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Case Report

Recurrent Ischemic Stroke in A Child with Thiamine Responsive Megaloblastic Anemia Syndrome

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ABSTRACT

Thiamine responsive megaloblastic anemia syndrome (TRMA) (OMIM 249270) is a rare, autosomal recessive inherited disorder characterized by a triad of megaloblastic anemia, diabetes mellitus and sensorineural deafness. Mutations in the SLC19A2 gene, encoding a high-affinity thiamine transporter protein, THTR-1, are responsible for the clinical features associated with TRMA. Here, we report a 20 month-old boy with TRMA. During evaluation of recurrent stroke and megaloblastic anemia homozygous mutation in SLC19A2 gene (c.242-243 insA) was detected. Additionally homozygote MTHFR C677 and heterozygote MTHFR A1298 mutations were also detected in thrombosis panel. As far as we know this is the first TRMA case with homozygote MTHFR C677 and heterozygote MTHFR A1298 mutations in the literature.

Keywords: *Thiamine, Anemia, Stroke.*

ÖZET

Tekrarlayan İnme Olan Bir Çocukta Tiamin Yanıtlı Megaloblastik Anemi Sendromu

Tiamin yanıtlı megaloblastik anemi sendromu (TRMA) (OMIM 249270), megaloblastik anemi, diabetes mellitus ve sensorinöral sağırlık triadı ile karakterize, nadir görülen otozomal resesif geçişli bir hastalıktır. Yüksek afiniteli bir tiamin taşıyıcı protein olan THTR-1'i kodlayan SLC19A2 genindeki mutasyonlar, TRMA ile ilişkili klinik özelliklerden sorumludur. Burada TRMA tanısı alan 20 aylık bir erkek hasta sunulmuştur. Tekrarlayan inme ve megaloblastik anemi nedeniyle tetkik edilen hastada SLC19A2 geninde (c.242-243 insA) homozigot mutasyon saptandı. Ayrıca tromboz panelinde homozigot MTHFR C677 ve heterozigot MTHFR A1298 mutasyonları tespit edildi. Bildiğimiz kadarıyla olgumuz literatürde homozigot MTHFR C677 ve heterozigot MTHFR A1298 mutasyonlarının eşlik ettiği ilk TRMA vakasıdır.

Anahtar Sözcükler: *Tiamin, Anemi, İnme.*

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Thiamine responsive megaloblastic anemia syndrome (TRMA) (OMIM 249270) is a rare, autosomal recessive inherited disease characterized by a triad of diabetes mellitus, sensorineural deafness and megaloblastic anemia. Besides the characteristic triad of TRMA aminoaciduria, congenital heart disease, abnormalities of optic nerve and retina, arytmias, stroke like episodes and, situs inversus were also reported (1-4). Mutations in the SLC19A2 gene leads to TRMA(5). The location of this gene is on chromosome 1q23.3, spanning 6 exons. SLC 19A2 gene encodes a high-affinity plasma membrane thiamine transporter (THTR-1SLC19A2) that is expressed in most of the human tissues such as brain, fibroblasts, heart, bone marrow, pancreas, retina, liver, lung, skeletal muscle, fibroblasts, kidney, colon, small intestine, lymphocytes and placenta (5-6). The mechanism responsible for the neurological syndrome of TRMA is thought to be related to the low activity of two oxidative decarboxylation enzymes, with a consequent dysfunction in the Krebs cycle and decreased mitochondrial energy production (7). Here, we report a 20 month-old boy who was diagnosed as TRMA, during evaluation of his recurrent stroke and megaloblastic anemia. Besides homozygote MTHFR C677 and heterozygote MTHFR A1298 mutations were also detected in the patient's thrombosis panel. We reported this case because as far as we know this is the first TRMA case with homozygote MTHFR C677 and heterozygote MTHFR A1298 mutations in the literature.

CASE REPORT

Twenty-month-old male baby was admitted to our emergency department due to generalized tonic-clonic seizures. The history revealed that the patient was hospitalized due to acute infarct in the left middle cerebral

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artery (MCA) when he was ten-months-old and low molecular heparin treatment had been given for three months. He was second living child of his parents who were first-degree cousins. Two brothers died before one-year age due to unknown etiology. One pregnancy was ended with abortus. The patient's vital signs were in normal ranges. In physical examination she was lethargic. His pupils were isochoric, and direct and indirect light reflexes were normal Complete blood count revealed hemoglobin (Hb) of 9.6 g/dl, mean corpuscular volume (MCV) of 97 fl, white blood cell count of 11.8x109/L, and platelet count of 262x109/L. His fasting blood glucose was 213 mg/dl. Homozygote MTHFR C677 and heterozygote MTHFR A1298 were detected in the evaluation of his thrombosis panel. Serum biochemistry, homocysteine and other thrombosis panel values were in the normal range. Levels of serum folate and vitamin B12 were also found within normal ranges. . In cranial MR images chronic infarct in the left MCA and acute infarct in the right basal ganglia were detected. Following a deterioration in the general condition, the patient was connected to a mechanical ventilator. Supraventricular tachycardia was seen in ECG, while echocardiography was normal. Anticonvulsant and LMW heparin treatments were given. Follow-up on the high blood glucose, 0.1 U/kg insulin treatment was started. TRMA was considered in the patient due to megaloblastic anemia, higher fasting blood glucose, supraventricular tachycardia and recurrent thrombosis. Since the patient was intubated and mechanically ventilated, his hearing could not be tested. The gene analysis result which showed homozygous mutation in SLC19A2 gene (c.242-243 insA), confirmed TRMA. Thiamine treatment was started in addition to the other treatments but the patient's clinical status did not improve. He was lost in the fifteenth day of hospitalization.

DISCUSSION

TRMA can be observed anytime between infancy and adolescence and usually all the cardinal findings are not present at the beginning (1-4). Although diabetes mellitus, deafness and anemia are the clinical traid of the TRMA, other clinical symptoms or signs such as arythmias, congenital heart disease, abnormalities of the retina and aminoaciduria are also reported. Although they are seen only in a few cases stroke or stroke like episodes are certain features of TRMA. Shaw-Smith et al (8) reported that stroke occurred in 4/30 (13%) of patients in a previous study with 30 patients. Villa et al (9) reported a 20 years old woman with TRMA admitted to hospital because of acute ischemic stroke. They have reported that stroke might be due to the oral contraceptive that the patient used previously. We considered TRMA in our patient because of megaloblastic anemia, hyperglycemia, arrhytmia and stroke. Gene analysis confirmed our diagnosis since TRMA related SLC19A2 mutation was shown.

Fullerton et al (10) risk factors in children with recurrent ischemic stroke; children receiving antithrombotic therapy, arteriopathies, cardiac embolism, moyamoya disease, arteriel disection and infections as shown. They defined the greatest risk as arteriopathy. Our patient had two stroke attacks in different locations without any signs of arteriopathy. He was not under antithrombotic therapy. Since his echocardiography was in normal ranges we ruled out cardiac embolism. That's why we primarily suspected the hematological etiologies in the differentional diagnosis of recurrent stroke. While investigating the etiology of stroke, homozygote MTHFR C677 and heterozygote MTHFR A1298 mutations were detected in his thrombosis panel. Normal values of serum biochemistry and other thrombosis panel were established. Especially in the presence of low serum folate levels reduced enzyme activity of MTHFR is considered a genetic risk factor for hyperhomocysteinemia. However mild to moderate hyperhomocysteinemia has been identified as one of the risk factors for venous thrombosis and it has also been associated with other cardiovascular diseases, like coronary artery disease. In general, the genotypes below at the moment appear unlikely to to have clinical significance: "thermolabile" variant c.665C→T heterozygote, c.1286A→C homozygote, or (c.665C→T); (c.1286A→C) compound heterozygot (11). There is theoretical reason to consider that the rare individuals with triple variant MTHFR genotypes (i.e, individuals who are homozygous for one variant and heterozygous for the other) may have clinical risks, although that is currently speculative.

As far as we know our patient is the first case in the literature with recurrent stroke and a mutation in SLC19A2 gene besides two more mutations that may cause thrombosis. In TRMA no recurrent ischemic stroke attacks due to other thrombotic factors were defined before our case. In patients with stroke TRMA should be considered in differential diagnosis. Hovewer in TRMA patients especially with stroke, the other congenital risk factors should also be investigated.

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