

# Thiamine responsive megaloblastic anemia syndrome associated with patent ductus arteriosus: First case report from Kashmir Valley of the Indian subcontinent

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### ABSTRACT

Thiamine responsive megaloblastic anemia syndrome, an autosomal recessive inherited disorder characterized by a triad of anemia, diabetes mellitus and sensorineural deafness is caused by a deficiency of a thiamine transporter protein. The disorder is rare and has not been reported from our community which has high background of consanguinity. We report a six years old girl who presented with diabetes mellitus which remitted after thiamine replacement. The girl in addition had sensorineural deafness, reinopathy, atrial septal defect and megaloblastic anemia which responded to high doses of thymine. This is the first case reported from Kashmir valley and third from India. The presentation and management in such cases is discussed.

**Key words:** Diabetes mellitus, India, patent ductus arteriosus, Roger's syndrome, sensorineural deafness, thiamine transporter, thiamine responsive megaloblastic anemia syndrome

## INTRODUCTION

Thiamine responsive megaloblastic anemia syndrome (TRMA), also called Rogers syndrome after its discoverer in 1969, is an autosomal recessive inherited disorder characterized by a triad of anemia, diabetes mellitus, and sensorineural deafness.<sup>[1]</sup> TRMA is exceedingly rare outside of consanguineous pairings or isolated populations and fewer than 40 pedigrees are known world over.<sup>[2]</sup> The cases or case series have been reported in Israeli Arab, Lebanese, Alaskan natives, kindreds from Brazil, Japan, Oman, Tunisia, Italy,

Iran, Pakistan, Kashmiri families in Great Britain, ethnic kurds, Caucasians, and African Americans.<sup>[2-4]</sup> The condition is caused by mutation of a gene (SLC19A2) encoding thiamine transporter protein, a member of the solute carrier family.<sup>[5]</sup> The protein is known to be responsible for effective utilization of thiamine in various tissues and its defect in pancreatic beta cell is responsible for diabetes mellitus.<sup>[4]</sup> Onset of megaloblastic anemia is between infancy and adolescence. Anemia is corrected with pharmacologic doses of thiamine (vitamin B1) (25--75 mg/day compared to recommended daily allowance of 1.5 mg/day); however, the red cells remain macrocytic and anemia can recur when thiamine is withdrawn.<sup>[6]</sup> The diabetes mellitus being nontype 1 in nature is a monogenic defect, with age of onset from infancy to adolescence. The thiamine replacement is variously reported to cause remission of diabetes mellitus and has also been reported to develop diabetic ketoacidosis, although the mechanism is not known.<sup>[7]</sup> Progressive sensorineural hearing loss has generally been early onset, is irreversible, and may not be prevented by thiamine treatment.<sup>[2]</sup>

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The diagnosis of TRMA is based on the above obligate triad of clinical features and the bone marrow revealing megaloblastic anemia with erythroblasts often containing iron-filled mitochondria (ringed sideroblasts). The disorder being rare has not been reported from our community even in the presence of a high background of consanguinity. We report a 6-year-old girl who presented with juvenile onset diabetes mellitus and subsequently manifested with megaloblastic anemia, sensorineural deafness, retinal abnormalities, and patent ductus arteriosus (PDA). The diabetes mellitus and anemia went into total remission after thiamine replacement. The literature search did not reveal any association of PDA with TRMA. To the best of our knowledge, this is the first case of TRMA from our valley and probably the first description of association of TRMA with PDA in the world.

## CASE REPORT

SA, a 23-month-old girl, a second baby of consanguineous marriage, born of an uneventful full-term delivery by cesarean section had presented to her pediatrician with severe hyperglycemia. She was put on insulin therapy, although she had no evidence of ketosis in the face of severe hyperglycemia, negative anti-GAD antibodies, and detectable postmeal C-peptide. There was no history of fever, jaundice, haematemesis, malena, bleeding from any site or lymphadenopathy. Her anthropometry was in the expected range. Her developmental milestones were normal till at the age of 4 years when her parents had noticed delayed development of speech. The speech evaluations lead to the discovery of bilateral sensorineural hearing loss on pure tone audiometry. She was brought to our clinic at the age of 5 and a half years with poor attainment of linear growth, poor school performance, and complaints of easy fatigability with lassitude. The clinical examination revealed pallor, height of 115 cm (50th centile by CDC), weight of 18 kg (50th centile by CDC) [Figure 1a]. Her IQ was 91.66 and tuning fork testing revealed bilateral sensory neural hearing loss. Systemic examination revealed a grade III/IV holosystolic murmur at apex. Rest of the examination was unremarkable. Investigative workup revealed normochromic macrocytic anemia with mild anisocytosis (Hb = 4.8 g/dl) [Table 1]. Liver function, kidney function, urinalysis, chest roentgenography, and electrocardiography were normal. A direct antihuman globulin test was negative and bone marrow aspiration and biopsy was suggestive of late myeloid maturation arrest with a paucity of erythroid cells and megakaryocytes. The iron profile was normal [serum iron = 15.99 (6.6–26.0  $\mu\text{mol/l}$ ), total iron binding capacity = 44.20 (46.4–69.5  $\mu\text{mol/l}$ ) and transferrin saturation = 36% (16–40)] as was serum LDH (216 IU/l) and plasma lactate [23.65 mg/dl (4.5–20)]. Blood glucose levels were within acceptable range while on insulin 9–12 units

**Table 1: Comparison of blood glucose and hemogram before and after thiamine therapy**

	Prethiamine therapy		Postthiamine therapy	
	Fasting	Post meal	Fasting	Post meal
Blood glucose (mg/dl)	228	287	112	116
	224	259	99	117
	259	305	92	122
<b>Hemogram</b>	<b>Prethiamine therapy</b>		<b>Postthiamine therapy</b>	
Hb (g/dl)	4.8		11.1	
MCV (70–90 fl)	95.0		86.8	
MCH (25–33 pg)	31.4		25.3	
MCHC (32–36 g/dl)	33.7		30.0	
RDW (11–16%)	24.2		30.0	

of Insulin as part three times a day [Table 1]. Visual-evoked potential was normal bilaterally but electroretinography (ERG) revealed evidence of severe degree of macular involvement with associated axonal involvement of the peripheral retinal ganglionic cells. The pattern reversal stimulation did not evoke anything on ERG but on flash stimulation amplitude was reduced and latency was normal [Figure 1b]. Audiogram was suggestive of profound bilateral sensorineural type of hearing loss [Figure 1c]. Echocardiography revealed a 3.2 mm small PDA with left to right shunt (maximum pressure gradient across 45 mmHg), intact IAS/IVS, and LVEF of 65% [Figure 1d]. The PDA was corrected at the age of 6 years and postoperative echocardiography was normal.

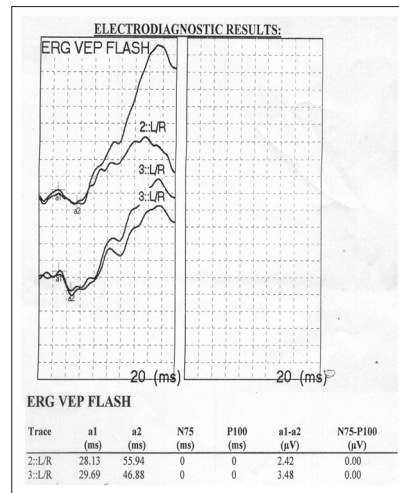
With the above clinical data a diagnosis of Roger's syndrome was entertained and the patient was put on high dose of oral thiamine (75 mg daily). The patient was followed closely and clinical assessment and investigation were done every three to 4 weeks of treatment. The patient required gradually decremental doses of insulin till she went off insulin in a period of 10 weeks. Currently her blood glucose is in the normal range [Table 1] and hemoglobin showed a steady rise (to Hb = 11.1 g/dl) with peripheral blood smear showing normal morphology except mild anisocytosis [Table 1]. She was given a hearing aid and is planned for cochlear implant.

## DISCUSSION

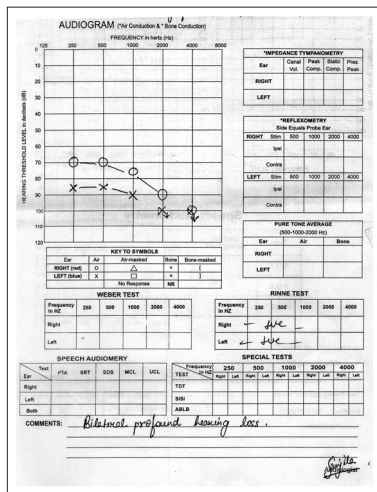
TRMA, also known as Roger's syndrome, is an autosomal recessive disorder characterized by megaloblastic anemia, diabetes mellitus, and sensorineural hearing loss.<sup>[1]</sup> Since fewer than 40 pedigrees are known, it is exceedingly rare outside of consanguineous pairings or isolated populations. The reported cases are from populations such as Israeli Arab, Lebanese, Russians, Brazilian, Japanese, Italian, Iranian, and Pakistani kindreds.<sup>[2–4]</sup> The disorder is due to genetic defects in thiamine transfer protein an thiamine is



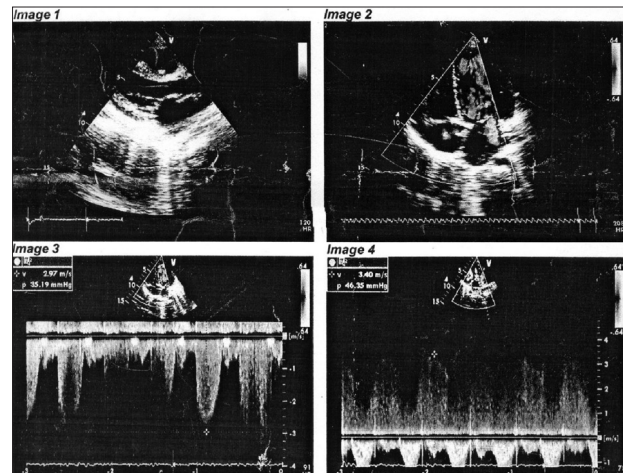
**Figure 1a:** Photomicrograph of the patient with Thiamine responsive megaloblastic anemia syndrome



**Figure 1b:** Visual evoked potential of the patient with Thiamine responsive megaloblastic anemia syndrome



**Figure 1c:** Pure tone audiometry showing bilateral sensorineural hearing loss



**Figure 1d:** Echocardiography of the patient showing patent ductus arteriosus

converted into the active form, i.e., thiamine pyrophosphate (TPP), which is incorporated into four mammalian enzymes: the pentose phosphate shunt enzyme transketolase and three multienzymatic complexes involved in oxidative decarboxylation reactions: (1) pyruvate dehydrogenase, (2) ketoglutarate dehydrogenase, and (3) branched chain keto-acid dehydrogenase. Based on the finding of reduced ketoglutarate dehydrogenase in the lymphocytes of a patient with TRMA, Abboud *et al.* proposed that defective TPP binding to the enzyme was implicated in the genesis of the syndrome.<sup>[8]</sup> Poggi *et al.* first noted a low TPP content in TRMA erythrocytes and postulated that the lack of high affinity thiamine transporter might be associated with the syndrome.<sup>[9]</sup> This hypothesis has recently been confirmed by Stagg *et al.* who documented the absence of the high affinity thiamine transporter on fibroblasts of TRMA patients and demonstrated that a low thiamine concentration may cause cell death by apoptosis.<sup>[10]</sup>

The case, we are reporting is the first observed case from Kashmir valley although from a consanguineous marriage. Our case had history of abortion in mother and one normal sib. All other family members were normal. Diabetes mellitus in this syndrome is likely due to insulin insufficiency that initially responds to thiamine supplements; however most patients become fully insulin dependent after puberty.<sup>[11]</sup> Our case became insulin independent only after 10 weeks and is continuing to be so 12 months after. Sensorineural hearing loss is caused by abnormalities of the inner ear (hair cell loss) during early childhood,<sup>[12]</sup> and remains generally irreversible as in our case. Although animal studies have shown reversibility of hearing loss with thiamine supplementation,<sup>[13]</sup> early diagnosis has been, however, shown to reverse the deafness partially in humans.<sup>[14]</sup> Retinal abnormalities such as retinitis pigmentosa, optic atrophy, cone-rod dystrophy, etc. are other components of the disorder.<sup>[15]</sup> In our

case electroretinography revealed evidence of severe degree of macular involvement with associated axonal involvement of the peripheral retinal ganglionic cells. Various types of anemia are described in TRMA including megaloblastic, sideroblastic or aplastic that all responding to thiamine therapy suggesting the role of thiamine at various levels such as in DNA metabolism (megaloblastic changes) and heme synthesis (ringed sideroblastic changes). Examination of the bone marrow reveals megaloblastic anemia with erythroblasts often containing iron filled mitochondria (ringed sideroblasts).<sup>[7-9]</sup> SLC19A2, which encodes the high affinity thiamine transporter, gene known to be associated with TRMA, is shown to induce these abnormalities. The reduced nucleic acid production through impaired transketolase catalysis is the underlying bio-chemical disturbance that likely induces cell cycle arrest or apoptosis in bone marrow cells and leads to TRMA syndrome in patients with defective high affinity thiamine transport.<sup>[3-9]</sup> Treatment of TRMA focuses on lifelong use of pharmacologic doses (25--75 mg/day) of thiamine in affected individuals<sup>[11]</sup> as early as possible. Our case had severe anemia with megaloblastic picture that reversed dramatically and completely after therapy. Although disorders such as Wolfram syndrome, Kearns Sayre Syndrome and Pearson syndrome have similar phenotype, the response of anemia and diabetes to thiamine therapy is a strong support to the diagnosis, in the absence of genetic analysis. Pearson syndrome is a rare, multisystemic, mitochondrial cytopathy manifesting by refractory sideroblastic anemia, pancytopenia, defective oxidative phosphorylation, exocrine pancreatic insufficiency, and variable hepatic, renal, and endocrine failure. Death often occurs in infancy or early childhood due to infection or metabolic crisis. Patients may recover from the refractory anemia. Older survivors have Kearns--Sayre syndrome (KSS), which is a mitochondriopathy characterized by progressive external ophthalmoplegia and weakness of skeletal muscle. Wolfram syndrome caused by mutation of WFS-1 gene on chromosome 4p16.1 with diabetes mellitus, diabetes insipidus, deafness, and optic atrophy is not responsive to thiamine.<sup>[16]</sup>

Cardiovascular problems of TRMA involve a spectrum of disorders such as congenital heart disease and/or arrhythmias, backwardness, situs viscerum inversus, structural defects heart defects.<sup>[17]</sup> Recently a case of atrial stand still probably caused by a two base-pair deletion in exon four (1147delGT) of the gene SLC19A2 has been reported.<sup>[18]</sup> To date only 14 TRMA cases with cardiac defects have been reported in the literature and our case is the first case with PDA and TRMA association. Our case also supports the reversibility of diabetes mellitus. In conclusion we report first case of TRMA from

Kashmir valley, third from India<sup>[19,20]</sup> and incidentally the first association of TRMA with PDA in the world. This case report stresses the need toward early diagnosis and treatment with thiamine in children presenting with anemia, diabetes and deafness. Hence children presenting with this triad should be evaluated for TRMA syndrome, especially in this part of the world with high background consanguinity.

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