syndrome (OMIM # 249270). Both of the observed variations were in exon 2.

She was started on thiamine supplementation (100 mg/day). Within 6 months, she had better control of her blood glucose (HbA1c of 6%) and haemoglobin level of 12.2 g/dl. However, the rod-cone dystrophy being a permanent damage could not be reversed. She did not develop hearing impairment on follow-up.

DISCUSSION

TRMA is an autosomal recessive disease, characterized by mutations in *SLC19A2* gene on chromosome 1q23.3, which encodes thiamine transporter protein 1 (THTR1), whereby intracellular uptake of thiamine is disturbed. The typical features include megaloblastic anaemia, diabetes mellitus and sensorineural hearing loss. In addition, it can also present with retinal

Aster MIMS, Kozhikode, Kerala, India
VIMAL MAVILA VEETIL, DIVYA PACHAT, K. NIKITHA, JESHEERA MOHAMMED KUTTY

Correspondence to VIMAL MAVILA VEETIL; *vimalnambiar78@gmail.com*

[To cite: Veetil VM, Pachat D, Nikitha K, Kutty JM. Thiamine-responsive megaloblastic anaemia. *Natl Med J India* 2023;**36:**314–15. DOI: 10.25259/NMJI_20_21]

degeneration, optic atrophy, cardiac arrhythmias, cardiomyopathy or neurological manifestations such as stroke (Table I).[2]

Thiamine uptake in the cells is mediated by two pathways. An active saturable pathway which uptakes thiamine even at low concentrations and a passive non-saturable pathway, which causes thiamine uptake at high concentrations. Thiamine is phosphorylated by thiamine pyrophosphate kinase (TPK) and absorbed in the form of thiamine pyrophosphate, which forms the cofactor for many enzymes. In TRMA, the active transport mechanism is ineffective and TPK is defective, both of which lead to deficient cellular uptake of thiamine.[3]

The pathogenesis of megaloblastic anaemia in thiamine deficiency is not clearly identified. It is postulated that the defective RNA ribose synthesis is the pathology. Thiamine, being the cofactor for transketolase in the pentose pathway, when deficient inhibits the RNA synthesis by limiting the availability of the ribose sugar moiety. This causes defective maturation of the cells and induces apoptosis.[3]

Thiamine is important for the exocrine and endocrine function of the pancreas. Islet cells have an intermediate sensitivity to thiamine deprivation and hence the insulin requirement can be significantly reduced by thiamine supplementation. THTR1 is expressed in the inner hair cells of the cochlea, and in the auditory pathway. This makes auditory symptoms characteristic of TRMA. Thiamine transport protein is also present in the heart, eyes, retina and CNS. Ocular manifestations are mainly in the form of optic nerve atrophy, retinal dystrophy or retinitis pigmentosa. Rod-cone dystrophy can also be present. It can be due to apoptosis induced by the energy deprivation as thiamine is an important cofactor for Krebs cycle, which contributes to the bioenergetics. The same holds true for CNS, as neurons have high energy requirements.[4]

Wolfram syndrome (DIDMOAD) with the clinical stigmata of diabetes mellitus, diabetes insipidus, optic atrophy and deafness is a differential diagnosis (Table II). The differentiation can be made with the abssence of megaloblastic anaemia and thiamine responsiveness in the same. However, thiamine deficiency could be a part of the spectrum of DIDMOAD and thiamine supplementation can be of some benefit in alleviating symptoms.[5] Mitochondrial inherited disorders such as Kearns–Sayre syndrome and Pearson syndrome also have some overlapping phenotypes. The pattern of inheritance is a differentiating feature. Specific diagnosis is confirmed with the genetic analysis. There is a case report of TRMA from the same geographical area, but it has not mentioned the specific genotype.[6] The first one, c.759del (p.Ile253MetfsTer7), was a pathogenic frameshift variation, previously reported (as Del253f s/ter260) in a compound heterozygous state in an Indian patient affected with TRMA.[1]

Thiamine supplementation is the treatment in TRMA. The haematological and glycaemic disturbances can be well controlled by therapeutic doses of thiamine. Potter *et al.* illustrated in their case series that prophylactic thiamine supplementation delayed the onset of diabetes and increasing the dose influenced the severity of the disease and insulin requirement.[7] However, hearing loss in TRMA could not be delayed or prevented with thiamine supplementation. Akin *et al.* concluded in their report that though debatable, the role of early supplementation in hearing loss has to be studied further as the symptoms and timing of therapy currently are undefined.[8] The role of thiamine in megaloblastic anaemia was emphasized in a case report by Porter *et al.*, when anaemia recurred after stopping thiamine supplementation.[9]

TABLE I. Clinical and biochemical hallmarks of thiamine-responsive megaloblastic anaemia

Young-onset diabetes mellitus: brittle diabetes on conventional antidiabetic drugs
Progressive visual impairment: optic atrophy, rod-cone dystrophy, retinitis pigmentosa
Progressive sensorineural deafness
Anaemia not responding to iron, folic acid or B12 supplementation, megaloblastic anaemia or dimorphic anaemia in peripheral smear/ bone marrow examination
Response of symptoms and biochemical abnormalities to thiamine therapy

TABLE II. Differential diagnosis of thiamine-responsive megaloblastic anaemia

Disease	Differentiating features
DIDMOAD syndrome	Absence of megaloblastic anaemia and thiamine responsiveness, presence of diabetes insipidus
Pearson syndrome	Pattern of inheritance, no response of anaemia and diabetes to thiamine, exocrine pancreatic insufficiency
Kearns–Sayre syndrome	Pattern of inheritance, myopathy
Autoimmune polyglandular syndrome 2 (Type 1 DM with pernicious anaemia)	Pattern of inheritance, absence of ocular/auditory involvement

DIDMOAD diabetes insipidus and mellitus with optic atrophy and deafness
DM diabetes mellitus

Conclusion

TRMA is a rare clinical entity and needs a strong index of suspicion for diagnosis. Early diagnosis and early supplementation of thiamine helps in correction of anaemia and delays the onset of diabetes. It also prevents the development of visual and auditory complications, which improves the quality of life of the patient.

Conflicts of interest. None declared

REFERENCES

1 Bergmann AK, Sahai I, Falcone JF, Fleming J, Bagg A, Borgna-Pignati C, *et al.* Thiamine-responsive megaloblastic anemia: Identification of novel compound heterozygotes and mutation update. *J Pediatr* 2009;**155:**888–920.
2 Bay A, Keskin M, Hizli S, Uygun H, Dai A, Gumruk F. Thiamine-responsive megaloblastic anemia syndrome. *Int J Hematol* 2010;**92:**524–6.
3 Boros LG, Steinkamp MP, Fleming JC, Lee WN, Cascante M, Neufeld EJ. Defective RNA ribose synthesis in fibroblasts from patients with thiamine-responsive megaloblastic anemia (TRMA). *Blood* 2003;**102:**3556–61.
4 Meire FM, Van Genderen MM, Lemmens K, Ens-Dokkum MH. Thiamine-responsive megaloblastic anemia syndrome (TRMA) with cone-rod dystrophy. *Ophthalmic Genet* 2000;**21:**243–50.
5 Borgna-Pignatti C, Marradi P, Pinelli L, Monetti N, Patrini C. Thiamine-responsive anemia in DIDMOAD syndrome. *J Pediatr* 1989;**114:**405–10.
6 Mathews L, Narayanadas K, Sunil G. Thiamine responsive megaloblastic anemia. *Indian Pediatr* 2009;**46:**172–4.
7 Potter K, Wu J, Lauzon J, Ho J. Beta cell function and clinical course in three siblings with thiamine-responsive megaloblastic anemia (TRMA) treated with thiamine supplementation. *J Pediatr Endocrinol Metab* 2017;**30:**241–6.
8 Akýn L, Kurtoðlu S, Kendirci M, Akýn MA, Karakükçü M. Does early treatment prevent deafness in thiamine-responsive megaloblastic anaemia syndrome? *J Clin Res Pediatr Endocrinol* 2011;**3:**36–9.
9 Porter FS, Rogers LE, Sidbury JB Jr. Thiamine-responsive megaloblastic anemia. *J Pediatr* 1969;**74:**494–504.