THIAMINE–RESPONSIVE MEGALOBLASTIC ANEMIA, SENSORINEURAL DEAFNESS AND DIABETES MELLITUS

T. Zaman, M. Kadivar and R. Moradian

Department of Metabolic Diseases, Children's Medical Center, Medical Sciences/University of Tehran, Tehran, Iran

Abstract- The syndrome of diabetes mellitus, sensorineural deafness and megaloblastic anemia dose not result from thiamine deficiency. The previous reported patients had no sign of beriberi, had normal nutrition, and had no evidence of malabsorption. The features of this syndrome with apparent inheritance of autosomal recessive trait may define this puzzling syndrome as a true thiamine dependency state. The first Iranian patient was described by Vossough *et al.* in 1995. We found nine new cases with diagnostic criteria of thiamine responsive megaloblastic anemia during eight years of our study. In two patients, presentation of diabetes and anemia was concomitant. All of them were deaf with sensorineural hearing loss which was detected in infancy up to two years of age. The presence of congenital valvular heart disease was eliminated by normal echocardiography, but cardiomyopathy was discovered in two. Nonspecific amino-aciduria was discovered in three but urinary screening tests for hereditary orotic aciduria were negative. Ox-Phos biochemistry of muscle mitochondria which demonstrates severe defect in complexes I, III, IV in diabetes mellitus associated with deafness, were done but was unremarkable in our patients. Urinary methylmalonic acid and methyl malonyl carnitine by GS/MS and TMS was done in our patients and showed abnormal results in six patients. Thiamine gene, SLC 19A2, was detected in four patients.

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INTRODUCTION

Megaloblastic anemias are not uncommon in the world (1). They are found mainly in folic acid and vitamin B_{12} deficiency states or as the initial presentation of preleukemic leukemia, the congenital cases resistant to the administration of folic acid and vitamin B12, such as congenital defects in folate or vitamin B12 utilization, hereditary orotic aciduria and pyridoxine responsive refractory anemia are infrequent (1).

In 1969, Rogers *et al.* described a case of unexplained anemia in association with diabetes mellitus, aminoaciduria and sensorineural hearing loss (2). The anemia responded only to pharmacologic doses of thiamine. Since then, other children with the same findings have been reported (3, 4), including two patients with DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, deafness) (5).

The diagnosis was based on the following criteria: 1) no response to the prior administration of folic acid, vitamin B_{12}, or pyridoxine; 2) normal levels of serum folic acid and vit B_{12}; 3) immediate, striking response to the administration of thiamine alone, but hematologic relapse after discontinuing the thiamine supplementation (6); 4) The association of megaloblastic anemia with sensorineural deafness and diabetes mellitus. The possibility of association of hereditary orotic aciduria has been reported (7). Cardiac manifestations including heart rhythm

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*** Corresponding Author:**
T. Zaman, Department of Metabolic Diseases, Children's Medical Center, School of Medicine, Medical Sciences/Tehran University, Tehran, Iran
Tel: +98 21 9937567
Fax: +98 21 9929234
E-mail: Talieh_zaman @gmail.com

abnormalities and cardiomyopathy have been reported by Lorber *et al.* in 2003 (8). The wide spectrum of this syndrome that may respond to treatment with vitamin B_1 indicate that thiamine has a pivotal role in multiplicity of major physiologic process. Further study of thiamine metabolism may clarify the pathophysiology of this syndrome.

The association of this syndrome with deficient α-ketoglutarate dehydrogenase activity was described by Abboud *et al.* in 1985, and thiamine pyrophosphokinase deficiency by Grill *et al.* in 1991(7). Neufeld and co-workers initiated a positional cloning effort to identify the disease gene by performing a genome scan with several affected kindreds of Alaskan, Italian, and Israeli-Arab origin. Using a genome scan linkage of this disorder to chromosome 1q23 was found and haplotype analysis defined a 16-CM critical region. The molecular genetic analyses of four unrelated patients' families inheriting TRMA confirmed linkage. The gene associated with this disease SLS19A2 encodes for thiamine triamine transporter 1 (THTR1), a member of the SLC19 encodes family including THTR2 and the reduced folate carrier (RFC) (9-13).

The first Iranian patient with thiamine responsive megaloblastic anemia was described by Vossough *et al.* in 1995 (11). In this paper, we present nine other cases.

CASE REPORTS

We reviewed retrospectively nine new cases with diagnostic criteria of thiamine responsive megaloblastic anemia during 8 years of our study.

Seven of our patients were male. Four of them were siblings (brother and sister). In addition to these cases, family history of diabetes mellitus, sensorineural deafness and/or anemia was positive in two of them who unfortunately had died before (Table 2). All of our patients except one were the offspring of consanguineous marriages, this latter patient had also family history of diabetes mellitus and anemia.

The initial hemoglobin estimations of the patients were between 4.9 to 9.4 g/dl, four of them with macrocytic changes in red blood cells. Unfortunately, three of our patients received monthly blood transfusions, so that exact judgment of red blood cell morphology was not possible. Leucocytes and platelet counts were normal, also serum levels of foliate and vitamin B12.

Bone marrow aspiration in all of these patients showed findings compatible with megaloblastic changes, only one of them had concomitant mild hyperplastic changes. The bone marrow aspirates recorded in the literature showed normal to mild increase in cellularity but abnormal erythropoiesis, with striking megaloblastic and dyserythropoietic changes with ring sideroblasts.

According to previous studies these cases are responsive to therapeutic doses of thiamine. After initial workup for other causes of megaloblastic anemias, we started treatment with thiamine 100mg/day orally, decreasing the dosage after two weeks to 25 mg/day. We detected reticulocytosis after 5-7 days and rising of hemoglobin 7-10 days after initial dose. No changes in hemoglobin occurred after reducing the dosage of thiamine.

Table 1. Clinical features of the 10 previously published patients in the literature

Patient no	1	2	3	4	5	6	7	8	9	10
Reference no	4	5	1	1	3	3	3	2	2	6
Sex	F	F	M	F	M	M	M	F	F	M
Diabetes at age (yr)	3	10 yr and 9 mo	7.5	2 yr and 3 mo	6	6	3	3	2	3
Deafness age (yr)	4.5	Infancy	8.5	1	6	3	2	3	4	1
Anemia at age (yr)	12	1.5	6	7	13	-	4	9	4	2
CHD	-	+	-	-	+	+	-	-	-	-
Other findings*	+	-	-	-	-	-	-	+	+	-
Consanguinity	-	+	-	+	+	+	+	-	-	-

Abbreviations: F, female; M, male; CHD, congential heart disease.
* Mental retardation and aminoaciduria in patients No 8 and 9 with Wolfram syndrome or DIDMOAD syndrome (DI, DM. Optic atrophy, sensorineural deafness).

Table 2. Salient features of our patients

Patient	1	2	3	4	5	6	7	8	9
Age (yr)	11	6	2	13	5	12	11	12	8
Sex	F	M	M	M	M	M	F	M	M
Parent's consanguinity	+	+	-	+	+	+	+	+	+
Anemia	+	+	+	+	-	+	+	+	+
Diabetes mellitus	+	+	+	+	-	+	+	+	+
Deafness	+	+	-	+	+	+	+	+	+
Positive family history of	+*	+†	+‡	+‡	+	+¶	+¶	+	+
age at onset of anemia	7 yr	4 mo	3 mo	6 yr	5 yr	5 yr	6 yr	4 mo	1 yr
Diabetes mellitus	4 yr	1 yr	3 mo	1.5 yr	5 yr	7 yr	6 yr	2 yr	2 yr

* Sister of patient 2.
† Brother of patient1.
‡ Two affected sibling
¶ 1 affected sibling.

Despite normalization of megaloblastic changes of bone marrow, macrocytic red blood cells continued to exist in all of these patients. In spite of rising in hemoglobin concentration, insulin dose except in one could not be tapered during 8 years of study.

Treatment with pharmacologic doses of thiamine had no effect on the hearing loss. Cardiomyopathy was discovered in two.

Ox-Phos biochemistry of muscle mitochondria for complex I, III, IV was done in all nine patients but was unremarkable.

DISCUSSION

As stated before, the inheritance of this syndrome is most probably autosomal recessive. Here, it is strongly suggested because of consanguinity (Table 2). In two of our patients the presentation was concomitant. All of our patients are deaf with sensorineural hearing loss which was detected in infancy up to two years of age, documented by audiometric evaluation. Chromatographies of urine for amino acids were positive in three of our patients as weak bands but not significant for especial metabolic disorders.

Table 3. Results of paraclinical studies before and one year after treatment

Patient no	1	2	3	4	5	6	7	8	9
Amino aciduria	+	-	+	+	-	-	-	-	-
Increased urine MMA	+	-	+	-	+	-	-	+	+
CBC (initial)									
Hb(g/dl)	7.3	9.4	4.9	7.9	7.2	10	10	12	10
MCV(fl)	96	87	110	128	125	125	115	118	110
Retic (%)	1	0.8	1.96	1	2	0.5	0.8	0.2	0.3
WBC(/ml)	9200	9000	4600	8100	7900	7	8	7	8
Plt ($x10^3$o/ml)	240	158	192	112	190	140	150	120	150
Blood level of	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
folate and B_{12}									
Megaloblastic changes	+*	+	+	+	+	+	+	+	+
Response to therapy with	12.3	13	11.7	13.8	10.9	†	†	11.7	12.8
increased Hb(g/dl)									

Abbreviation: WNL, within normal limits.
* Plus erythroid hyperplasia.
† These two patients died before diagnosis and treatment.

Urinary screening test for hereditary orotic aciduria was also negative (Table 3).

The diabetes mellitus, which is non Type I, may respond to thiamine therapy as evidenced by a decreased insulin requirement but long-term follow-up of two patients documented a slow progression of the pancreatic endocrine insufficiency with ultimate insulin dependence (9). In our patients dose of insulin except in one was not changed during 8 years of study.

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