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Clinical and Genetic Studies of Thiamine Metabolism Dysfunction Syndrome 4: Case Series and Review of the Literature

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Abstract

Thiamine metabolism dysfunction syndrome-4 (THMD-4) is an autosomal recessive inherited rare disease (OMIM #613710) characterized by febrile illness associated episodic encephalopathy, leading to transient neurological dysfunction and progressive polyneuropathy. We report 3 patients from two different families with normal development, episodic encephalopathy, gait disorder, progressive chronic polyneuropathy characterized by motor difficulties, distal weakness, and hoarseness (dysphonia). We identified a homozygous missense c.576G>C, p.(Gln192His) variant in the *SLC25A19* gene in both families by whole exome sequencing. Following genetic diagnosis, thiamine replacement therapy was started, and improvement observed in all affected patients. We highlight the associated phenotypes of an *SCL25A19* mutation leading to clinical features of THMD-4.

Keywords

Phenotypic Expansion; *SCL25A19*; Whole-Exome Sequencing

Introduction

Thiamine metabolism dysfunction syndrome-4 (THMD-4) is an extremely rare neurological disease (less than 1 in 1,000,000) characterized by transient neurologic dysfunctions

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including acute encephalopathic episodes, seizures, chronic progressive polyneuropathy, dysarthria, areflexia, and skeletal muscle atrophy. These features of THMD-4 are often associated with a febrile illness, and usually show complete resolution after attacks. Additionally, mild distal weakness, gait abnormality, dysarthria, areflexia, and paralysis with possible radiological changes have also been reported (Iacobazzi, Ventura et al., 2001, Nabokina, Valle et al., 2013, Ortigoza-Escobar, Molero-Luis et al., 2016, Spiegel, Shaag et al., 2009). The differential diagnosis of the condition includes mitochondrial myopathies and thiamine metabolism disorders. The clinician should consider a diagnosis of THMD-4 when abnormal gait is accompanied by clinical features of encephalopathy, fever episodes, and muscle weakness.

We present three cases of THMD-4 with dysphonia, episodic gait abnormalities, and bilateral striatal necrosis from two families. Relevant investigations and radiographs were undertaken. Whole-exome sequencing analysis of index cases from both families revealed a homozygous missense NM_001126122.1(SLC25A19_v001):c.576G>C; p.(Gln192His) variant in the *SCL25A19* gene. Following the first identification of the *SLC25A19* pathogenic variants in this disorder in 2009 (Spiegel, Shaag et al., 2009), fewer than 15 patients have been described in the literature (Bottega, Perrone et al., 2019, Gowda, Srinivasan et al., 2019, Li, Song et al., 2020, Ortigoza-Escobar, Molero-Luis et al., 2016, Porta, Siri et al., 2021) (Table 1). These additional patients with the same *SCL25A19* variant highlight the associated phenotypes of THMD-4.

Methods and Results

The study was approved by the committee of Erciyes University, 2019. Patient's families signed Informed Consent Forms, according to the rules of Erciyes University Medical Faculty Institutional Reviewer Board. Consent forms were signed by both parents for the use of the patients' images and information.

Case reports

Patient 1 (P1), The index case, was an 11-year-old boy, with increasingly frequent episodes of fever, abnormal gait, and dysphonia who was admitted to a Pediatrics Neurologic Clinic. He was the second child of consanguineous parents with normal birth and Apgar scores, birth weight, and psychomotor development. Family history was notable because of the death of a sibling at 20 months old, diagnosed to have Guillain-Barré Syndrome, and a further sibling, with milder but similar symptoms with the index case. The episodic attacks of fever started at around two years of age and occurred every 2–3 years, triggered by respiratory tract infections (2, 4, and 10 years of age). Each attack lasted for about 2 or 3 weeks, and he was given intravenous immunoglobulin (IVIG). The patient had complete recovery after all episodes.

On admission, his growth was normal with a height on the 25th and weight on the 50th percentiles. He had an abnormal gait with muscle weakness (3/5) and truncal ataxia. His tone and deep tendon reflexes were normal. Physical examination revealed trigger finger and pes equinovalgus deformities (Fig. 1). Examinations of the joints and systems were unremarkable, with normal eye movements and respiratory patterns. He had dysarthria.His

intelligence quotient (IQ) and Denver Developmental Screening Test were in the normal range. Complete cardiovascular and ophthalmologic examinations (clinical examination, echocardiography, electrocardiography, visual field, optical coherence tomography) were normal.

Laboratory investigations showed normal full blood count and biochemical findings. Serology was negative for antinuclear-antibodies (ANA) and anti-double-stranded-DNA-antibody (anti-dsDNA). The plasma immunoglobulin and complement levels were normal except for mild elevation of IgE and IgM concentrations. Magnetic resonance imaging (MRI) and MRI spectroscopy showed hyperintense changes in the white matter and necrotic degenerations of caudate nucleus, putamen, and thalamus with a reverse lactate peak in the region of the basal ganglia; however, no signs of trauma or encephalitis were detected (Fig. 2). Various therapeutic approaches were undertaken to suppress inflammation and try to prevent further episodes, such as daily physiotherapy, IVIG therapy, biotin therapy, and steroid therapy. However, there was no improvement.

The second patient, (P2) was the brother of the index case, first admitted to the hospital at the age of 13 years old. He had the same complaints of abnormal gait with toe walking, muscle weakness (3/5), and truncal ataxia which was mostly visible when shifting when walking heel-to-toe. Birth history and developmental history were normal. There was a history of afebrile seizures and episodic gait abnormalities, lasting for a couple of days, 1–2 times annually, with complete recovery. He was also given IVIG with a presumed diagnosis of Guillain-Barré Syndrome. However, lower limb spasticity persisted on follow-up.

On examination, his growth was also within normal percentiles. He had an abnormal gait with decreased muscle strength in limbs (3/5), and specific truncal ataxia. There was a loss of deep tendon reflexes and an equinovalgus foot deformity. He had dysarthria. Developmental Screening Tests gave results within the normal range. Examinations of the body systems were unremarkable (including echocardiography, electrocardiography, visual field, optical coherence tomography).

The full blood count and biochemical exams, plasma immunoglobulin, and serology were normal. The EMG of the patient was compatible with axonal myopathy. Magnetic resonance imaging (MRI) showed degenerative changes in both caudate nuclei. Tandem mass spectrometry using dried blood spot, serum quantitative amino acid and acylcarnitine analysis, lactate, and pyruvate levels were normal.

Patient 3 (P3) A 16-year-old girl, was unrelated to the first two patients and was admitted to our clinic with abnormal gait with rigidity, muscle weaknesses (3/5), and limb ataxia (Fig. 1). Her medical history revealed similar febrile episodes with progressive polyneuropathy and transient neurologic changes, recurring every two years from the age of four (4, 6, and 13 years of age). The family history was unremarkable. Despite treatment with various combinations of carnitine, coenzyme Q10, riboflavin, IVIG, she continued to have episodic attacks with impaired awareness at a frequency of 1 every 1–5 per year. Her physical examination revealed an abnormal gait, increased muscle tone in the limbs, and ataxia with

rigidity. There were hyperactive deep tendon reflexes accompanying trigger finger and pes equinovarus.

Laboratory tests were normal, including full blood count, immunoglobulins, serology, tandem mass spectrometry quantitative amino acid and acylcarnitine analysis, lactate, and pyruvate. Brain MRI and MRI spectroscopy demonstrated bilateral striatal necrosis. Additionally, an increased reverse lactate peak in the basal ganglia was also detected (Fig. 2).

Methods and Results

Whole-exome sequencing was performed on the index patients (NG1976-1 and NG1599-1) from both families as previously described (Bilguvar, Ozturk et al., 2010). A homozygous NM_001126122.1(SLC25A19_v001): c.576G>C; p.(Gln192His) variant was identified. We classified this variant as likely pathogenic (PM1, PM2, PP2, and PP3) based on the American College of Medical Genetics and Genomics - the Association for Molecular Pathology criteria (Richards, Aziz et al., 2015) (Fig. 3). This variant is in the transmembrane domain of the mitochondrial thiamine pyrophosphate carrier protein and its translational effect has been recently shown by Bottega et al. (Bottega, Perrone et al., 2019). Sanger sequencing confirmed the homozygous variant in Patient 2 and heterozygosity in both parents.

Thiamine supplementation (300 mg/day) was given following the genetic diagnosis to Patient 1. The axonal neuropathy and febrile episodes showed excellent improvement. The disease is currently controllable without additional drugs. Thiamine (300 mg/day) supplementation and baclofen therapy for spasticity (10–15 mg/day) were started in Patient 2 following which the febrile episodes came under control. Thiamine treatment also controlled the seizures of the patient effectively without changes in antiepileptic drugs. Thiamine supplementation and baclofen therapy at the same doses were started in patient with significant improvement in peripheral neuropathy, transient neurological changes, and febrile episodes.

Discussion

We present clinical and genetic features of three Turkish THMD-4 patients, with a confirmed pathogenic *SLC25A19* variant. Thiamine (vitamin B1) is an essential nutrient that serves as a cofactor for many enzymes, mostly with mitochondrial or peroxisomal localization (Nabokina, Valle et al., 2013). *SLC25A19* directly encodes a membrane protein called “mitochondrial thiamine pyrophosphate carrier” which mediates the uptake of thiamine pyrophosphate (ThPP) into mitochondria (Kang and Samuels, 2008, Nabokina, Valle et al., 2013). Therefore, thiamine metabolism plays a vital role in maintaining the body’s energy balance (Dhir, Tarasenko et al., 2019).

Thiamine metabolism disorders cover a broad spectrum of neurogenetic diseases, mainly divided into two major groups: Thiamine-responsive dysfunction syndromes (TRDS, OMIM #PS249270) and Thiamine-responsive megaloblastic anemia syndrome (TRMAS). THMD-1 (*SLC19A2*, OMIM # 603941) is a member of TRMAS and leads to diabetes mellitus,

megaloblastic anemia, and sensory-neural hearing loss (Marcé-Grau, Martí-Sánchez et al., 2019). THMD-4 (*SLC25A19*, OMIM #613710) and the more severe allelic phenotype Amish-type microcephaly THMD-3 (*SLC25A19*, OMIM #607196) are both members of TRDS (Kelley, Robinson et al., 2002, Siu, Ratko et al., 2010). THMD-2 (biotin-responsive basal ganglia disease, *SLC19A3*, OMIM #607483), and THMD-5 (*TPK1*, OMIM #606370) are further TRDS which result in episodic encephalopathy, basal ganglia necrosis, dystonia, gait abnormality, and possible early death (Kelley, Robinson et al., 2002, Siu, Ratko et al., 2010).

THMD-4 is distinguished from other THMDs by its neurological and systemic features (Table 2). Therefore, the identification of new phenotypic features is useful for differential diagnosis.

It is a complex metabolic syndrome characterized by acute febrile encephalopathic episodes in childhood. Spiegel et al. (2009) firstly reported 4 siblings from a consanguineous Arab Muslim family with acute encephalopathic episodes in childhood between ages 3 and 7 years (Spiegel, Shaag et al., 2009). The episodes were characterized by a nonspecific febrile illness with striatal necrosis on brain imaging as well as a progressive chronic polyneuropathy (Spiegel, Shaag et al., 2009). Ortigoza-Escobar et al. (2017) subsequently identified that THMD-4 was characterized by radiological associated bilateral symmetric brain lesions and proposed diagnostic criteria to help clinicians to establish a faster and accurate diagnosis so that vitamin supplementation could be started (Ortigoza-Escobar, Molero-Luis et al., 2016). They all described phenotypes that included distal muscle weakness, abnormal gait, dysarthria, areflexia, skeletal muscle atrophy, paralysis, impaired sucking, and swallowing (Spiegel, Shaag et al., 2009). Ortigoza-Escobar et al. (2017) also pointed out that thiamine supplementation may be beneficial in improving peripheral neuropathy (Ortigoza-Escobar, Molero-Luis et al., 2016).

In 2019, Roberta Bottega et al. reported a 20-year-old patient with cognitive delay, bilateral pes cavus, tremor, hypotonia, gait difficulty, dysphagia, and episodic encephalopathy. (Bottega, Perrone et al., 2019). Additionally, Gowda et al. reported Indian patients, two 36-month-old and a 5-year-old, with episodic febrile encephalopathy, who benefited from thiamine replacement (Gowda, Srinivasan et al., 2019). The literature is summarized in Table. 1, including two recently published papers on a Chinese and an Italian patient (Li, Song et al., 2020, Porta, Siri et al., 2021).

THMD-4 is distinguished from other thiamine metabolism disorders by its neuroradiological features. The most common presenting features, displayed by all patients, were lower extremity problems, such as abnormal gait, dysarthria, areflexia, and skeletal muscle atrophy accompanied by degenerative caudate nuclei (Gowda, Srinivasan et al., 2019, Marcé-Grau, Martí-Sánchez et al., 2019). Our patients demonstrated many of the neurological manifestations typical of THMD-4, including bilateral striatal necrosis (Bottega, Perrone et al., 2019). Diabetes mellitus, megaloblastic anemia, and sensory-neural hearing loss findings were absent in our patients. Only P1 had areflexia, while P3 had normal or increased tendon reflexes. Both displayed characteristic trigger finger and pes equinovalgus features. In the cases of thiamine deficiency, the most affected brain regions seem to be the mammillary

bodies and basal ganglia, including the striatum, and globus pallidus, in addition to the frontal lobes (Dhir, Tarasenko et al., 2019, Kornreich, Bron-Harlev et al., 2005, Marcé-Grau, Martí-Sánchez et al., 2019). In addition to striatal degeneration hyperintense changes in the frontal white matter and a reverse lactate peak in the basal ganglia were detected in patients 1–3, a finding that has not previously been documented in TMD-4. There is only one THMD-4 adult patient with diffuse T2W hyperintensity of brain white matter in the literature (Marcé-Grau, Martí-Sánchez et al., 2019).

Phenotypes linked to SLC19A3 (more than 130 patients) deficiency include subacute encephalopathy, with confusion, dysarthria, and dysphagia, and occasional feeding difficulties, respiratory distress facial nerve palsy or ophthalmoplegia with mostly residual dystonia, seizures, and pyramidal signs with diffuse leukoencephalopathy, and sparing of the basal ganglia (Marcé-Grau, Martí-Sánchez et al., 2019, Zeng, Al-Yamani et al., 2005). Confusion, respiratory problems, and facial or ocular abnormalities did not occur in our patients.

In THMD-5, pathogenic variants in *TPK1* result in thiamine metabolism dysfunction because of thiamin pyrophosphokinase deficiency (Mayr, Freisinger et al., 2011, Banka et al. 2014). Many THMD-5 patients have recurrent encephalopathy triggered by fever or infections, seizures, dysarthria, ataxia, dystonia, ophthalmoplegia, nystagmus, and potential psychomotor regression (Dhir, Tarasenko et al., 2019). Radiographic assessment of THMD-5 patients demonstrated involvement of the cerebellum and dentate nuclei (100%), striatum (75%), Globus pallidus (50%), and spinal cord (25%) (Dhir, Tarasenko et al., 2019). All our patients had normal development without ophthalmoplegia, nystagmus, and degeneration of the cerebellum or dentate nuclei.

Amish lethal microcephaly is a more severe allelic *SLC25A19* disorder to THMD-4 TH, characterized by congenital microcephaly, seizures, profound global developmental delay, and poor life expectancy (Bottega, Perrone et al., 2019, Marcé-Grau, Martí-Sánchez et al., 2019).

We suggest that thiamine metabolism or transport disorders should be considered in all patients with episodes of encephalopathy, dysarthria, ophthalmoplegia, seizures, nystagmus, tremor, abnormal gait, dystonia and truncal ataxia, and in patients with degeneration of dentate nuclei or striatum. The diagnosis may be present in children with normal development. Early recognition is important, since thiamine supplementation improves prognosis in most children.

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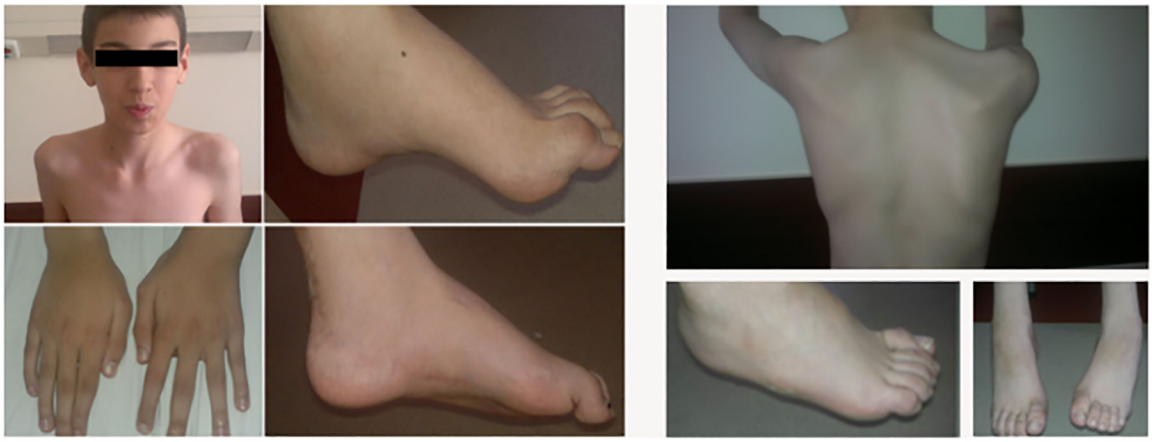

Figure 1.
Clinical findings of the P1 and P2 show upper and lower limbs with spasticity, trigger finger, and pes equinovarus deformity, and other dysmorphic features.

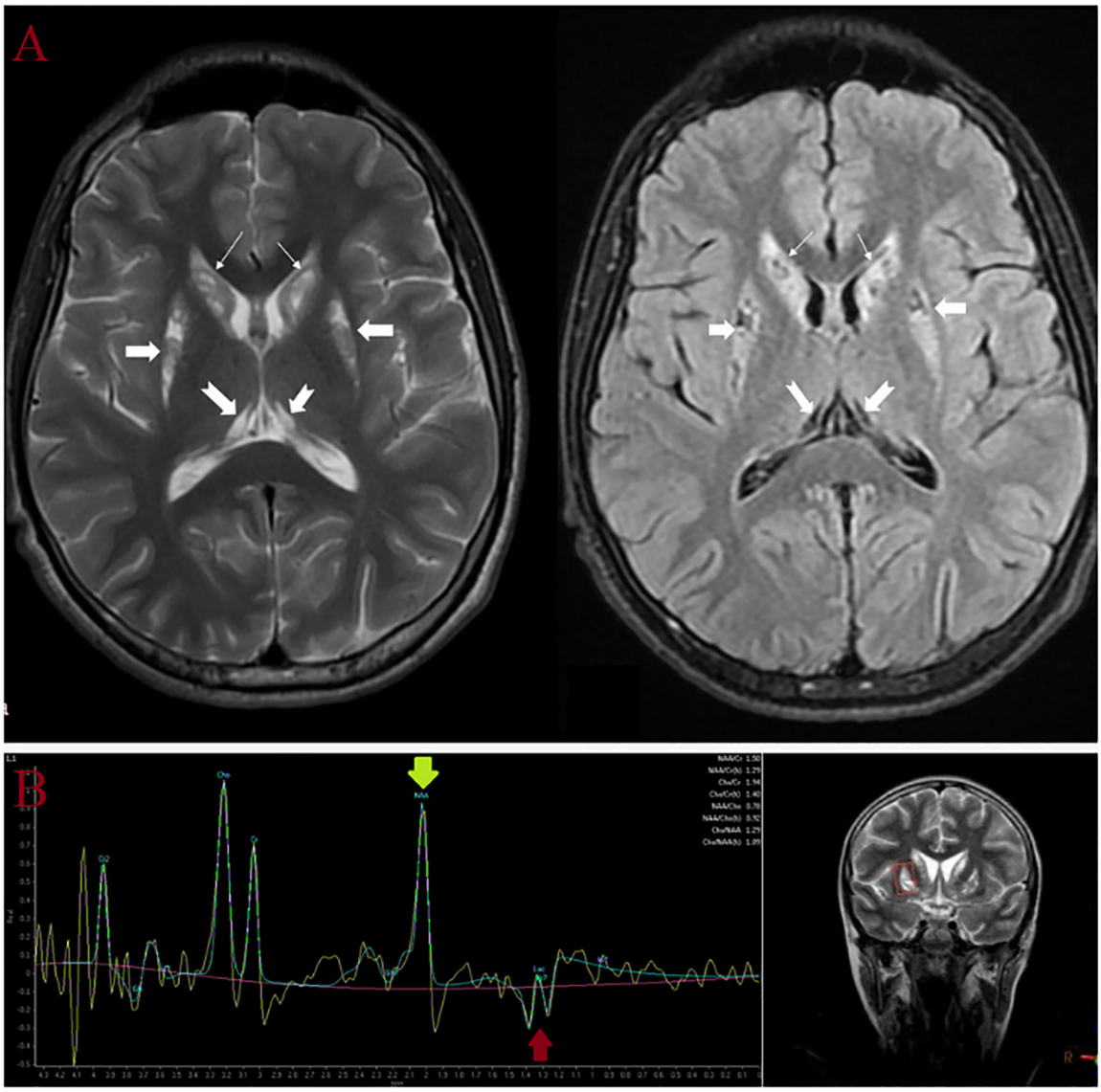

Figure 2.

A. Axial T2 Weighted Brain MRI (left) and FLAIR Brain MRI (right) sequences of P1 revealed hyperintense changes and necrotic degenerations of bilateral caudate nucleus (The superior marks), bilateral putamen (The middle marks), and bilateral posterolateral thalamus (The inferior marks). **B**. Single Voxel Proton MRI Spectroscopy (TE: 135 msn) findings of P3 show relative decrease in NAA peak (The superior, green mark) and reverse lactate peak in the right-side basal ganglia (The inferior, red mark).

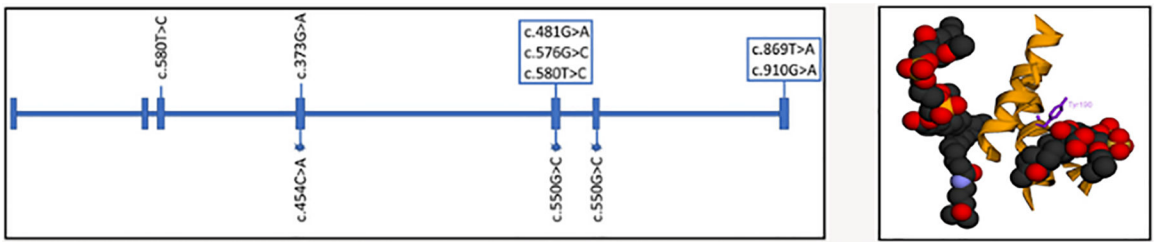

Figure 3.

Left Panel shows exonic view of *SLC25A19* gene and reported mutations associated with THMD-4. The ✸ symbol depicts mutations reported only compound heterozygous state. **Right Panel** shows part of PDB entry 1okc(A), representing the local structural environment of the Gln192 residue (colored purple and mapped to Tyr190 in the PDB structure).

Table.1

Review of genetically identified patients diagnosed with thiamine metabolism dysfunction syndrome-4 in the literature (1–6, 12, 13)

STUDY, YEAR	EPISODE AGE(S) / GENDER_ETHNICITY	INITIAL SYMPTOMS	BEFORE FEBRIL ILLNESS / AFTER RECOVERY	OTHER SYMPTOMS	SEIZURE	RADIOLOGY	CEREBROSPINAL FLUID	SLC25A19 MUTATION	RESPONSE TO THIAMINE SUPPLEMENT	
Present Report, 2021	Case.1–2 y, Boy, Turkish	Case.1: Episodic Weakness-Encephalopathy, Abnormal gait, Dysphonia, and Polyneuropathy.	+/+	Dysarthria, Muscle weaknesses, Ataxia, Trigger finger, and Pes equinovalgus	+	Striatal degeneration, bilateral cerebellar white matter hyperintense lesions, reverse lactate peak in the basal ganglia	Normal, mildly elevated protein level	Homozygous, c.576G>C p.(Gln192His)	Positive for neuropathy	Positive for episodes
	Case.2: 4–13 y, Boy, Turkish	Case.2: Episodic Weakness-Encephalopathy, Abnormal Gait with toe walking, Ataxia, and Polyneuropathy.		Dysphonia, Muscle weaknesses, Areflexia of DTR, Seizures						
	Case.3: 4 y, Boy, Turkish	Case.3: Episodic Weakness-Encephalopathy, Abnormal Gait with toe walking, Ataxia, and Polyneuropathy		Abnormal gait, Increased muscle tone & hyperactive DTR, Ataxia, Trigger finger, Pes equinovalgus						
Porta et al., 2020	Case: 13 m, Boy, Italian	Case: Episodic Weakness-Encephalopathy, Hypotonia, Dysarthria	+/+	Mild axial hypotonia (Birth), Delayed Motor Functions, Weakness, Tremors, Orofacial Dyskinesia, Dysphagia	+	Bilateral hyperintensity signals in the caudate nucleus and putamen, relative decrease in NAA peak, high lactate spectroscopic signal in the basal ganglia and thalamus	-	Compound Heterozygous, c.673G>A p.(Gly225Arg) and c.373G>A p.(Gly125Ser)	Substantial improvement for neuropathy	Positive for episodes
Dongxiao Li et al., 2020	Case.18 m, Girl, China	Case.1: Febrile Convulsion, Encephalopathy	+/+	Slightly Delayed Motor Functions,	+	Symmetrical abnormal signals in the	Increased lactate level (1.9–3.51 mmol/L)	Compound Heterozygous, c.194C>T p.	Positive for neuropathy	Positive for episodes

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STUDY, YEAR	EPISODE AGE(S) / GENDER_ETHNICITY	INITIAL SYMPTOMS	BEFORE FEBRIL ILLNESS / AFTER RECOVERY	OTHER SYMPTOMS	SEIZURE	RADIOLOGY	CEREBROSPINAL FLUID	SLC25A19 MUTATION	RESPONSE TO THIAMINE SUPPLEMENT	
	Case.2: 15 m, Boy, China	Case.2: Febrile Convulsion		Limb Shaking, Somnipathy, Hypertonia of Lower limbs, Coma		caudate nucleus and putamen		(Ala65Val) and c.454C>A p.(Pro152Thr) / c. 481G>A p.(Ala161Thr) and c.550G>C p.(Ala184Pro)		
Gowda et al., 2019	Case.1 26 m, Boy, Indian	Case.1: Episodic Weakness-Encephalopathy, Areflexia	+/+	Drowsiness, Dystonia, Diminished Tendon Reflexes	+	Hyperintensities in the bilateral basal ganglia and thalami	Mildly elevated lactate	Homozygous, c.910G>A p.(Glu304Lys) / c.869T>A p.(Leu290Gln)	Positive for neuropathy	Positive for episodes
	Case.2: 5, Girl, Indian	Case.2: Episodic Weakness-Encephalopathy, Seizures, Areflexia		Dystonia, Generalized tonic–clonic seizures, Quadriparesis						
Roberta Bottega et al., 2019	Case1:4 y, Boy, İtalian	Case.1: Episodic Weakness-Encephalopathy, Dysphagia, Dysphonia, and Tremors	+/+	Tremor, Hypotonia, Gait difficulty, Dysphagia, Dysphonia, Bilateral pes cavus, Areflexia	−	Striatal Degeneration, symmetrical atrophy of the insula cortex	Mildly elevated lactate	Homozygous, c.576G>C p.(Gln192His)	Substantial improvement for neuropathy	Negative for episodes
Ortigoza-Escobar et al., 2017	Case1:20 m, Girl, German	Case.1: Episodic flaccid weakness-Encephalopathy, and dysarthria,	+/+	Polyneuropathy, Hypotonia, Areflexia, Pes equinus	−	Striatal Degeneration, cavitated lesion in the medial thalamus	Increased lactate level (2.9–4.2 mmol/L)	Homozygous, c.580T>C p.(Ser194Pro)	Positive for neuropathy	Positive for episodes
Spiegel et al., 2009	Case.1 3–5 y, Boy, Arab	Case.1 Episodic Weakness-Encephalopathy, Areflexia	+/−	Polyneuropathy, Hypotonia Lethargy, Areflexia, Dysarthria, Dystonia, Truncal ataxia, , Sensory loss, obtundation, aphasia, and disorientation	−	Striatal degeneration	Mildly elevated Lactate (2.9–4.2 mmol/L)	Homozygous, c.373G>A p.(Gly125Ser)	Negative for neuropathy	Positive for episodes
	Case.2: 4 y, Girl, Arab	Case.2: Episodic Weakness-Encephalopathy, Microcephaly								
	Case.3: 6 y, Girl, Arab	Case.3: Episodic								

STUDY, YEAR	EPISODE AGE(S)	INITIAL SYMPTOMS	BEFORE FEBRIL ILLNESS / AFTER RECOVERY	OTHER SYMPTOMS	SEIZURE	RADIOLOGY	CEREBROSPINAL FLUID	SLC25A19 MUTATION	RESPONSE TO THIAMINE SUPPLEMENT
	GENDER_ETHNICITY								
		Weakness-Encephalopathy, Areflexia Encephalopathy							
	Case.4: 6 y, Girl, Arab	Case.2: Episodic Weakness-Encephalopathy, Areflexia Encephalopathy							

Table.2

Spectrum of Thiamine-responsive dysfunction syndromes (12, 13, 17)

NAME OF SYNDROME	SYNONYM	GENE	OMIM	DYSFUNCTİON	CLINIC
Thiamine metabolism dysfunction syndrome 1	Thiamine-responsive megaloblastic anemia syndrome	SLC19A2	603941	Deficiency of thiamine transporter-1 responsible for free-thiamine uptake	A clinical triad including megaloblastic anemia, nonautoimmune diabetes mellitus, and sensorineural deafness. Neurological symptoms: ataxia, seizures developmental delay, episodic attacks, spastic quadriplegia, cerebral atrophy, and systemic disease (Cardiological, Endocrinological, Ophthalmological). **Plus:** High excretion of alpha-ketoglutaric acid in urine. **Radiologic:** Stroke like findings the middle cerebral artery area.
Thiamine metabolism dysfunction syndrome 2	Type of Biotin or Thiamine responsive encephalopathy	SLC19A3	607483	Deficiency of thiamine transporter-2 responsible for free-thiamine uptake	A episodic encephalopathy with/without abnormal gait, dystonia, ophthalmological dysfunction, ataxia, seizures, and psychomotor regression **Plus:** Low free-thiamine in CSF. **Radiologic:** Degeneration in the caudate, putamen, cortico/subcortical areas.
Thiamine metabolism dysfunction syndrome 3	Amish-type microcephaly	SLC25A19	607196	Dysfunction of TPP enters the mitochondria	A episodic encephalopathy with/without progressive peripheral neuropathy, severe congenital microcephaly with global brain malformations. **Plus:** Increased lactate in blood and/or CSF. **Radiologic:** Global degeneration.
Thiamine metabolism dysfunction syndrome 4	Type of Bilateral Striatal Degeneration And Progressive Polyneuropathy	SLC25A19	613710	Dysfunction of TPP enters the mitochondria	A episodic encephalopathy with/without abnormal gait, muscle weakness, dystonia, ataxia, seizures, progressive peripheral neuropathy, striatal degeneration, normal development. **Plus:** Increased lactate in blood and/or CSF. **Radiologic:** Degeneration in the caudate and putamen.
Thiamine metabolism dysfunction syndrome 5	Type of Episodic encephalopathy	TPK1	606370	Thiamine pyrophosphokinase deficiency	A episodic encephalopathy with/without dystonia, ataxia, seizures, dystonia, nystagmusand early-onset global developmental delay. **Plus:** Low TPP in blood, muscle, and/or fibroblasts with/without High excretion of alpha-ketoglutaric acid in urine. **Radiologic:** Degeneration in the dentate nuclei and cerebellum.