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Research article

Identification of novel mutations in *TPK1* and *SLC19A3* genes in families exhibiting thiamine metabolism dysfunction syndrome

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ABSTRACT

Background and aims: The occurrence of thiamine metabolism dysfunction syndrome (THMD), a rare autosomal recessive condition, may be linked to various mutations found in the *TPK1* and *SLC19A3* genes. The disease chiefly manifests through ataxia, muscle hypotonia, abrupt or subacute onset encephalopathy, and a decline in developmental milestones achieved during the early stages of infancy. We present findings from an investigation that involved two individuals from Iran, both of whom experienced seizures along with ataxia and hypotonia. The underlying genetic causes were found with the use of next-generation sequencing (NGS) technology, which has facilitated the detection of causal changes in a variety of genetic disorders.

Material and methods: The selection of cases for this study was based on the phenotypic and genetic information that was obtainable from the Center for Comprehensive Genetic Services. The genetic basis for the problems observed among the participants was determined through the application of whole-exome sequencing (WES). Subsequently, sanger sequencing was employed as a means of validating any identified variations suspected to be causative.

Results: The first patient exhibited a homozygous mutation in the *TPK1* gene, NM_022445.4:c.224 T > A:p.I75 N, resulting in the substitution of isoleucine for asparagine at position 75 (p.I75 N). In our investigation, patient 2 exhibited a homozygous variant, NM_025243.4:c.1385dupA:pY462X, within the *SLC19A3* gene.

Conclusions: Collectively, when presented with patients showcasing ataxia, encephalopathy, and basal ganglia necrosis, it is essential to account for thiamine deficiency in light of the potential advantages of prompt intervention. At times, it may be feasible to rectify this deficiency through

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the timely administration of thiamine dosages. Accordingly, based on the results of the current investigation, these variations may be useful for the diagnosis and management of patients with THMD.

1. Introduction

Thiamine, commonly known as vitamin B1, is a crucial water-soluble vitamin in human nutrition. The majority of thiamine absorption occurs in the small intestine and is taken in by cells and tissues. Afterward, it is transformed into thiamine pyrophosphate (TPP) through the action of cytosolic enzyme thiamine pyrophosphokinase (TPK) [1]. TPP plays a key role in various metabolic processes occurring in cytosol, peroxisome, and mitochondria, accounting for eighty percent of thiamine present in the body. In the cytosol, it acts as a cofactor for transketolase enzyme and aids in the pentose phosphate pathway. TPP serves as a cofactor in several mitochondrial complexes. These include a complex responsible for converting pyruvate into acetyl-coA, a complex in the Krebs cycle that catalyzes the decarboxylation of alpha ketoglutarate, and a complex that carboxylates branched, short-chain alpha-ketoacids. TPP functions as a cofactor of 2-hydroxyacyl-coA lyase (HACL1) in the peroxisome, which is involved in the breakdown of fatty acids [2].

Thiamine metabolism dysfunction syndrome (THMD) is a condition brought on by a shortage in thiamine metabolism. This condition is linked to four genes, namely *SLC19A3*, *SLC25A19*, *SLC19A2*, and *TPK1*. THMD is categorized into five subtypes based on defective genes and phenotypic characteristics. The aforementioned gene mutations contribute to five different types of THMD. THMD1 is attributable to mutations in the *SLC19A2* gene, THMD2 is linked to mutations in the *SLC19A3* gene, THMD3 and THMD4 are caused by mutations in the *SLC25A19* gene, and THMD5 is typically the result of *TPK1* gene mutations [3]. According to Marcé-Grau et al., 10 pathogenic variants of *TPK1* gene have been identified, and they are all responsible for THMD5 [2]. It is a rare subset of the illnesses caused by mutations in *TPK1*, which encodes for thiamine pyrophosphokinase 1 [4]. The *TPK1* gene is located on chromosome 7q34-q35. The *TPK1* gene exhibits intense activity in the small intestine, where it is linked to the assimilation of thiamine, and in the kidney, where it plays a role in the re-absorption of thiamine. Additionally, it is also present in the liver, brain, placenta, and spleen [1]. THMD2 is a rare metabolic condition inherited in an autosomal recessive manner and caused by *SLC19A3* gene mutations. Early identification and treatment with vitamin supplementation are crucial because this condition is curable [5].

In the current investigation, two Iranian children who frequently experienced ataxia, hypotonia, and seizures were found to have novel mutations in the *TPK1* and *SLC19A3* genes. In addition, we looked over those reported instances to learn more about the clinical and genetic characteristics of this rare metabolic disorder. On the basis of the current investigation, these variants can also aid in the accurate identification and management of patients with THMD.

2. Materials and methods

The specimens were procured from two families who were referred to the Center for Comprehensive Genetic Services (CCGS) at Shahid Beheshti University of Medical Sciences (SBMU) for the purpose of genetic counseling and exploration of the underlying etiology of the illness in their families. The Ethical Committee, Deputy of Research Affairs of Shahid Beheshti University of Medical Sciences, Tehran, Iran with approval ID: IR.SBMU.MSP.REC.1398.575 approved all procedures performed in this study, following with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Also, written informed consent was obtained

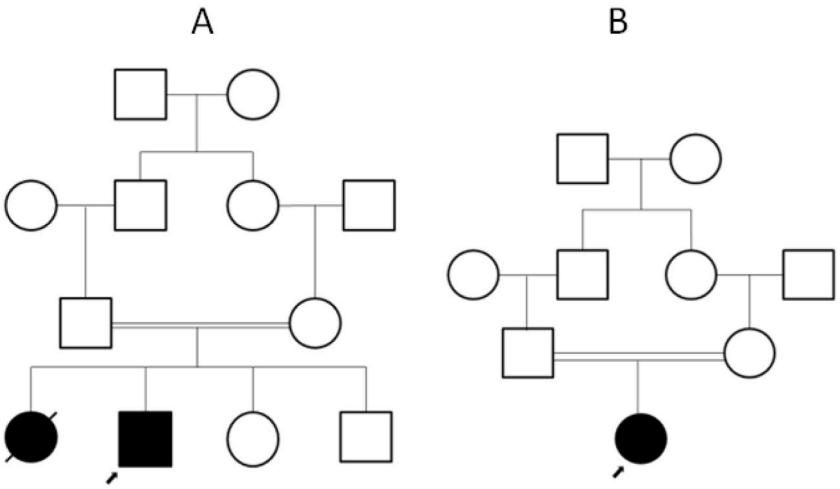

Fig. 1. Pedigrees of two families with thiamine metabolism dysfunction syndrome. Fig. 1A and B represent the patient 1 and 2 pedigrees, respectively. Black symbols represent the affected individuals, and open symbols represent normal individuals. The proband is represented by the black arrow (↑).

from each participant.

2.1. Case presentation

2.1.1. Patient 1

Patient 1 (proband) was a male toddler of 20 months of age (as illustrated in Fig. 1A) with hypotonia, developmental regression, and increased levels of lactate and CPK (1940 IU/L). The individual in question was delivered via a cesarean section procedure. Magnetic resonance imaging (MRI) of the brain revealed bilateral signal alterations in both the dentate nucleus and basal ganglia. The study subjects' parental relationship is consanguineous, as evident from Fig. 1A. The demise of the younger sibling, who perished at the age of eight months with identical clinical manifestations, was the second such occurrence within the family. The patient under investigation presents with siblings who are free from any known medical conditions, indicating their good state of health. The proband exhibited no signs of illness at the time of birth; however, at the age of 6–7 months, the individual began to display symptoms of hypotonia, fever, diarrhea, and vomiting. Currently, the patient 1 is five years of age, and both his stature and mass development are within typical parameters. The patient displays no difficulty in verbal communication or mastication; however, ambulation proves to be arduous. The individual in question is afflicted with gastroesophageal reflux disease. The administration of pharmacological interventions, namely levebel syrup, thiamine, riboflavin, and L-carnitine, has been found to effectively regulate the aforementioned condition to normal levels.

2.1.2. Patient 2

Proband, identified as Patient 2, was a female infant of 2.5 months old as illustrated in Fig. 1B which from a consanguineous marriage with normal vaginal delivery. At the time of birth, the proband possessed good health condition and had a weight of 3 kg and a height of 49 cm. There was no indication of jaundice in her physical condition. The symptoms of the child's illness manifested when she was only two months old, and she experienced seizures that required hospitalization for a duration of one month and three days. The quantities of lactate have risen in both the plasma and CSF. The person experienced seizures, deterioration of the basal ganglia, and increased levels of lactate (45.2 mg/dL) and ammonia (185 μg/dL). The LC-MS/MS method was used to evaluate the amino acid composition. The results indicated that apart from citrulline, all other amino acids were within normal limits. At present, the subject is a 2-year-old who lacks the ability to support her own neck. Furthermore, she can't sit and speak. With the help of recommended medications such as levebel syrup, prednisolone, biotin, and thiamine, the child's state has been restored to stability. Although her development is typical, occupational therapy is being utilized. There does not seem to be any psychological issue. The functioning of both the kidneys and liver appears to be normal. Her intracranial pressure and cerebrospinal fluid are within normal range. An electroencephalogram was conducted recently and the findings indicated no abnormalities.

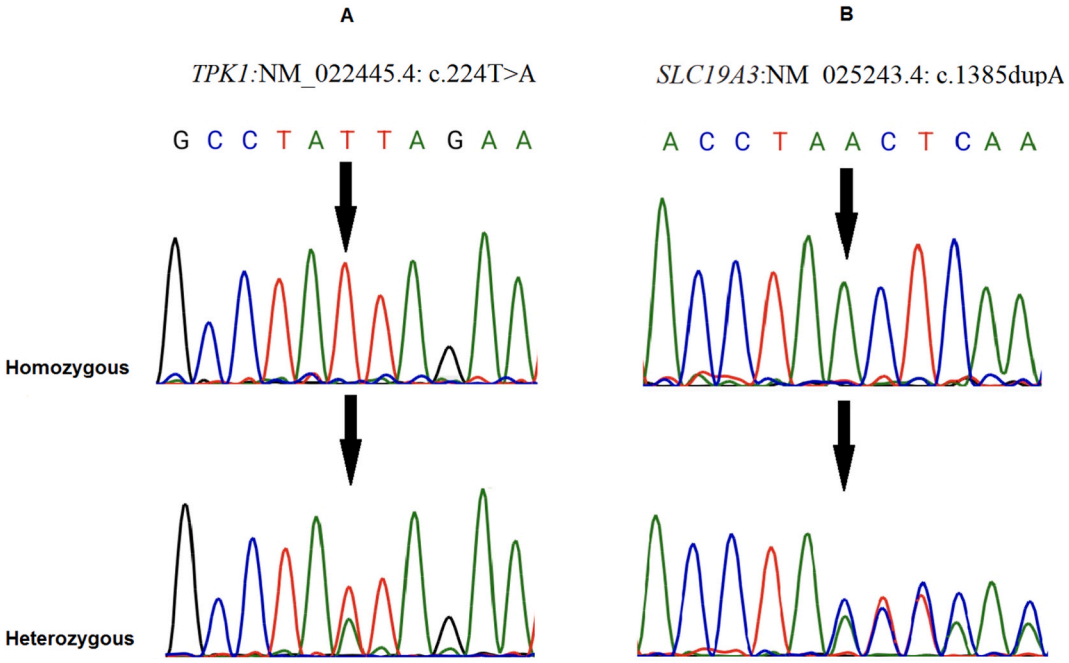

Fig. 2. A. For the patient 1 Sanger sequencing analysis of the proband showed one novel homozygous variant in the *TPK1* gene, NM_022445.4: c.224 T > A, while his parents are heterozygous for this variant. B. For the patient 2 Sanger sequencing analysis of the proband showed one novel homozygous variant in the *SLC19A3* gene, NM_025243.4: c.1385dupA, while his parents are heterozygous for this variant. The arrow symbol indicates the location of mutation.

2.2. Samples preparation and Whole-Exome Sequencing (WES)

Using the salting out method, the genomic DNA was extracted from both the participants and their parents' peripheral blood samples. The concentration and purity of genomic DNA were measured using NanoDrop 1000, manufactured by Thermo Fisher Scientific, Inc. Located in Wilmington, DE, USA. The genomic DNA from the probands was utilized in WES, which was carried out on an Illumina HiSeq4000 with paired-end sequencing with a read length of 101bp and a coverage of 100X system. The SureSelectXT2 V6 kits were utilized to enrich both exonic and adjacent exon-intron boundary areas. Following the filtration of substandard reads, the human genome reference (hg19 build) was utilized in mapping the remaining reads through the Burrows-Wheeler Aligner (BWA) [6]. SAM tools were utilized to identify and eliminate duplicates [7]. Afterward, the process of recalibrating and identifying SNP/indel was undertaken. The genome analysis toolkit (GATK) was applied for variant identification and filtration, following recommended protocols [8]. The annotated variations were subjected to filtering and prioritization using an internally developed workflow after being processed through ANNOVAR [9].

2.3. Sanger sequencing and comparative research in silico

Sanger sequencing was employed to confirm the *TPK1* and *SLC19A3* gene variations discovered in each WES proband (Fig. 2A and B). Parents were also sequenced for segregation analyses. The primer pairs were designed for PCR amplification of the *TPK1* and *SLC19A3* genes' specific mutations (Table 1). The Sanger sequencing was carried out on an ABI Sequencer 3500XL PE using the BigDye Terminator v3.1 Cycle Sequencing Kit (Life Technologies; Thermo Fisher Scientific, Shanghai, China) (Applied Biosystems, CA, USA). The 3D protein structural model of *TPK1* and *SLC19A3* was visualized using PyMol software (Figs. 3 and 4) (The PyMOL Molecular Graphics System, Version 1.2r3pre, Schrödinger, LLC).

3. Results

Using WES, a total read bases of 7 million bp was obtained for each case. Almost 90,000 variations were observed in each patient. By using allele frequency-based filtration, approximately 1500 variants were obtained. The prioritization of homozygous variations was based on the level of pathogenicity, with emphasis on mutations such as stop gain, frameshift, and those affecting splicing regions, that are most severe. Various predictors were utilized to prioritize the level of pathogenicity of nonsynonymous mutations by evaluating the amino acid changes. A novel missense gene variant (NM_022445.4: c.224 T > A, p.I75 N) in *TPK1* was found in patient 1 WES analysis. (ClinVar Accession Number: SCV003926638). Sanger sequencing was performed to validate the variant uncovered through whole-exome sequencing in the proband 1 and their parents. Based on the findings, the parents exhibit heterozygosity while Patient 1 is mutant homozygous, as illustrated in Fig. 2A. The mutation in this gene is linked to a medical condition known as thiamine metabolism dysfunction syndrome 5 (also called episodic encephalopathy type), which is distinguished by recurring episodes of encephalopathy. This variant was previously classified as a variant of uncertain significance (VUS) according to the American College of Medical Genetics (ACMG) guideline [10]. *In silico* analysis predicted the variant as a pathogenic moderate (DEOGEN2 , EIGEN, EIGEN PC, Mutation assessor, MutPred, and MVP), pathogenic supporting (LRT, PROVEAN, SIFT, and SIFT4G), and uncertain significant (BLOSUM, DANN, FATHMM, M CAP, MutationTaster, and Illumina/PrimateAI" title = "https://github.com/-Illumina/PrimateAI">PrimateAI) (https://varsome.com). This variant has not been reported in gnomAD and ExAC databases [11].

Subsequently, the novel findings indicated that the individual 2 has a mutant homozygous state for the (NM_025243.4:c.1385dupA: pY462X) mutation in the *SLC19A3* gene, ClinVar Accession Number: SCV003926639. A variation in this particular gene has been associated with thiamine metabolism dysfunction syndrome 2, also known as biotin- or thiamine-responsive encephalopathy type 2. The parent's Sanger sequencing revealed a heterozygous state for this variant, as shown in Fig. 2B. Moreover, based on the American College of Medical Genetics (ACMG) guideline, this gene mutation was deemed to be likely pathogenic. This variant has not been reported in gnomAD and ExAC databases.

4. Discussion

Thiamine is an essential nutrient and plays a crucial role in cell growth and function [12]. Metabolic problems can result from thiamine deficiency [13]. THMD, is a rare group of genetically and clinically diverse encephalopathies caused by deficiency in thiamine that is inherited in an autosomal recessive manner [3]. There are four genes associated with this syndrome: *SLC19A3*, *SLC25A19*, *SLC19A2*, and *TPK1* [3]. Our study investigates participants with mutations in two of these genes, *TPK1* and *SLC19A3*.

We evaluated the *TPK1* gene mutation (NM_022445.4:c.224 T > A:p.I75 N) in a 20-month-old boy in our investigation. This mutation is associated with thiamine metabolism dysfunction syndrome 5. The position of mutated amino acid in the TPK1 protein is

Table 1
Primer sequences list for PCR amplification of mutations c.224 T > A and c1385dupA and their flanking regions in the *TPK1* and *SLC19A3* genes, respectively.

Genes	Forward primer	Reverse primer	Exon	Amplicon size (bp)
TPK1	CTCTTTGGTCCTTATAATCACAG	TAGTGGTGGACTTCCCCGAA	5	758
SLC19A3	CTCTTAGTCACCGTATTGCTT	GGTCACATAGAGAACTCATC	6	556

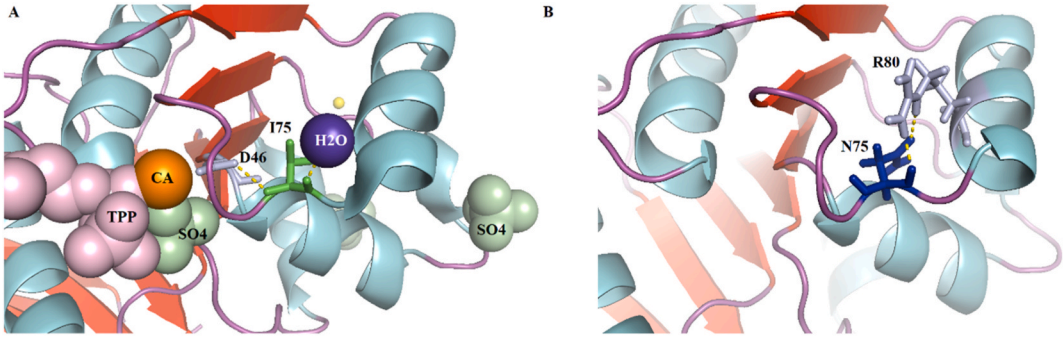

Fig. 3. Close-up of the *TPK1* gene mutation at protein level based of PDB 3s4y. The protein is coloured by element; α-helix = cyan, β-strand = red, and loop = pink. The side chains of both the wild-type (A) and the mutant residue (B) are shown and coloured green and blue respectively. CA=Calcium Ion, SO4=Sulfate Ion, TPP=Thiamine Diphosphate. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

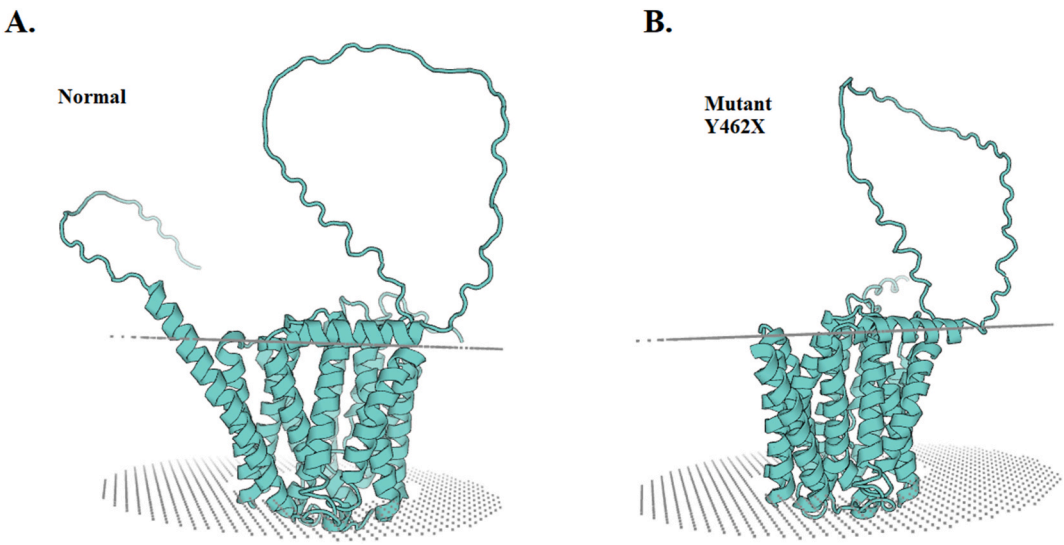

Fig. 4. Protein modeling SLC19A3 protein based on templates Q4R877.1.A and Q9BZV2.1.A with Seq Identity 94.76–100%, Seq Similarity 0.59–0.61, coverage 1.00, and range 1–496 amino acid, and Global Model Quality Estimate (GMQE) 0.82–0.84. Predicted wild-type (Fig. 4A) and mutant (Fig. 4B) SLC19A3 are shown. Protein modeling result showed loss of C-terminal of SLC19A3 in the cytoplasm of cell (4B).

depicted in Fig. 3A, B. The mutant residue is larger and less hydrophobic than the wild-type residue. Moreover, the wild-type residue was positioned in the core of the protein. As a result, the mutant residue may not fit well, and the mutation could lead to a loss of hydrophobic interactions in the protein's core. While the mutated residue does not come into contact with metal, one of the neighboring residues forms a metal-contact that could be influenced by the mutation in its vicinity. Although the wild-type residue is highly conserved, other residue types have been identified at position 75 in some homologous proteins. However, the mutant residue was not among these residue types. Despite this, residues that share some properties with the mutated residue have been identified, indicating that this mutation may not damage the protein in some cases. The mutated residue is located in an essential domain for the protein's activity and interacts with another crucial domain. Therefore, this interaction could be disrupted by the mutation, which could impact the protein's function. However, functional studies are needed to elucidate the exact effect of p.I75 N mutation on the TPK1 protein. Since the first report of THMD5, which is caused by mutations in TPK1 in 2011, a total of 26 cases of this disease have been reported. The onset of symptoms is usually in childhood, and may exhibit a normal psychomotor development until the symptoms begin. Recurrent episodes of encephalopathy, psychomotor regression, seizure, ataxia, dystonia, and dysarthria are among the common findings in patients with THMD5 disease. Cerebellum and dentate nuclei involvement is the most common finding in the brain MRI of these patients. Increased lactate levels in plasma and CSF during the episodes of encephalopathy can usually be observed in patients [2]. Elevation of various organic acids and transaminases has also been reported [14]; however, CPK elevation, which was observed in patient 1 has not been reported in the literature. In a THMD5 case reported by Eckenweiler et al., thiamine therapy led to normal motor development and cognition and even regression of lesions in the dentate nuclei and putamen in the repeated brain MRI [15]. Other studies have also shown that early treatment leads to normal neurodevelopment and even ameliorates brain lesions [2,16]. This is in

line with the findings in patient 1 in this study, where supplementation of thiamine recovered the normal condition in the patient. These findings underscore the importance of early diagnosis of THMD5, which is crucial in providing effective treatment for these patients. Therefore initiation of high-dose thiamine is necessary immediately after diagnosis or even upon suspicion [16].

The *SLC19A3* gene, which has five exons, is found on human chromosome 2q37 (NM_025243) [17]and encodes a 496 amino acid thiamine receptor type 2, and its deficiency is related to biotin- or thiamine-responsive basal ganglia disease (BTRBGD) [2]. A 2.5-month-old girl patient in our study had a *SLC19A3* gene mutation, which is consistent with reports from earlier articles [2,3,6] and is linked to thiamine metabolism dysfunction syndrome 2 (THMD2) (biotin- or thiamine-responsive encephalopathy type 2). Fig. 4 shows that converting tyrosine 462 to a stop codon results in the loss of the C-terminal domain of the SLC19A3 protein, which contains phosphorylation sites for regulation and plays a role in signal transduction for conformational changes in the thiamine transport channel. A deficiency in thiamine transport can potentially lead to the development of neurological conditions in individuals with mutations in this gene. Patients with THMD typically experience a progressive clinical course that, if untreated, results in severe impairment and even death [3]. Four Japanese patients with early-onset epileptic spasms, severe psychomotor impairment, brain atrophy, and bilateral thalamic and basal ganglia lesions were described by Yamada et al. [18] in their study. Patients described by Yamada et al. could be classified as early infantile Leigh syndrome, which is the most severe *SLC19A3*-related phenotype. Seven patients from Chinese families who experienced seizures, hypotonia, and developmental regression were investigated by Li et al. [3]. Four of these patients exhibited the *SLC19A3* gene mutations [(c.265A > C; p.Ser89Arg), (c.197 T > C; p.Leu66Pro), (c.962C > T; p.Ala321Val), (c.850 T > C; p.Trp284Arg)], which were novel. Savasta et al. [19] described the clinical and radiological characteristics of two siblings with tonic seizures and hypotonia who were diagnosed with BTRBGD. WES of the family members revealed a novel *SLC19A3* mutation (c.548C > T; p.Ala183Val). Patients with SLC19A3 deficiency usually have normal psychomotor development until the first episode of encephalopathy, which infections could trigger. The characteristics of BTRBGD are early onset encephalopathy, seizure, ataxia, bulbar dysfunction, and dystonia/hypotonia [20]. Brain MRI is abnormal in all symptomatic cases, and usually symmetrically distributed lesions could be seen, especially in caudate nuclei, putamen, and medial thalami. Lactate elevation in plasma and CSF could be detected in some patients, as we have observed in patient 2 in this study [2]. Several studies have shown that patients with thiamine transport and metabolism disorders respond well to thiamine supplementation, leading to clinical and biochemical improvements [2]. High doses of vitamin B2, L-carnitine, and coenzyme Q10 are also commonly used as therapy options in addition to vitamin B1 (thiamine) [12]. Thiamine was the same medication that was used to treat both cases in this study. One of the limitations of this study is the lack of functional studies due to the lack of facilities. These variants are suitable candidates for future functional studies.

In conclusion, the early diagnosis of thiamine deficiency is of great importance since it could be resolved with thiamine supplementation if it is diagnosed in time. However, due to the widely varied clinical appearance and clinical overlap with other inborn errors of metabolism, it is hard to diagnose in the early stages. In patients with encephalopathy, ataxia, and basal ganglia necrosis, thiamine deficiency should be considered. WES could aid in the early detection of this disorder and provide an effective treatment plan. Accordingly, based on the results of the current investigation, these variations may be useful for the diagnosis and management of patients with THMD.

In summary, this study provides two cases with thiamine deficiency, expands the genotypic spectrum of these disorders, and helps establish the genotype-phenotype correlation.

Data availability statement

The data that support the findings of this study are available from the corresponding authors, upon request. Two identified variants in this study obtained ClinVar accession numbers SCV003926638 and SCV003926639.

CRediT authorship contribution statement

Fatemeh Norouzi Rostami: Data curation, Investigation, Methodology, Writing – original draft. **Hossein Sadeghi:** Conceptualization, Software, Supervision, Validation, Writing – review & editing. **Farzad Hashemi-Gorji:** Formal analysis, Methodology, Software, Validation, Visualization, Writing – review & editing. **Sahand Tehrani Fateh:** Methodology, Software, Visualization, Writing – review & editing. **Reza Mirfakhraie:** Conceptualization, Supervision, Validation. **Parvaneh Karimzadeh:** Data curation, Formal analysis, Investigation, Methodology. **Milad Davarpanah:** Data curation, Investigation. **Sanaz Jamshidi:** Data curation, Investigation, Resources. **Rasoul Madannejad:** Investigation, Methodology. **Parinaz Moghimi:** Conceptualization, Data curation, Formal analysis, Validation. **Mahdis Ekrami:** Methodology, Software. **Mohammad Miryounesi:** Conceptualization, Formal analysis, Project administration, Resources, Supervision, Validation, Writing – review & editing. **Mohammad-Reza Ghasemi:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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