This case report describes a patient with a rare syndrome known as Thiamine-responsive Megaloblastic Anemia Syndrome (TRMA) which is an autosomal recessive disorder caused by gene mutation identified by megaloblastic anemia, progressive sensorineural hearing loss, and diabetes mellitus. We report a case of TRMA in a female child, born to a consanguine family. The child present with classical symptoms of the syndrome. Further assessment and mutation analysis confirmed a diagnosis of TRMA syndrome. By this report, we are hoping we can increase the awareness of the possible diagnosis of the syndrome for patients presenting with similar clinical manifestation especially where the rate of consanguineous marriages is high.

**Keywords:** Neonatal diabetes, Megaloblastic anemia, Deafness.
Thiamine-responsive megaloblastic anemia syndrome: A rare case report.

Table 1. Laboratory findings at the patient’s initial presentation and after diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>First Presentation Before Treatment</th>
<th>After Confirming the Diagnosis and Starting Thiamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>6.6 g/dL</td>
<td>10 g/dL</td>
</tr>
<tr>
<td>Mean Corpuscular Volume</td>
<td>83.8 fL</td>
<td>73.8 fL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>13.3%</td>
<td>301%</td>
</tr>
<tr>
<td>Red blood cell count</td>
<td>1.59 (10^9/µL)</td>
<td>4.2 (10^9/µL)</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>14 (10^9/µL)</td>
<td>10 (10^9/µL)</td>
</tr>
<tr>
<td>Platelet count</td>
<td>132 (10^9/µL)</td>
<td>576 (10^9/µL)</td>
</tr>
<tr>
<td>Ferritin level</td>
<td>241.97 ng/mL</td>
<td>246.97 ng/mL</td>
</tr>
<tr>
<td>Vitamin B1 (thiamine)</td>
<td>3.5 µg/dL</td>
<td>4.0 µg/dL</td>
</tr>
</tbody>
</table>

Discussion

We present a novel mutation of SLC19A2 in a child with TRMA, which is a rare autosomal recessive disease with a high occurring rate among consanguineous families. Thiamine is an essential water-soluble vitamin that plays a fundamental role in many chemical reactions and cellular processes, including carbohydrate utilization and amino acid catabolism (Figure 1). Further, thiamine plays a role in neuronal signaling. Thiamine absorption occurs predominantly in the intestine, and its reabsorption from the renal tubules and other active cellular uptake is regulated by thiamine transporter (THTR-1), expressed by the SLC19A2 gene and THTR-2 expressed by the SLC19A3 gene. The three THTR-1 dependent cells, namely the β-cells of the pancreas, cochlear cells in the inner ear, and hematopoietic stem cells in the bone marrow, are the most affected in case of vitamin B1 deficiency [7-9]. A homozygous mutation in the SLC19A2 gene will lead to a decrease in intracellular thiamine in the THTR-1-dependent cells and result in the classical triad of symptoms of the syndrome megaloblastic anemia, monogenic diabetes mellitus, and sensorineural deafness [8]. A mutation in the gene will lead to the production of a non-functional thiamine transporter that will disrupt the active uptake of thiamine, resulting in thiamine deficiency. Cells in other body tissues have compensatory THTR-2 and will be less affected. On the other hand, thiamine shows a normal plasma range, implying that the THTR-2 transporter is maintaining adequate absorption and keeping plasma thiamine within the normal range [10]. An adequate level of intracellular thiamine is necessary for normal pancreatic function, insulin secretion, and development of the auditory system [9-13].

Most children present with signs of anemia [1], which was the first observed symptom in our case. Pathological analyses of bone marrow samples in cases with TRMA typically show megaloblastic alterations, with erythroblasts usually having iron granule-filled mitochondria surrounding the nucleus (called sideroblasts) [3].

The anemia is classically corrected with thiamine treatment (Table 1). Leucopenia is less commonly seen in TRMA children, which explains the varying level of thiamine participation in each precursor of the hematopoietic stem cells [5]. In our case, the first clinical presentation was skin pallor, and a peripheral blood film showed normocytic hypochromic anemia with anisocytosis, polychromasia, poikilocytosis, and spherocytosis. The patient also had thombocytopenia. In a previous case of homozygous SLC19A2 mutation in a diabetic patient with TRMA, a peripheral blood smear revealed macrocytic cells with no hemolytic findings [5]. In another case, the investigators did not find hematological changes typical of megaloblastic anemia [2]. Some investigators isolated cells from rats to assess the consequences of thiamine deficiency on the secretion of insulin; they showed that less insulin was secreted from the rats’ pancreatic islets cells [14-20]. Thiamine-responsive megaloblastic anemia syndrome is a good example of secondary diabetes due to a rare single gene disorder [5]. Many TRMA patients respond to vitamin treatment; however, others require insulin treatment, as was the case in our patient [9]. Other studies found that in the long-term, most cases become insulin-dependent by the time they reach puberty [12]. Selective loss of inner hair cells of the cochlea occurs due to thiamine deficiency caused by a mutation in the SLC19A2 gene.

Figure 1. Pedigree of the child family to show autosomal recessive inheritance
This will result in irreversible sensorineural hearing loss, regardless of thiamine replacement therapy [3]. Unlike studies conducted on rats, thiamine can reverse deafness in human subjects [9]. In another case of TRMA in a one-month old infant, hearing loss was not detected at the time of diagnosis and afterward [3,21].

Conclusion

Any child presenting with a triad of diabetes, hearing impairment and megaloblastic anemia should be suspected to have TRMA. A mutation analysis is warranted to detect the actual mutation and confirm the diagnosis. We believe that pre-symptomatic genetic testing may be helpful in detecting treatable conditions.

References


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