Thiamine deficiency syndrome (Rogers Syndrome) with recurrent thrombosis and pulmonary embolism with a novel mutation

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Abstract

Thiamine-Responsive Megaloblastic Anemia syndrome (TRMA syndrome) also known as Roger syndrome is rare syndrome. It is characterized by thiamine-responsive megaloblastic anemia, diabetes mellitus, and sensor neural deafness. TRMA syndrome has been reported in less than 100 cases worldwide. There are variable phenotypic variations of this syndrome, we report a case of Rogers syndrome in a woman with recurrent thrombosis and pulmonary embolism, and examined the underlying causative mutation using next-generation sequencing. This case represents a unique phenotype of Roger syndrome. The recurrent venous thromboembolism was not described as an associated phenomenon in this syndrome with novel mutation.

Keywords: Thiamine deficiency syndrome; Rogers Syndrome; mutation; TPK1

Introduction

Thiamine-responsive megaloblastic anemia (TRMA syndrome), also known as Rogers syndrome, is an inherited autosomal recessive condition. The cardinal clinical manifestations of this syndrome include thiamine-responsive megaloblastic anemia, diabetes mellitus, and sensorineural deafness (1).

Thiamin Pyrophosphokinase 1(TPK1) mutation sites in TRMA are heterogeneous and include heterozygous compound mutations. TRMA shows phenotypic variability, which may lead to diagnostic delay; the average time between symptom onset and diagnosis is 8 years (2). At the cellular level, deficiency of the thiamine transport mechanism results in inadequate intracellular concentrations of thiamine and subsequent apoptosis. Treatment of the disease with pharmacological doses of thiamine improves megaloblastic anemia and diabetes mellitus; however sensorineural hearing loss is irreversible and may not be prevented even if the treatment is started in infancy(3). Congenital heart disease(4), stroke(5), and short stature (6) are also observed as symptoms in Rogers syndrome. In this study, we came across a case of Rogers's syndrome in a woman with recurrent thrombosis and pulmonary embolism, and examined the underlying causative mutation using next-generation sequencing.

Case report

Thirty-one-year-old lady who was found to have Roger's syndrome, while being evaluated for pancytopenia. She had a significant history of deafness which started at her age of 5 and type 1 diabetes mellitus. She is a child of consanguineously married couple otherwise nothing significant in family history. On physical examination: the patient does not have any dysmorphic signs. Her physique is appropriate to her age. She had multiple bruises over lower limbs Her neurological exam: showed sensorineural hearing loss There was history of receiving multiple blood products packed red cells and platelets since childhood Later she was investigated by a hematologist and her Bone marrow aspiration and biopsy showed hyper cellular bone marrow with megaloblastic maturation. Many binucleate and multinucleate erythroid forms are noted. Myeloid elements are significantly reduced. Megakaryocytes show micro megakaryocytes and megakaryocytes with nuclear separation and naked nuclei. Blast count less than 3%. The patient developed progressive pancytopenia and hypersplenism was diagnosed and she underwent splenectomy, which did not improve the pancytopenia

Later on, level of thiamine was found to be low and she was started on parenteral thiamine replacement. In view of constellation of deafness, type 1 diabetes mellitus and thiamine deficiency, Roger syndrome was suspected. After she became compliant to parenteral thiamine replacement, she did not need any PRBC or platelet transfusion. At the age of 17 years old, she had multiple recurrent unprovoked pulmonary embolisms and portal vein thrombosis. The thrombophilia

workup was negative including protein c, S and AT III deficiency, antiphospholipid antibodies and factor V Leiden. She was started on rivaroxaban and she did not have any recurrent VTE episodes since then.

She is being followed up in hematology clinic for recurrent pulmonary embolism and thiamine deficiency. Her recent CT pulmonary angiogram revealed multiple filling defects along the left lower lobe segment and sub segmental pulmonary artery branches as well as sub segmental superior segment at the right lower lobe pulmonary artery branch compatible with acute and subacute pulmonary emboli. Echocardiogram in August 2018 showed mild-to-moderate tricuspid regurgitation with estimated pulmonary artery systolic pressure of 55 mmHg along with elevated right atrial pressure and no pericardial effusion. The right heart catherization showed no evidence of pulmonary hypertension. The mean pulmonary artery pressure was 20 and the pulmonary capillary wedge pressure is 6, the right atrial pressure is 3. Her pro BNP levels were in normal limits. On her routine visit to our clinic, she was doing well on anticoagulant and thiamine replacement every 2weekly. As her thrombophilia workup done for evaluation of recurrent pulmonary embolism were all negative and there is no association of venous thromboembolism with Rogers Syndrome , we thought of conducting Whole exome sequencing study .

Whole exome sequencing (WES) was conducted and showed a heterozygote mutation (single nucleotide variant -SNV) in the TPK1 was identified which is chr7:g.144245545A>G (NC_000007.13:g.144245545A>G). The novel intronic substitution variants in TPK1 gene (TPK1:NC_000007.13(TPK1_v002): c.613+39T>C was reported as the causative variant in this case. The variant was classified as a pathogenic variant.

Exome analysis

Whole exome sequencing (WES) was conducted. Briefly, genomic DNA was extracted using the Gentra Puregene Blood Kit (Qiagen) and used for library preparation. Each library was barcoded using the Ion Xpress™ Barcode Adapters 1-96 Kit (Life Technologies). Barcoded libraries were used for template preparation by emulsion PCR, followed by enrichment. The Ion Torrent Proton platform was used for DNA sequencing with an Ion PI™ Hi-Q™ Sequencing 200 Kit and Ion PI™ Chip Kit v3. The reads were aligned with the hg19 reference sequence through the tMap program.

Aligned reads were investigated for variant calling through the Torrent Suite Variant Caller TVC program. The variants were annotated the Saudi Genome Program. Finally, the pipeline, non-relevant variants were filtered out based on their quality, functional characteristics, and frequency in the data sets. All the nonsense, frameshift, and canonical splice site variants that were considered pathogenic were reported.

Results

Exome analysis

Considering the genetic heterogeneity in the reported case, we performed whole exome sequencing analysis to identify the most likely causative variants. A heterozygous mutation (single nucleotide variant -SNV) in TPK1 was identified, which was chr7:g.144245545A>G (NC_000007.13:g.144245545A>G). A novel intronic substitution variant in TPK1 gene: (TPK1:NC_000007.13) (TPK1_v002):c.613+39T>C, was found as the causative variant in this case. This variant was thus classified as a pathogenic variant.

Discussion

Thiamine responsive megaloblastic anemia is a rare disorder and the phenotype associated with this syndrome comprises sensorineural hearing loss and insulin dependent diabetes mellitus (7). Other clinical associations include optic atrophy, congenital heart disease and short stature(2). TRMA syndrome was first described by Rogers et al. in 1969 and was thus named as Rogers syndrome(7). Later, Viana and Carvalho in 1978 (8), Haworth et al. in 1982 (9), and Mandel et al. in 1984 (10) also reported this syndrome. Several mutations were identified as causative driver mutations in many diseases (11, 12). The genetic mutation typically described in patients with this phenotype is a homozygous mutation in SLC19A2 [2], which encodes a thiamine responder protein in chromosome 1q23.3. The inheritance is reported to follow an autosomal recessive pattern (9); the age of presentation or diagnoses could be as early as 3 months (10), but some patients are diagnosed after the age of 6 years (10). Mutations in other genes including SLC19A3 (13), SLC25A19 (14), and TPK1 have also been described to affect thiamine metabolism. These mutations usually are associated with different phenotypes, including encephalopathies and polyneuropathy syndromes.

Our patient showed the typical phenotype of Rogers's syndrome: thiamine responsive megaloblastic anemia, sensorineural hearing loss, and type 1 diabetes mellitus.

We then performed next generation sequencing, which identified a mutation in the TPK1 gene (TPK1:NC_000007.13 (TPK1_v002):c.613+39T>C). TPK1 is a protein-coding gene and mutations in this gene cause thiamine metabolism dysfunction syndrome and megaloblastic anemia. Its related pathways include metabolism of water-soluble vitamins.

Although the phenotype of our patient was consistent with that of Rogers syndrome, she did not harbor the typically associated mutation in SLC19A3. Instead, NGS showed a different mutation in TPK1, which is also associated with thiamine metabolism. Upon follow-up, the anemia was shown to improve after regular thiamine replacement parenterally. However, she surprisingly developed multiple unprovoked thrombotic events in the form of pulmonary embolism and portal vein thrombosis. These thrombotic events were not explained by the thrombophilia screen, which showed negative results for common pro-thrombotic disorders. Splenectomy could possibly explain the thrombotic event, and therefore, we undertook a literature review to find any similar cases. We found another patient reported by Villa et al. (5), who showed the phenotypes of Rogers syndrome (no genetic profile was described in the case report). This patient developed an ischemic cerebrovascular accident at the age of 20 years, and all thrombophilia investigations were negative. This patient did not have a history of splenectomy. Our results, therefore, suggest an association of the Rogers Syndrome phenotype with thrombophilic tendency and a mutation in TPK1:NC_000007.13 (TPK1_v002):c.613+39T>C. The present case study demonstrates the power of next generation sequencing analysis in identifying novel genetic causes of disorders with a genetic basis.

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