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Case Report
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Thiamine Responsive Megaloblastic Anemia Syndrome: A Novel Mutation and Review 2 of Turkish Patients

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Abstract

Thiamine responsive megaloblastic anemia is a rare autosomal recessive disorder with a classical triad of megaloblastic anemia, sensorineural hearing loss and diabetes mellitus. TRMA is caused by mutations in the *SLC19A2* gene.

A 22-month-old male with anemia, diabetes mellitus and hearing loss was referred to our center. Sequence analysis of the *SLC19A2* gene identified a novel homozygous mutation c.1000G>C p.(Gly334Arg) in exon 3. Lipophilic thiamine therapy (150 mg/day) was initiated. After one month of treatment, we were able to stop insulin treatment. Macrocytic anemia also resolved during the follow-up. Our patient did not benefit from thiamine treatment in terms of hearing loss.

There are 14 Turkish patients with a diagnosis of TRMA in literature. All of the Turkish patients were molecularly confirmed to have homozygous mutations in *SLC19A2* gene except for one patient and in 11 of 13 patients (84%) there was consanguinity between parents indicating that autosomal recessive rare disorders are seen more commonly in Turkey.

TRMA should be kept in mind when a patient present with one or more of the classical symptoms and complete blood count, fasting blood glucose and hearing tests must be a part of the evaluation in these patients. Lifelong use of oral thiamine is recommended in TRMA patients.

Keywords: TRMA; Rogers' syndrome; Thiamine; Anemia; *SLC19A2*

Introduction

Thiamine Responsive Megaloblastic Anemia syndrome (TRMA) (OMIM #249270) also known as Rogers' syndrome is a rare autosomal recessive disorder with a classical triad of megaloblastic anemia, sensorineural hearing loss and diabetes mellitus. TRMA has been identified in more than 183 individuals from more than 138 families so far. Other findings include short stature, congenital heart defects (ASD, VSD), arrhythmia, optic nerve and retina abnormalities, including optic atrophy, nystagmus, maculopathy, retinitis pigmentosa and neurological problems, such as seizure and stroke. Patients usually present in infancy or early childhood and anemia is generally the first recognized feature [1].

TRMA is caused by mutations in the *SLC19A2* gene which has 6 exons and is located on chromosome 1q23.2. The product of this gene is high affinity Thiamine Transporter 1 (THTR1). Thiamine is an essential vitamin absorbed through upper small intestine by two transporters; THTR1 and THTR2, of which the acquired or inherited deficiencies may cause a variety of symptoms [2,3].

Case Presentation

A 22-month-old male was born to third degree consanguineous parents at term after an uneventful pregnancy. Ventricular septal defect was detected at birth and closed spontaneously during follow-up. He had normal medical history up to 10 months of age when breath holding spells appeared. Initial laboratory work-up revealed high blood glucose and anemia and subcutaneous insulin was initiated with a diagnosis of diabetes mellitus. At 20 months hearing problems were noticed and the patient was referred to our center at 22 months.

On physical examination he had low weight (<3 percentile), pallor, unresponsiveness to vocal stimulus and speech delay. Other than that physical examination was normal. Laboratory results showed macrocytic anemia (hemoglobin 9.1 g/dL, MCV 93.4 fL). White Blood Cell Count (WBC) was 5.3 × 10^9/L, thrombocytes 321 × 10^9/L, absolute neutrophil count was 1.6 × 10^9/L and absolute lymphocyte count was 3.4 × 10^9/L. Reticulocytes count, vitamin B12 and folate levels

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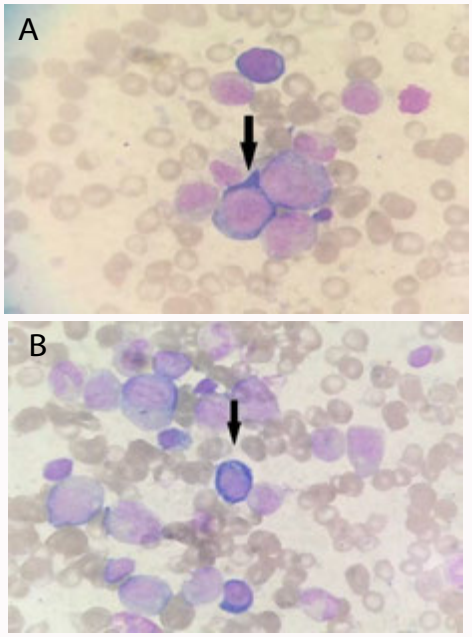

Figure 1A-1B: Severe megaloblastic changes, bone marrow aspiration.

were within normal range. Bone marrow aspiration showed severe megaloblastic changes and vacuolization in erythroid precursors. No ring sideroblasts were exhibited by Prussian blue stain (Figure 1). He had been on subcutaneous insulin treatment and his fasting blood glucose level was 169 mg/dl, HbA1c was 6.4% (<6.5%). Anti GAD and islet cell antibody tests were negative. Audiological examination revealed bilateral sensorineural hearing loss. Diffusion-weighted MRI of the ear did not show any abnormality. With the suspect of TRMA ophthalmologic and cardiologic examinations were done and they were normal.

Lipophilic thiamine therapy (150 mg/day) was initiated. After two weeks of thiamine treatment, we were able to decrease insulin dose and after one month insulin was stopped. HbA1c was 5.4% in the fourth month of treatment. Macrocytic anemia also resolved during the follow-up (Table 1).

Our patient did not benefit from thiamine treatment in terms of hearing loss and cochlear implant was done 7 months after the start of thiamine treatment at the age of 29 months. Sequence analysis of the *SLC19A2* gene identified a novel homozygous mutation c.1000G>C p.(Gly334Arg) in exon 3 and both parents were found to be heterozygous for the same mutation.

Currently, he is on lipophilic thiamine (150 mg/day) for five years and followed with annual visits without anemia and normal blood glucose levels. Informed consent was received from the family.

Literature Review

The absence of a review of Turkish TRMA patients led us to review the literature and cases of Turkish TRMA patients were identified from PubMed (http://www.ncbi.nlm.nih.gov/pubmed). We included all the cases reported except one case reported by Doğan et al. [4] as the same patient has been reported by Aycan et al. [5] previously.

Turkish patients

We have found 14 Turkish patients with a diagnosis of TRMA in literature. All the patients had molecular confirmation of a diagnosis of TRMA except for Patient 1 and eight different disease-causing mutations are found in Turkish population [3,5-15]. Clinical details of each case, including the presented case here, are shown in Table 2.

Twelve (85%) of the 14 Turkish TRMA patients showed the classical triad of megaloblastic anemia, sensorineural hearing loss and diabetes mellitus at the time of the diagnosis of TRMA or during follow up. Patient 6 did not have diabetes mellitus and deafness and Patient 10 did not have deafness [3,10].

In this series of 14 patients nine (64%) of them had thrombocytopenia, four (28%) had growth retardation, three (21%) showed absent p wave on ECG, two (14%) had optic atrophy, two (14%) had neutropenia, two (%14) had ASD, one (7%) had myopia and astigmatism, one (7%) had mild pulmonary insufficiency, one (7%) had blurred p wave on ECG, one (7%) had supraventricular tachycardia, one (7%) had low QRS voltage, one (7%) had widened QRS complex, one (7%) and had heart failure after ASD closure. One patient (7%) was reported to have ataxic gait and frequent cramps in the left leg in terms of neurological problems. Electromyography revealed a slowing of the conduction velocity of the left sciatic nerve in this patient.

All of the Turkish patients were molecularly confirmed to have homozygous mutations in SLC19A2 gene except for Patient 1 and in 11 of 13 patients (84%) there was consanguinity between parents indicating that autosomal recessive disorders like TRMA are commonly seen in Turkey due to the consanguineous marriages.

Discussion

Thiamine is an essential vitamin and absorbed into the body in the upper small intestine by two transporters, THTR1 and THTR2, the products of the *SLC19A2* and *SLC19A3* genes respectively [2,3]. The active form of thiamine is Thiamine Pyrophosphate (TPP) and it is generated within cells from free thiamine by the enzyme Thiamine Pyrophosphokinase (TPK). TPP is the cofactor for a number of enzymes (pyruvate dehydrogenase, α- ketoglutarate dehydrogenase, branched chain α-ketoacid dehydrogenase, transketolase, 2-hydroxyacyl-CoA lyase). Defects in thiamine transport leads to impairment of these enzyme activities [2].

TRMA is characterized by megaloblastic anemia, sensorineural

Table 1: Complete blood count results before and after the start of thiamine treatment at 22 months.

	7 mo	10 mo	13 mo	22 mo	23 mo	26 mo
Hemoglobin (g/dL)	10.6	10	10.5	9.1	12.7	14
MCV (fL)	87.2	89.2	94.5	93.4	94.2	80.2
RDW (%)	17.4	23.3	22.8	26.8	18.4	13.9
WBC (10^3 µ/L)	18	10.6	19.7	5.3	7.2	10.2
Platelet (10^3 µ/L)	604	521	474	321	299	427

mo: months old; dL: deciliter; MCV: Mean Corpuscular Volume; RDW: Red Cell Distribution; WBC: White Blood Cell; fL: Femtoliter; µ: micro; L: Liter

Table 2: Clinical and genetic characteristics of Turkish TRMA patients.

	Gender	Age of Diagnosis			Neurocognitive Features	Ophthalmic	Cardiac	Others	Consanguinity	Follow-up Time	*SLC19A2* Mutation
		Anemia	DM	Deafness							
P-1	F	32 mo	20 mo	NA	Ataxic gait, cramps in the left leg	No deficit	No deficit	Thrombocytopenia, DKA	First degree	3 years	NA
P-2	M	NA	5 yo	NA	No deficit	No deficit	No deficit	Thrombocytopenia	Not present	1 year	Homozygous c.697C>T p.(Gln233Ter)
P-3+	F	7 mo	7 mo	7 mo	No deficit	Optic atrophy	Absent P wave, SVT, low QRS voltage	Thrombocytopenia, growth retardation, DKA	Third degree	8 years	Homozygous c.1107_1108delTT p.(Leu371Profs*14)
P-4+	F	18 mo	18 mo	18 mo	No deficit	Optic atrophy	Absent P wave	Thrombocytopenia, growth retardation, DKA	Third degree	8 years	Homozygous c.1107_1108delTT p.(Leu371Profs*14)
P-5	F	24 mo	24 mo	24 mo	No deficit	No deficit	No deficit	No deficit	Present	9 months	Homozygous c.697C>T p.(Gln233Ter)
P-6	F	1 mo	Not present	Not present	No deficit	No deficit	No deficit	Thrombocytopenia, neutropenia	Present	31 months	Homozygous c.242dupA p.(Tyr81Ter)
P-7	M	5 mo	7 mo	8 mo	No deficit	No deficit	No deficit	Thrombocytopenia	Present	11 months	Homozygous c.242dupA p.(Tyr81Ter)
P-8	M	8 mo	4 mo	NA	No deficit	No deficit	ASD, atrial standstill, widened QRS complex, absent P wave, heart failure after ASD closure	Growth retardation	Present	4 months	Homozygous c.1148_1149delTG p.(Val383Glyfs*2)
P-9	F	4 mo	4 mo	20 mo	No deficit	No deficit	No deficit	Thrombocytopenia	Not present	2 years	Homozygous c.566_567delGCin sTCT p.(Ser189Ilefs*52)
P-10	F	2 yo	2 yo	Not present	No deficit	No deficit	ASD	No deficit	Present	6 months	Homozygous c.95T>A p.(Leu32Ter)
P-11	F	3 mo	3 mo	3 mo	No deficit	No deficit	No deficit	Neutropenia	First degree	4 years	Homozygous c.242dupA p.(Tyr81Ter)
P-12	M	5 yo	5 yo	5 yo	No deficit	Myopia, astigmatism	Mild pulmonary insufficiency	Thrombocytopenia	Third degree	8 months	Homozygous c.1265T>C p.(Leu422Pro)
P-13	M	NA	NA	NA	NA	No deficit	Blurred P wave	Thrombocytopenia	NA	6 years	Homozygous c.566_567delGCin sTCT p.(Ser189Ilefs*52)
Our case	M	10 mo	10 mo	20 mo	No deficit	No deficit	No deficit	Growth retardation	Third degree	5 years	Homozygous c.1000G>C p.(Gly334Arg)

F: Female; M: Male; P: Patient; DM: Diabetes Mellitus; mo: months old; yo: years old; DKA: Diabetic Ketoacidosis; NA: Data Not Available; ASD: Atrial Septal Defect; SVT: Supraventricular Tachycardia; + Siblings

hearing loss and diabetes mellitus and caused by mutations in the *SLC19A2* gene which is located on chromosome 1q23.2 and encodes high affinity Thiamine Transporter 1 (THTR1). *SLC19A2* gene has 6 exons, although most common mutations are in exon 2, mutations in the exons 1, 3, and 4 are also known [16]. In our case, sequence analysis of the *SLC19A2* gene revealed a novel homozygous mutation c.1000G>C (p.G334R) in exon 3.

Blood thiamine concentration is normal in TRMA, suggesting that THTR1 is not of major importance for intestinal absorption [2]. Biochemical studies on fibroblasts or erythrocytes of patients with TRMA showed that the cells from patients with TRMA contain low levels of thiamine compounds, due to either inability to take up and retain physiological concentrations of thiamine, as a result of transport defect or reduced thiamine pyrophosphokinase [17,18]. It is hypothesized that some tissues such as pancreatic β cells, cochlear cells and bone marrow cells depend more critically on THTR1 [19].

Although patients with TRMA usually present in infancy or early childhood and often anemia is the first recognized feature, the onset of symptoms might be variable. Shaw-Smith et al. [20] reviewed 30 cases of TRMA patients, in this cohort anemia started at birth to 7 years, diabetes mellitus started at birth to 11 years and sensorineural hearing loss started at 1 month to 30 years. Our patient was found to have anemia and high blood glucose levels when he had breath holding spells at 10 months and hearing loss started at 20 months.

Peripheral blood count shows a pattern of macrocytic anemia in the absence of deficiencies of folate and vitamin B12 in patients with TRMA. Bone marrow examination reveals megaloblastic changes with often containing ringed sideroblasts. Defective RNA ribose synthesis through impaired transketolase catalysis caused by intracellular thiamine deficiency is thought to be the cause of anemia and megaloblastic changes in TRMA [21]. A long-term follow-up of 13 TRMA patients published from UK has reported a significant rise in hemoglobin with oral thiamine treatment. However, on long-term follow up into adulthood, almost all patients became transfusion-dependent despite oral thiamine treatment [22]. On the contrary there are some reports of patients who have sustained control of anemia by thiamine treatment [23]. In our presented patient, thiamine treatment successfully maintained normal Hb levels during a five-year follow-up and transfusion has never been necessary.

Diabetes mellitus in TRMA is a non-immune disorder due to a defect of insulin secretion. *SLC19A2* knockout mouse models developed diabetes mellitus with reduced insulin secretion on a thiamine free diet and an enhanced response to insulin and diabetes resolved after 6 weeks of thiamine repletion in these models [24]. It has been reported that although dose of insulin can be reduced during thiamine treatment unresponsiveness to thiamine may develop especially after the onset of puberty and patients may become insulin dependent [22]. However, our patient is now 6 years old being followed up yearly and maintains good glycemic control and HbA1c

levels with no need to insulin as one of the patients reported by Borgna-Pignatti et al. [23].

THTR1 which is defective in TRMA is expressed in inner hair cells of cochlea and selective loss of inner hair cells in *SLC19A2* knock-out mice models was observed when they were challenged with a low-thiamine diet [25,26]. Most of the TRMA cases reported to date have been diagnosed after infancy and hearing loss was already present. Borgna-Pignatti et al. [23] reported a patient who was found to have TRMA mutation and remained symptom free until 3 years old. She was found to have high blood glucose level when she was 3 years old and began receiving thiamine-HCL 75 mg/day then gradually increased to 300 mg/day. She was followed for 16 years and sensorineural hearing loss started at the age of 5. In addition to the classical triad, other findings have been observed in TRMA patients including short stature, congenital heart defects (ASD, VSD), arrhythmia, optic nerve and retina abnormalities (optic atrophy, nystagmus, maculopathy, retinitis pigmentosa) and neurological problems (seizure, stroke). These features show considerable overlap with mitochondrial diseases and this would be consistent with the important roles of the α-ketoacid dehydrogenase complexes in energy metabolism [2]. One patient has been described with raised blood and cerebrospinal fluid lactate levels and high lactate/pyruvate ratio. In this patient, muscle biopsy did not show definite mitochondrial abnormalities, but there were reduced activities of complex I of the respiratory chain and pyruvate dehydrogenase, which had benefit from thiamine supplementation [27]. Our patient had normal blood lactate level and lactate/pyruvate ratio.

TRMA is a rare autosomal recessive disorder which has a typical clinical trial: Megaloblastic anemia, sensorineural hearing loss and diabetes mellitus. Due to the frequent consanguineous marriages autosomal recessive rare disorders are seen more commonly in Turkey. TRMA should be kept in mind when a patient present with one or more of the classical symptoms and complete blood count, fasting blood glucose and hearing tests must be a part of the evaluation in these patients. Lifelong use of oral thiamine is recommended in TRMA patients. Response to thiamine treatment is variable. Anemia and diabetes mellitus may benefit from thiamine treatment however the dosage may need to be increased or patients may become unresponsive especially after the onset of puberty. Although hearing loss seems to be irreversible it is questionable if it may be prevented by early thiamine treatment or not. Patients must be followed at least yearly to monitor the efficacy of the oral thiamine therapy and disease progression. Genetic counselling should be given to families.

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