

## Thiamine Responsive Megaloblastic Anemia

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This report describes a female child with thiamine responsive megaloblastic anemia syndrome (Rogers syndrome), presenting with anemia and diabetes mellitus responding to thiamine. She also had retinitis pigmentosa. The anemia improved and blood sugar was controlled with daily oral thiamine. Previously unreported olfactory abnormalities, as described in Wolfram syndrome, were also present in our patient.

**Key words:** *Megaloblastic anemia, Rogers syndrome, Thiamine.*

**T**hiamine responsive megaloblastic anemia syndrome is an extremely rare autosomal recessive disorder characterized by the triad of anemia responding to thiamine, diabetes mellitus and sensorineural deafness. Only 27 families have been described so far all over the world; none from India.

### CASE REPORT

A 10 year old girl was evaluated at the Institute of Maternal and Child Health attached to Medical College, Calicut in June 2000 for polydipsia and polyuria of one-month duration. She was first child of a nonconsanguineous marriage; her younger male sibling was healthy. At 2 years of age, she was evaluated for difficulty in vision and detected to have pigmentary changes in the retina. At 7 years she was evaluated for refractory anemia and started on vitamin B complex preparations, as bone marrow study suggested the possibility of sideroblastic anemia. She also had difficulty in appreciating and differentiating smells. There was no family history of anemia, diabetes mellitus or deafness. On examination she was pale, short statured, and with diminished visual acuity and nystagmus. Neurological examination was otherwise normal. There was no organomegaly. Fundus examination was consistent with retinitis pigmentosa. Pure tone audiometry was normal.

Investigations revealed fasting and post prandial blood sugar levels to be 304 mg%, and 424 mg%, respectively. Red blood cell indices were as follows; hemoglobin 8.7g/dL, MCV 101.9fL, MCH 27.9 pg, MCHC 29.8g/dL, and RDW 19.4. Peripheral smear showed anisocytosis with many macrocytes, polychromasia and nucleated red cells. Bone marrow showed megaloblastic anemia with ringed sideroblasts. Serum iron (189 microgram/dL) and ferritin (177 ng/mL) values were elevated. Total iron binding capacity (220 microgram/dL) was low. Renal and liver function tests, chest X-ray, and electrocardiogram were within normal limits. Ultrasonography of abdomen showed mild to moderate hepatomegaly. After stabilizing her blood sugar she was discharged on lente - plain insulin combination and B complex preparation. She was under follow up. At this time, she sought treatment at another centre where she was reevaluated and diagnosed as Kearns Sayre Syndrome (KSS) with congenital sideroblastic anemia. B complex preparation was discontinued and she was started on 40 mg pyridoxine daily along with insulin. Six months later she was readmitted in our hospital with poor diabetic control and severe anemia, which required blood transfusion. Insulin dose was readjusted. Review of history and examination suggested another condition with similar clinical picture, thiamine deficiency. Hence the possibility of

TRMA (thiamine responsive megaloblastic anemia) was considered and she was started on 75 mg thiamine daily oral dose.

She is now on high dose thiamine. Her insulin requirement has decreased and anemia has improved. She has not required any blood transfusion after starting 75mg thiamine for more than a year.

An attempt was made to prove the genetic origin of the disease and she was found to have a mutation of SLC19A2 gene responsible for TRMA syndrome.

## DISCUSSION

Rogers first described Thiamine responsive megaloblastic anemia syndrome in 1969(1). Megaloblastic anemia which is corrected with pharmacologic doses of thiamine (25-75 mg/day) occurs between infancy and adolescence. Anemia can recur when thiamine is withdrawn, which happened to our patient when she was on pyridoxine alone for a period of 6 months. Diabetes mellitus is non-type 1 in nature with onset from infancy to adolescence. High dose thiamine supplementation may delay onset of diabetes. Reports show a decrease in insulin requirement with institution of high dose of thiamine(2). This was observed in our patient. Progressive sensorineural deafness, which is irreversible, occurs in early life. Whether hearing can be improved or hearing loss delayed by high dose thiamine is not clear. But animal studies have shown reversibility of hearing loss with thiamine supplementation(3). In addition to the triad other features like optic atrophy, short stature, hepatosplenomegaly, retinal degeneration and cardiovascular abnormalities have been reported. Retinitis pigmentosa as in our case was observed in an African-American female with TRMA(4,5). Our patient had no deafness.

TRMA is caused by mutation of SLC19A2 gene located on 1q 23.3(6). It encodes a thiamine transport protein called THTR 1, which is essential for uptake of thiamine by cells. There is another transport protein with less affinity (THTR 2), which is not present in bone marrow, pancreas and cochlea. This could be the reason for clinical manifestations of TRMA. While giving high dose thiamine the low

affinity pathway is being utilized.

With megaloblastic red cell changes and ringed sideroblasts, most important differential diagnosis is megaloblastic disorders of premalignant potential. Wolfram syndrome caused by mutation of WFS-1 gene on chromosome 4p16.1 with diabetes mellitus, diabetes insipidus, deafness and optic atrophy is phenotypically related to TRMA. Olfactory abnormalities as described in Wolfram syndrome is present in our patient, which has so far not been reported in TRMA syndrome. Mitochondrial disorders like KSS and Pearson syndrome are other differential diagnosis. But response to thiamine as observed in our patient distinguishes TRMA from these.

Though no case has been reported from India, there are reports showing TRMA in families of Indian origin(7). So in a child with diabetes and refractory anemia, TRMA should be considered as a possibility.

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