Case Report
A Novel Mutation in the SLC19A2 Gene in a Turkish Female with Thiamine-responsive Megaloblastic Anemia Syndrome

by Ediz Yeşilkaya, a Aysun Bideci, a Meltem Temizkan, a Zühre Kaya, b Orhun Çamduran, a Altuç Koç, c Davut Bozkaya, a Ülker Koçak, b and Peyami Cinaz a

aDepartment of Pediatric Endocrinology, bPediatric Hematology, and cMedical Genetics, Gazi University Medical School, Ankara, Turkey

Summary
Reported here is a 2-year-old girl who was diagnosed to have thiamine-responsive megaloblastic anemia during evaluations for her bilateral neurosensorial deafness. Besides reporting a new mutation on the gene SLC19A2 for the first time in the literature, we highlight the recognition of this syndrome—when megaloblastic anemia and diabetes mellitus coexists—and the role of thiamine replacement for the treatment of both disorders.

Key words: thiamine-responsive megaloblastic anemia, novel mutation, diabetes mellitus.

Introduction
Thiamine-responsive megaloblastic anemia (TRMA) is an autosomal recessive disease whereby active thiamine uptake into cells is disturbed. The molecular basis underlying this disorder has been linked to mutations in the SLC19A2 gene that encodes a functional thiamine transporter. TRMA is characterized by megaloblastic anemia, sensorineural hearing loss and diabetes mellitus. In addition to these three cardinal findings, cardiovascular abnormalities and optic atrophy have also been described in some patients [1]. Herein, we present a 2-year-old girl who was diagnosed to have TRMA during evaluations for her bilateral neurosensorial deafness. A new mutation on the gene SLC19A2—that has not been described in the literature before—was also found.

Case Report
A 2-year-old girl—who was followed in the Ear Nose Throat Clinic for her bilateral sensorineural deafness—was consulted to our department due to fasting blood glucose level of 305 mg dl⁻¹ before cochlear implantation operation.

Acknowledgement
We are also indebted to Ellis J. Neufeld for genetic analysis of mutations in the SLC19A2 gene (Division of Hematology, Children’s Hospital, Boston, MA).

The girl was born to consanguineous Turkish parents at term by normal delivery after an uneventful pregnancy. There was no family history of diabetes mellitus, deafness or anemia.

During the initial examination, she could not hear or talk. Her weight was 11 kg (10–25th percentile) and height was 85 cm (50th percentile), temperature was 36.3°C, heart rate was 92 beats min⁻¹ and blood pressure was 75/42 mmHg. Except for a grade I/VI systolic, ejection-type murmur and her skin being pale, the physical examination was normal. Hand and wrist X-rays were consistent with a bone age of 1.5 years. Her brainstem auditory evoked potentials revealed bilateral sensory neural deafness. No congenital pathologies with regard to either the heart or the eye were present.

When the patient was admitted to our clinic her blood tests were as follows: serum glucose: 305 mg dl⁻¹ (not ketotic), serum insulin: 1.2 ulU ml⁻¹ (3–20 ulU dl⁻¹), plasma C-peptid: 0.87 ng ml⁻¹ (0.5–3.2 ng ml⁻¹) and HbA1c: 9.4% (0–6.5), anti-insulin and anti-islet cell antibodies: negative; folate: 6.6 ng ml⁻¹ (2.7–3.4), vitamin B12: 470 pg ml⁻¹ (189–883), ferritin 150 ng ml⁻¹ (4.6–204); haemoglobin: 7.6 g dl⁻¹, hematocrit: 22%, reticulocytes: 0.5%, MCV: 96fl. Peripheral smear showed anisopoikilocytosis, tear-drop cell and macrocytosis and no hemolytic findings (e.g. fragments or spherocytes). Osmotic fragility tests and hemoglobin electrophoresis were normal. Occult stool blood testing was negative. Bone marrow examination showed ringed sideroblasts with megaloblastic changes and giant metamyelocytes. After subcutaneous insulin of 0.5 U kg⁻¹ day⁻¹, normoglycemia was obtained. With the above constellation of clinical and laboratory findings, a diagnosis of
TABLE 1

Hematological findings of the patient during the follow-up

<table>
<thead>
<tr>
<th></th>
<th>Before thiamine treatment</th>
<th>10th day of treatment</th>
<th>1st month of treatment</th>
<th>3rd month of treatment</th>
<th>9th month of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g dl⁻¹)</td>
<td>7.6</td>
<td>9.2</td>
<td>11.3</td>
<td>12.8</td>
<td>13.4</td>
</tr>
<tr>
<td>MCV</td>
<td>96</td>
<td>89.9</td>
<td>80.7</td>
<td>83</td>
<td>78.3</td>
</tr>
<tr>
<td>WBC (mm⁻³)</td>
<td>9500</td>
<td>9200</td>
<td>8100</td>
<td>8700</td>
<td>9100</td>
</tr>
<tr>
<td>Platelets (mm⁻³)</td>
<td>258.00</td>
<td>312.000</td>
<td>275.00</td>
<td>315.00</td>
<td>278.00</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>9.4</td>
<td></td>
<td>6.6</td>
<td></td>
<td>6.1</td>
</tr>
</tbody>
</table>

TRMA with diabetes mellitus was established. Serum thiamine was also found to be decreased (22 µg dl⁻¹, N: 25–75). After 100 mg day⁻¹ of thiamine was added to her treatment, the insulin need decreased dramatically and insulin was stopped on 4th day of thiamine treatment. Glycosylated haemoglobin has remained in the normal range thereafter throughout the follow-up without any hypoglycemic agent (Table 1). The patient’s anemia also recovered rapidly.

The genetic evaluation of the patient (performed by Ellis J. Neufeld, Division of Hematology, Children’s Hospital, Boston) showed that the proband was homozygous for a novel mutation, 697C_T, in the high-affinity thiamine transporter gene, SLC19A2. The parents and one sibling were all heterozygotes for the same mutation.

Discussion

The deficiency of gene product thiamine transport protein results in defect in intracellular thiamine transport. It is presumed that thiamine transport protein may play a role in facilitating the transport of thiamine not only into hemopoietic tissues but also into pancreatic islet cells, cochlear cells and many other cells and tissues in the body [2, 3]. The major features associated with this rare autosomal recessive disease include diabetes mellitus, megaloblastic anemia and sensorineural deafness; all of which respond in varying degrees to the administration of thiamine [4].

The onset of disease is in infancy or in early childhood and most of the TRMA patients originated from consanguineous families [5]. Our patient who was 2 years old and she was born to consanguineous Turkish parents.

The diabetes mellitus is non-type I in nature, with age of onset from infancy to adolescence, generally appears before school age. Insulin secretion is present but defective. The response to thiamine therapy in majority of them is either absent or partial in terms of insulin requirement whereas in some cases, insulin requirements are reduced with thiamine therapy because either the β-cells of the pancreas or the target tissue have intermediate sensitivity to cellular thiamine deficiency. However, long-term follow-up of patients documented a slow progression of the pancreatic endocrine insufficiency with ultimate insulin dependence. Neither anti-insulin nor anti-islet cell antibodies have been found in individuals with TRMA, but pancreatic histopathology has not been investigated [6, 7]. Puberty may deteriorate the metabolic control and the reinstitution of insulin therapy may become necessary. In our patient, subcutaneous insulin was given for her diabetes, but with the initiation of thiamine treatment, insulin was no longer necessary. Throughout the follow-up, the patient remained normoglycemic.

Megaloblastic anemia occurs between infancy and adolescence. The anemia is corrected with pharmacologic doses of thiamine. However, the red cells remain macrocytic. The anemia can recur when thiamine is withdrawn [5]. In our patient, anemia rapidly recovered with thiamine therapy.

Progressive sensorineural hearing loss has generally been early, irreversible and may not be prevented by thiamine treatment. The basis of the sensorineural deafness is obscure; it is not known if the deafness is caused by abnormalities of the cochlea or the auditory nerve. However, recent animal studies suggest that selective inner hair cell loss in the cochlea might be the cause of hearing defects in TRMA [4].

A nucleus contour device was implanted to our patient.

In addition to the cardinal clinical manifestations of the syndrome, some patients may have congenital heart disease and/or arrhythmias, sudden death, stroke, high-output heart failure, backwarsness, situs viscerum inversus as well as abnormalities of the retina and the optic nerve. Abnormal appearance of the retina and functional retinal dystrophy have been reported [4–8]. No congenital pathologies with regard to either the heart or the eye were present in our patient.

The TRMA syndrome has been mapped to chromosome 1q23.2–23.3 and the SCLA19A2 was identified as the responsible gene for this syndrome [9]. To date, 16 distinct clinical mutations have been identified in SLC19A2 comprising point mutations as well as premature truncations resulting from missense, nonsense and frame-shift mutations [10]. We have defined a new female case homozygous for a novel mutation with two base pair deletion and three base insertion, 566_567delGCinsTCT, which results in an immediate frameshift in the protein.
and a downstream termination, Insdel189fs/ter239. Actually, a previous report from Turkey has identified a homozygous 697C>T mutation in a boy with TRMA [4]. Presence of different mutations of SCL19A2 gene found in the presented case and the case of Ozdemir et al. [4], shows that further reports of TRMA from our region are needed to clarify the genetic diversity of this syndrome.

Overall, reporting a new mutation on the gene SLC19A2, we call attention of physicians to this syndrome in their differential diagnosis in case they face with coexistent megaloblastic anemia and diabetes mellitus. This is not only important for diagnosis but also is required for prompt treatment since thiamine replacement is all that will be necessary.

References