

CASE REPORT

THIAMINE RESPONSIVE MEGALOBLASTIC ANEMIA IN TWO FEMALE SIBLINGS

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ABSTRACT: Thiamine responsive megaloblastic anemia (TRMA) is an autosomal recessive disorder, which is caused by loss of function mutations in the SLC19A2 gene. TRMA is characterized by anemia, deafness, and diabetes mellitus. We now report two sisters, the eldest of which presented to a different hospital during childhood with sensorineural deafness, which was treated with a hearing prosthesis, insulin requiring diabetes, megaloblastic anemia. The younger sister is also affected with sensorineural deafness along with diabetes and megaloblastic anemia. Because a diagnosis of TRMA was suspected, therapy with insulin and thiamine was started to which the child is responding. Diabetes associated with deafness and megaloblastic anemia, suggests a diagnosis of TRMA.

KEYWORDS: Diabetes mellitus; Deafness; Megaloblastic anemia; Thiamine.

INTRODUCTION: Thiamine responsive megaloblastic anemia (TRMA) is an autosomal recessive disorder, which is caused by loss of function mutations in the SLC19A2 gene.¹ TRMA is characterized by anemia, deafness, and diabetes mellitus. It can be associated with retinitis pigmentosa and olfactory abnormalities² as described in wolfram syndrome. It can also be associated with cone-rod dystrophy,² heart rhythm abnormalities and structural cardiac anomalies.³

CASE REPORT: A 7.5 year old girl was admitted to with extremely high blood sugar levels, severe pallor and mild grade temperature. Her mother noticed an increase in body temperature two days ago and the blood sugars remaining constantly high since three to four days even on subcutaneous insulin.

Previously the child was admitted with similar complaints of high blood sugars and severe pallor thrice, during 2 years, 3 years and 6.5 years of age, which were managed with insulin infusion and blood transfusions. The child also suffered from three to four episodes of seizures when she was 3 years old which was explained because of hyperglycemia.

The mothers prenatal, child's natal and postnatal period was uneventful. The child is fully immunized according to the IAP immunization schedule. She attained all developmental milestones according to the appropriate age. The first time the parents took the child to a hospital when she was a year old as she would respond to any sound, when she was diagnosed as having sensorineural hearing loss as was given a hearing aid.

Then the parents noticed increased urine output at three years of age when she was diagnosed to have diabetes mellitus and anemia for which she was started on subcutaneous insulin and blood transfusions. She was admitted and treated for hyperglycemia and anemia on two other occasions. Her blood sugars are poorly controlled since the time of diagnosis of diabetes mellitus.

Present examination of the child revealed severe pallor with hepatosplenomegaly, very high blood sugars, and mild fever. The child was immediately started on insulin infusion with blood

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transfusions; sugars were greatly fluctuating in spite of the insulin infusion. Peripheral blood smear showed normocytic hypochromic red blood cells with hypersegmented neutrophils, severe thrombocytopenia. Bone marrow aspiration was hypercellular and contains RBC precursors called megaloblasts and hypersegmented megakaryocytes. The child's parents are unaffordable for gene analysis.

On second day of admission the child's younger sister, aged 5 years was visiting her and we happened to notice that she was very pale. On investigating her blood picture she was also found to be anemic with megaloblasts on the peripheral smear. Hence, a bone marrow aspirate was taken for her too which revealed a similar picture.

In history we found that this child was also diabetic since she was three years old and her hearing loss was detected at a much earlier age, i.e. 1.5 years. She was already on insulin but had never undergone any blood transfusions in the past and she has been using a hearing since 3.5 years. Her hyperglycemia was not as variant as her sisters but would have drastically changed periodically.

The child has a younger brother as well, aged 3 years, who is perfectly healthy without any anemia, diabetes or hearing loss.

The child and her sister were started on oral thiamine, within 10 days their blood sugars were on borderline levels and our patient's appetite started improving. After one month of treatment our patient's blood sugars are well controlled on subcutaneous insulin and no anemia was detected on repeated investigations in either of the sisters. Based on the above examination, lab investigations and response to treatment and inheritance pattern the female siblings were diagnosed as thiamine responsive megaloblastic anemia.

DISCUSSION: Thiamine responsive megaloblastic anemia (TRMA), also known as Rogers syndrome, is an autosomal recessive disorder, that was described in 1969.⁴ Which is caused by loss of function mutations in the SLC19A2 gene, that is responsible for encoding the high-affinity thiamine transporter protein⁵⁻⁷ and the locus has been localized to 1.4-cM Region of 1q23.⁸ Distinct mutations in SLC19A2 have been described in many families⁹ and lead to either a lack of the protein product or an altered structure of the protein so that it is not properly targeted to its site of function on the cell membrane.^{9,10}

TRMA is characterized by anemia, deafness, and diabetes mellitus. Hematological features consist of the unique combination of megaloblastic changes and the ring sideroblast abnormality, with variable degrees of neutropenia and thrombocytopenia.¹¹

The megaloblastic change is thought to result from impaired nucleic acid synthesis via nonoxidative branch of the pentose cycle, where transketolase requires thiamine as a cofactor¹². Some of the recent data indicate defective heme synthesis,¹³ which would explain the ring sideroblasts, but the mechanism is undefined. It may relate to the role of thiamine as a cofactor for α -ketoglutarate dehydrogenase.¹⁴

Further reports on TRMA described congenital heart disease, arrhythmias, abnormalities of the retina and optic nerve, aminoaciduria, situs inversus, and stroke-like episodes in addition to the characteristic triad.¹⁵⁻²⁰ Thiamine in pharmacologic doses usually ameliorates the anemia and diabetes initially, but it has become ineffective in adulthood.²¹

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BIBLIOGRAPHY:

1. Mathews L, Narayan D, Sunil K. Thiamine responsive megaloblastic anemia. *I Pediatr* 2009; 46: 172-174.
2. Meire FM, Van Gendered MM, Lemmens K, Ens-Dokkum. Thiamine responsive megaloblastic anemia with cone-rod dystrophy. *Optha Gen* 2000; 21: 243-250.
3. Lorber A, Gazit AZ, Khoury A, Schwartz Y, Mandel. Cardiac manifestations in thiamine responsive anemia syndrome; *Pediatr Cardio*; 2003; 24: 476-481.
4. Porter FS, Rogers LE, Sidhury JB Jr. Thiamine responsive megaloblastic anemia. *J. Pediatr* 1969; 74: 494-504.
5. Labay V, Raz T, Baron D, et al. Mutations in SCL19A2 cause thiamine responsive megaloblastic anemia associated with diabetes mellitus and deafness. *Nat Genet* 1999; 22: 300-304.
6. Fleming JC, Tartaglino E, Steinkamp MP, et al. The gene mutated in thiamine responsive anemia with diabetes and deafness (TRMA) encodes a functional thiamine transporter, *Nat Genet* 1999; 22: 305-308.
7. Diaz GA, Banikazemi M, Oishi K, et al. Mutations in a new gene encoding a thiamine transporter cause thiamine responsive megaloblastic anemia syndrome, *Nat Genet* 1999; 22: 309-312.
8. Maryan B, George AD, Parvaneh V, et al. Localization of the thiamine responsive megaloblastic anemia syndrome locus to a 1.4cM region of 1q23; *Mol Gen and Meta*; 1999; 66: 193-198.
9. Baron D, Asaraf YG, Cohen N, et al. Lack of plasma membrane targeting of a G172D mutant thiamine transporter derived from Rogers syndrome family. *Mol Med* 2002; 8: 462-494.
10. Subramaniam VS, Marchant JS, Parker I, et al. Cell biology of thiamine transporter-1 (hTHTRD). *J Biol Chem* 2003; 278: 3976-3984.
11. Neufeld EJ, Fleming JC, Tartaglino E, et al. Thiamine responsive megaloblastic anemia syndrome; a disorder of high-affinity thiamine transport. *Blood Cell Mol Dis* 2001; 27: 135-138.
12. Boros LG, Steinkamp MP, Fleming JC, et al. Defective RNA ribose synthesis in fibroblasts from patients with thiamine responsive megaloblastic anemia. *Blood* 2003; 102: 3556-3561.
13. Sahai I, Montefusco C, Fleming JC, et al. Role of defective high-affinity thiamine transporter slc19a2 in marrow from a mouse model of thiamine responsive megaloblastic anemia; evidence for defective deoxyribose and heme synthesis (Abstract). *Blood* 2005; 106: 154a.
14. Abboud MR, Alexander D, Najjar SS. Diabetes mellitus, thiamine dependent megaloblastic anemia, and sensorineural deafness associated with deficient alpha-ketoglutarate dehydrogenase deficiency. *J Pediatr* 1985; 107: 537-541.
15. Viana MB, Carvalho RI. Thiamine-responsive megaloblastic anemia, sensorineural deafness, and diabetes mellitus: a new syndrome? *J Pediatr* 1978, 93:235-238.
16. Mandel H, Berant M, Hazani A, Naveh Y. Thiamine-dependent beriberi in the thiamine-responsive anemia syndrome. *N Engl J Med* 1984, 311:836-838.
17. Abboud MR, Alexander D, Najjar SS. Diabetes mellitus, thiamine-dependent megaloblastic anemia, and sensorineural deafness associated with deficient alpha-ketoglutarate dehydrogenase activity. *J Pediatr* 1985, 107:537-541.
18. Neufeld EJ, Mandel H, Raz T, Szargel R, Yandava CN, Stagg A, Faure S, Barrett T, Buist N, Cohen N. 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, 61:1335-1341.

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19. Raz T, Barrett T, Szargel R, Mandel H, Neufeld EJ, Nosaka K, Viana MB, Cohen N. Refined mapping of the gene for thiamine-responsive megaloblastic anemia syndrome and evidence for genetic homogeneity. *Hum Genet* 1998, 103:455–461.
20. Bazarbachi A, Muakkit S, Ayas M, Taher A, Salem Z, Solh H, Haidar JH. Thiamine-responsive myelodysplasia. *Br J Haematol* 1998, 102:1098–1100.
21. Ricketts CJ, Minton JA, Samuel J, et al. Thiamine responsive megaloblastic anemia syndrome; long-term follow-up and mutation analysis of seven families. *Acta Paediatr* 2006; 95: 99-104.



Figure 1

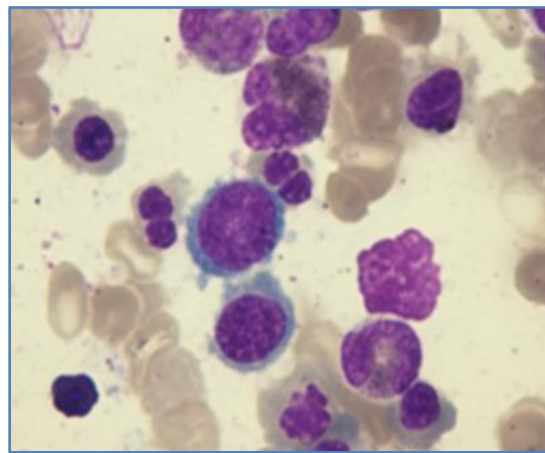


Figure 2



Figure 3

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