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Thiamine Responsive Megaloblastic Anemia in a sibling

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Abstract

This case report is presenting a 2-year-old girl admitted to Ali Asghar Tertiary Pediatric Hospital with periorbital edema, petechia and purpura. Her manifestations were weakness, low appetite, irritability, weight loss, aphasia, from 6 months before admission. After evaluation of the heart, endocrine, neurologic system and genetic consulting it was revealed the exact nature of it. The diagnosis was a very rare autosomal recessive anemia called Thiamin Response Megaloblastic Anemia (TRMA). After 3 years, his brother developed similar symptoms with the same diagnosis.

Keywords: Thiamin-Responsive Megaloblastic Anemia, children, Sibling

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Clinical History

This case report is presenting a sister and brother with thiamin-responsive megaloblastic anemia. The first patient was a 32-month-old girl admitted to Ali-Asghar Tertiary Pediatric Hospital. Her chief complaints were weakness, pre-orbital edema, easy bruising and irritability. In her past medical history, she had experienced weakness, weight loss (about 5 kilograms), restlessness, sleeplessness and loss of appetite from 6 months before admission. In physical examinations, vital sign was normal. However, pre-orbital edema, paler of mouth and mucous membrane, lower extremities edema, hepatomegaly, deafness and hyperglycemia (BS > 200 mg/dl) were detected. After consultations with heart pediatric department, we were informed about dilatation in right ventricular and right atrium and cardiomegaly as reported in echocardiography. Also, loss of function in systolic right ventricular was seen. However, the left heart was intact. Because of mild hypertension, some antihypertensive drugs were started. In addition, we consulted with an endocrinologist and she was categorized in diabetic group. All finding reveals the mitochondrial abnormalities. In neurologic consultation neuro developmental delay, bilateral sensory neural hearing loss and seizure-like symptom such as breath holding were found. We observed macro-ovalocyte and hypersegmented neutrophil in peripheral blood smear. Based on genetic consultation, a rare mutation was detected that it was indicated as uncommon megaloblastic anemia. According to DNA extraction analysis, PCR and direct sequencing examined all exons and UTRs of the SLC19A2 gene. Therefore, TRMA was diagnosed as her problem. After about 3 years, her brother was admitted to hospital with the same symptoms. He was 9-month-old. Because, their parents were relatives and the same symptoms, we suspected to TRMA. The genetic studies of both children were similar. These presentations had showed us a very rare autosomal recessive disease in a family. For both of them antihypertensive drugs (lasix, aldacton, lanoxin,

Table 1. Laboratory data of the affected sibling at diagnosis.

	Sister's lab test	Brother's lab test
WBC	6100	4300
RBC	2.95	2.56
Hb	8.9	7.5
Hct	29.5	25.6
MCV	100	100
MCH	30.2	29.3
MCHC	30.2	29.3
Plt	804000	198000
Retic	0.5	0.8
FBS	200	145

and captopril) were started. Vitamin B1 tablet was also initiated for treatment (Table 1).

Discussion

Thiamine-responsive megaloblastic anemia (TRMA) syndrome is described by megaloblastic anemia, progressive sensorineural hearing loss and diabetes mellitus. It initiates between infancy and adolescence periods. This anemia can be treated by thiamine, however, red blood cells remain macrocytic and therefore, the anemia may relapse after stopping the treatment (1). Progressive sensorineural hypoacusis is often observed in lower ages and can be diagnosed in toddlers. This hypoacusis is irreversible and may be not preventable by thiamine. The nature of diabetes mellitus in these patients differs with type I diabetes and its initiation is in infancy to adolescence periods. In some patients, thiamine treatment may delay the diabetes (2).

The first findings on significant bone marrow problems were in the first years of life and the last findings were observed in adolescence. Blood cell count in peripheral blood shows macrocytic anemia pattern with low hemoglobin and high mean cell volume (MCV) in the absence of folate and vitamin B12. Bone marrow shows dysplastic hematopoiesis along with several megaloblasts.

Hearing impairments may occur in early ages and even observed in the time of birth in some families (3). Progressive sensorineural hypoacusis is irreversible and may not be prevented by thiamine treatment, its basics is unknown; it is not clear that this type of hypoacusis is originated from cochlea or hearing nerves. Animal studies however suggest that the death of some cells in cochlea hair could result in hearing impairment in TRMA (4).

In many people with glycosuria and hyperglycemia, none- type I diabetes occurs before school age. in some cases, diabetic ketoacidosis was reported (5). At the beginning, the patients respond to hypoglycemic factors but they become dependent to insulin in long term.

In addition to three clinical features that are TRMA specifications, other findings were also observed in some special subgroups of the patients:

Optic atrophy appears to be common in case reports. Abnormal appearance and functional retina dystrophy have been reported (6-7). Genetic analyses have revealed that families with DIDMOAD (Diabetes insipidus, Diabetes Mellitus, optic Atrophy and Deafness) have TRMA as reported in BURGA-PIGNATI work (8); currently, optic atrophy is not a regarded as characteristic of TRMA.

In 27% of TRMA, cardiovascular disorders such as sudden death, stroke, high output heart failure, proximal atrial tachycardia, atrial fibrillation and congenital heart defects such as ventricular or atrial fibrillation were reported (9).

In 27% of TRMA cases, significant neurological deficits such as stroke and focal or generalized epilepsy were reported in early childhood (10).

TRMA is very rare outside the families with common dynasties or isolated populations. This disease has been observed in various ethnics including Arabs, Israeli, Lebanese, Alaska natives, natives of Russia, Brazil, Japan, Tunisia, Italians (Venetians and others), Iran, India, Pakistan and also families in Kashmir, Great Britain, Kurds, North Europeans and African Americans (11).

A combination of megaloblastic variations in red blood cells and ring sideroblasts are unique in TRMA patients among the metabolic and nutrition-based anemia cases. Among the adventitious anemia, this combination is mainly due to Myelodysplastic syndromes in which megaloblastosis and Sideroblasts are observable. TRMA should not be mistaken with Myelodysplastic disorders due to initial malignancies.

TRMA diagnosis in a proband can be confirmed as follows: Having megaloblastic anemia

and normal level of vitamin B12/folic acid (with or without diabetes or hypoacusis) which responds to oral thiamine (vitamin B1); and/or identification of two-allele pathogenic variants in SLC19A2 gene through genetic molecular test.

There are some overlaps between TRMA and Wolfram syndrome, also called DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness); these overlaps are diabetes mellitus, optic atrophy and deafness. Megaloblastic anemia and response to thiamine are the two specifications that are not observed in Wolfram Syndrome. This syndrome is caused by WFS1 pathogenic variants. Coded protein is a 100-kDa transmembrane glycoprotein in endoplasmic network which is assumed to have role in membrane transfer, protein processing or calcium hemostasis regulation.

A combination of diabetes mellitus and deafness refers to mitochondrial disorders, but macrocytic anemia, megaloblastostic bone marrow and response to thiamine therapy makes TRMA differnet from these disorders (refer to book-part://mt-overview). Inheritance of TRMA is recessive autosomal which makes it different from mother-transferred disorders and mitochondrial inheritance.

To determine the extent of the disease and the patient needs, following evaluations are recommended if they were not conducted before: 1) CBC of peripheral blood and bone marrow analysis for evidences on megaloblastostic anemia, 2) Folate and vitamin B12 serum concentration and investigation of iron serum concentration to overrule other disorders, 3) Auditory test, 4) Fasting serum glucose concentration, oral glucose tolerance test (OGTT) and urine analysis to diagnose diabetes mellitus, 5) Optometric evaluations, 6) Cardiac evaluations including echocardiography, 7) Neural imaging including brain MRI at the time of indication, 8) Consulting with a genetic expert or genetic counseling

Regardless of patient age, treatment management should be focused on life-long administration of pharmacological dosages of oral thiamine (50-100 mg/day).

High dosages of thiamine supplement Improves the hematologic condition significantly. Based on some studies, this treatment does not prevent from development of hypoacusis in infants having TRMA (12-13). Investigation of the effectiveness of thiamine in high dosages on auditory improvement or delay in hypoacusis is difficult and has not yet been understood. It may delay the initiation of diabetes mellitus and improve diabetes mellitus for several decades in short term (14). In some cases, the need for insulin reduced by thiamine therapy (15). It has not been investigated as a treatment for optic atrophy, cardiovascular disorders or neurological disorders related to TRMA.

Conflicts of interest: Authors declared none.

References

1- Kliegman R, Stanton B, St Geme J, Schor N, Nelson Textbook of Pediatric. Elsevier; Chapter 454, Megaloblastic Anemia, p 2319; 2016.

2- Valerio G, Franzese A, Poggi V, Tenore A. Long-term follow-up of diabetes in two patients with thiamine-responsive megaloblastic anemia syndrome. Diabetes Care. 1998; 21:38–41.

3- Setoodeh A, Haghighi A, Saleh-Gohari N, Ellard S, Haghighi A. Identification of a SLC19A2 nonsense mutation in Persian families with thiamine-responsive megaloblastic anemia. Gene. 2013;519:295–7.

4- Liberman MC, Tartaglini 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.

5- Kurtoğlu S, Hatipoglu N, Keskin M, Kendirci M, Akcakus M. Thiamine withdrawal can lead to diabetic ketoacidosis in thiamine responsive megaloblastic anemia: report of two siblings. J Pediatr Endocrinol Metab. 2008;21:393–7.

6- 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.

7- Kipioti A, George ND, Hoffbrand AV, Sheridan E. Cone-rod dystrophy in thiamine-responsive megaloblastic anemia. J Pediatr Ophthalmol Strabismus. 2003;40:105–7.

8- Borgna-Pignatti C, Marradi P, Pinelli L, Monetti N, Patrini C. Thiamine-responsive anemia in DIDMOAD syndrome. J Pediatr. 1989;114:405–10.

9- Lorber A, Gazit AZ, Khoury A, Schwartz Y, Mandel H. Cardiac manifestations in thiamine-responsive megaloblastic anemia syndrome. Pediatr Cardiol. 2003;24:476–81.

10- Shaw-Smith C, Flanagan SE, Patch AM, Grulich-Henn J, Habeb AM, Hussain K, Pomahacova R, Matyka K, Abdullah M, Hattersley AT, Ellard S. Recessive SLC19A2 mutations are a cause of neonatal diabetes mellitus in thiamine-responsive megaloblastic anaemia. Pediatr Diabetes. 2012;13:314–21.

11- Bergmann AK, Sahai I, Falcone JF, Fleming J, Bagg A, Borgna-Pignati C, Casey R, Fabris L, Hexner E, Mathews L, Ribeiro ML, Wierenga KJ, Neufeld EJ. Thiamine-responsive megaloblastic anemia: identification of novel compound heterozygotes and mutation update. J Pediatr. 2009;155:888–92.e1.

12- Borgna-Pignatti C, Azzalli M, Pedretti S. Thiamine-responsive megaloblastic anemia syndrome: long term follow-up. J Pediatr. 2009;155:295–7.

13- Akın L, Kurtoğlu S, Kendirci M, Akın MA, Karakükçü M. Does early treatment prevent deafness in thiamine-responsive megaloblastic anaemia syndrome? J Clin Res Pediatr Endocrinol. 2011; 3:36–9.

14- Valerio G, Franzese A, Poggi V, Tenore A. Long-term follow-up of diabetes in two patients with thiamine-responsive megaloblastic anemia syndrome. Diabetes Care.

15- 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; 61:1335–41.