THIAMINE DEFICIENCY: A REVIEW OF ACQUIRED AND GENETIC CAUSES

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1. Introduction

Thiamine, also known as vitamin B1, is a water soluble essential micronutrient. It belongs to the B vitamin complex and plays a vital role in many biochemical processes of the human body [1]. Thiamine functions as a coenzyme for a number of enzymatic reactions mostly involved in antioxidant production, in nucleic acid biosynthesis, and especially in energy production. Since these processes are of utmost importance for the nervous system, thiamine deficiency often presents with neurologic manifestations.

Thiamine biosynthesis occurs in bacteria, fungi and plants, but is not possible for mammalian cells. The only source of thiamine for mammals is dietary, with pork, poultry,beef, cerials, eggs, fish and nuts being rich in thiamine [2]. The human body stores are limited to approximately 30mg of thiamine, with daily requirements depending on carbohydrate and calorie consumption [3-5]. Symptoms of thiamine deficiency develop approximately 4-6 weeks after inadequate thiamine intake [6]. The recommended adult daily dose is 1.2 mg for men and 1.1 mg for women [4].

Thiamine deficiency disorders were first described by Carl Wernicke in 1881. Wernicke described a neuropsychiatric disorder characterized by the triad of opthalmoplegia, ataxia, and confusion [7]. Later, Korsakoff described a series of patients with memory loss and in 1897, Murawieff proposed that the two entities, described by Wernicke and Korsakoff, shared a common etiology: thiamine deficiency [8, 9]. In the 1880s, the work of Christiann Eijkman led to the discovery of the cause of beriberi. He observed that a diet comprising of processed rice led to symptoms of peripheral neuropathy in chickens and that an "antineuritic vitamin" contained in the pericarpium of the rice can treat this disorder. This discovery won him the Nobel prize for Medicine or Physiology in 1929 [10].

Thiamine deficiency has a wide variety of manifestations, ranging from neurologic to cardiovascular. In adults, Wernicke encephalopathy is the most common manifestation of thiamine deficiency, potentially leading to permanent sequelae if left untreated. In childhood, genetic disorders of thiamine absorption, transfer and utilization can present with complex phenotypes. The identification of both acquired and genetic disorders is important, and prompt treatment with thiamine supplementation leads to symptom reversal.

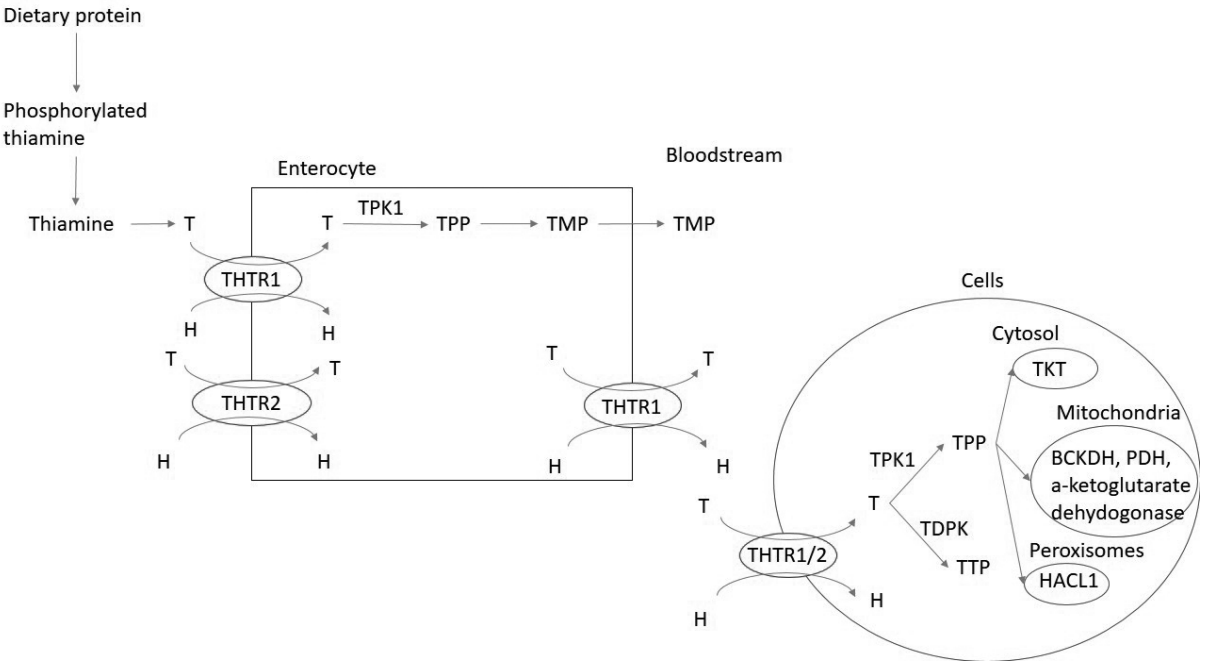
2. Epidemiology

Thiamine deficiency is considered a rare disorder in healthy individuals in food-secure settings. Although dietary thiamine is abundant in developed countries, diets containing mainly processed foods are increasingly prevalent, leading to thiamine deficiency [11]. Industrial food processing, leading to thiamine destruction, coupled with a diet high in carbohydrates can deplete thiamine and lead to a phenomenon known as high calorie malnutrition. Accordingly, in a recent study, individuals considered for bariatric surgery were found to be nutrient- and in many cases thiamine-deficient [12]. Thus, thiamine deficiency is more prevalent than commonly thought. To prevent this, in many high-income countries, some food supplies are fortified with thiamine [13].

In developing countries where low-thiamine food such as processed grains are the staples, thiamine deficiency is a common concern [14, 15]. Thiamine deficiency can also occur after consuming food with thiamine antagonists or thiamine metabolizing enzymes, like betel nut, raw fish and tea. Food scarcity is also a cause of thiamine deficiency in populations displaced due to war, famine or natural disasters [16, 17]. Worldwide, in regions of Asia, Africa, and the Americas, food scarcity, food preference, inequities in the nutrient content of food, and inadequate fortification of food supplies are causes of thiamine deficiency [17].

Infants, especially exclusively breastfed infants of thiamine-deficient mothers, are at the highest risk of thiamine deficiency [18]. Pregnancy and lactation increase thiamine needs and can lead to asymptomatic maternal thiamine deficiency, often manifesting as beriberi (described below) in breastfed infants [19].

Fig. 1. Thiamine metabolism



T: thiamine, **H**: hydrogen ions, **TPK1**: thiamine pyrophosphokinase, **TPP**: thiamine pyrophosphate, **TMP**: thiamine monophosphate, **THTR1**: thiamine/H+ antiporter 1, **THTR2**: thiamine/H+ antiporter 2, **TDPK**: thiamine diphosphokinase, **TKT**: transketolase, **BCKDH**: branched-chain α-ketoacid dehydrogenase (BCKDH), **PDH**: pyruvate dehydrogenase, **HACL1**: 2-hydroxyacyl-CoA lyase 1

Other populations at risk include alcoholics, patients after bariatric surgery or suffering from bulimia or anorexia nervosa, critically ill or cancer patients, and patients with HIV/AIDS, gastrointestinal disorders or receiving total parenteral nutrition, diuretics or renal replacement therapy [20-26].

However, despite a thiamine rich diet, deficiency may result from genetic abnormalities in thiamine absorption, transport and cellular handling [27]. These disorders are known as thiamine metabolism dysfunction syndromes.

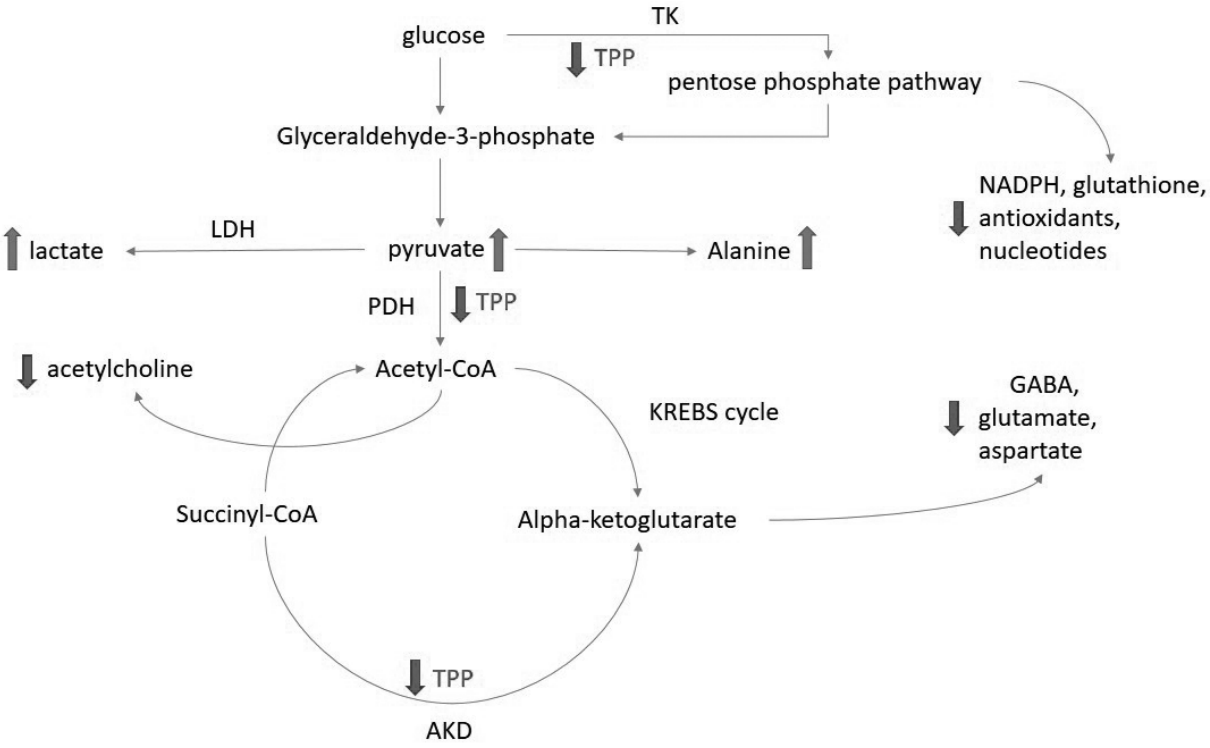
3. Thiamine metabolism

Thiamine is found in mammals either as free thiamine, or in phosphorylated forms. These are thiamine monophosphate (TMP), thiamine diphosphate (TDP) also known as thiamine pyrophosphate (TPP), and thiamine triphosphate (TTP) [11]. TPP is the active form of thiamine and accounts for 80% of the total body stores [28]. Multiple enzyme complexes in the cytosol (pentose phosphate pathway - transketolase), mitochondria (pyruvate dehydrogenase, oxoglutarate dehydrogenase, branched-chain alpha-ketoacid dehydrogenase) and peroxisomes (2-hydroxyacyl-CoA lyase)depend on the presence of TPP [29-31] (Figure 1)

Thiamine absorption mainly occurs in the jejunum [32]. Dietary proteins are hydrolyzed in the digestive tract, releasing phosphorylated thiamine. Unphosphorylated free thiamine is then released by alkaline phosphatases [33] There are two thiamine absorption mechanisms in the small intestine. The first one, passive diffusion, is dependent on high thiamine concentration, whereas the second functions at lower thiamine concentrations. When thiamine concentration is lower than 1μM, thiamine absorption depends on an energy-dependent saturable transporter (thiamine/H+ antiporter, also known as THTR1) [32]. After entering the enterocytes, thiamine is converted first to TPP by thiamine pyrophosphokinase (TPK1) and then to TMP. Thiamine then reaches the bloodstream either in the form of TMP by an energy-dependent transport system, or as free thiamine through the THTR1 transporter [34]. Once in the bloodstream, thiamine enters most cells via two transporters, THTR1 and THTR2 [35, 36]. In blood, it circulates primarily in red-blood cells and leukocytes, and is delivered to organs with high metabolic demands such as the skeletal and heart muscles, pancreas, liver and brain. In cells TPP is once more synthesized from thiamine by TPK1 or by thiamine diphosphokinase (Figure 1).

In a state of thiamine deficiency, all the aforementioned metabolic pathways are affected, albeit not equally. Accordingly, all tissues are not equally affected, with the brain and especially the cerebellum, mammillary bodies, thalamus, hypothalamus,

Fig. 2. Biochemical basis of thiamine deficiency



LDH: lactate dehydrogonase, **PDH**: pyruvate dehydrogonase, **TPP**: thiamine pyrophosphate, **TK**: transketolase, **AKD**: alpha-ketoglutarate dehydrogenase.
Modified from Calderón-Ospina CA, Nava-Mesa MO. B Vitamins in the nervous system: Current knowledge of the biochemical modes of action and synergies of thiamine, pyridoxine, and cobalamin. CNS *Neurosci Ther.* 2020;26(1):5-13.

and brainstem being more vulnerable [4, 37]. It seems that the α-ketoglutarate dehydrogenase pathway is the most sensitive to thiamine deficiency, and its dysfunction can quickly lead to reduced ATP synthesis, oxidative damage, and, ultimately, cell death [38].

4. Pathophysiology of thiamine deficiency

As stated above, thiamine deficiency leads to a cellular state of reduced energy synthesis and increased oxidative stress [39]. In this state, pyruvate, the main product of glycolysis, cannot be transformed to acetyl-CoA, due to low pyruvate dehydrogenase activity. Pyruvate, thus cannot enter the Krebs cycle, and is preferentialy transaminated to alanine or transformed to lactate via lactate dehydrogenase (Figure 2). This leads to elevated lactate and organic acid levels in CSF, urine, and blood in thiamine deficient patients. Tissues with high energy demand, such as the nervous system and the heart, are highly dependent on glucose metabolism and mitochondrial function. In a state of thiamine depletion, dysfunction of oxidative phosphorylation and the consequent impaired energy productionhave been associated with cytotoxicity, cytotoxic edema and cell death resulting in several neurologic and neurodegenerative conditions [40, 41], major psychiatric illnesses [42, 43], and heart failure.

Specific brain regions show pronounced sensitivity based on their metabolism, and symptoms in patients with thiamine deficiency are a direct result of the affected structures. In Wernicke encephalopathy, ocular symptoms are the product of brainstem lesions affecting the pons and midbrain [44, 45]. Ataxia and gait difficulties arise when the cerebellar vermis is damaged. Lesions in these areas reflect high metabolic demands. Pathology examinations of the brain show bilateral symmetric hemorrhagic/necrotic lesions, mainly affecting the aforementioned areas [46].

In the condition known as 'dry beriberi' (beriberi meaning extreme weakness in the Sinhalese language), lesions firstly occur in distal peripheral nerves [47, 48]. An axonal pattern of degeneration with preservation of small myelinated and unmyelinated axons is observed [47]. Degeneration of neurons in the spinal cord, mainly of the anterior horn cells and posterior ganglion cells, is also present. In wet beriberi, the heart is dilated, and cardiac myocytes show edema, fragmentation and vacuolization.

Table 1. Symptoms and syndromes associated with thiamine deficiency

	Adult	Child
General symptoms	nausea – abdominal discomfort, apathy, fatigue, sleep disturbance	anorexia, colics, vomiting, ataxia, obtundation
Clinical syndromes		
Infantile beriberi		loud piercing cry, vomiting, constipation, peripheral edema, tachycardia, agitation, nystagmus, obtundation
Adult beriberi	Wet: peripheral edema, tachycardia, dyspnea	
	Dry: lower limb paresthesias, calf pain, muscle cramps, foot drop, lower limb weakness	
Wernicke encephalopathy	opthalmopllegia, ataxia, confusion	
Korsakoff syndrome	amnesia (episodic memory), confabulations, apathy, irritability	

4. Clinical presentation

Thiamine deficiency has a variable presentation in children and adults (Table 1). In children, a broad range of neurologic symptoms can be present early in the course of the disease, such as anorexia, vomiting, colic pain, irritability, muscle pains, ataxia and reduced level of consciousness [49]. In adults, thiamine deficiency presents with atypical symptoms in early stages, such as nausea, apathy, fatigue, sleep disturbance, and abdominal discomfort [38]. Later, if the deficiency is not corrected, classical constellations of symptoms specific for thiamine deficiency arise. These can be classified into two categories, beriberi and Wernicke encephalopathy.

4.1. *Beriberi*

There are two types of this disorder, depending on the age of the patient affected, infantile beriberi and adult beriberi.

4.2.1. *Infantile beriberi*

Infantile beriberi presents in the age between two and three months and mainly affects breastfed infants of mothers with thiamine deficiency [50].The presenting symptom is often a characteristic "loud piercing cry" and gastrointestinal dysfunction with colics, vomiting and constipation [49]. Later signs of congestive heart failure appear with edema, tachycardia, dyspnea, cyanosis and pulmonary hypertension [51, 52]. A fulminant form of infantile beriberi is known as Shoshin syndrome and presents with severe decompensated heart failure and type B lactic acidosis [53]. In older infants, four to seven months-old, the presentation differs and neurologic symptoms, such as agitation, an aphonic (soundless) cry, nystagmus, altered consciousness, and seizures can be present [49]. This ''aphonic'' form later evolves into heart failure. Treatment with parenteral thiamine is curative, with most patients responding to doses of 100-150mg of thiamine within days [49].

4.1.2. *Adult beriberi*

Adult beriberi is classically described as having two phenotypes, dry beriberi characterized by peripheral neuropathy, and wet beriberi characterized by heart failure with or without peripheral neuropathy. In most patients, a clear phenotype cannot be determined and mixed presentations are more common [54].

Thiamine deficiency with neurologic symptoms is termed dry beriberi. It occurs most often in patients with low caloric and thiamine intake and relative inactivity. Most patients present with a distal symmetric sensorimotor neuropathy, with reduced deep tendon reflexes [55]. Symptoms of dry beriberi begin with paresthesias of the lower limbs, a burning sensation of the feet, calf pain and muscle cramps. Loss of vibration sense can be present, as well as calf tenderness and proximal weakness. Later, loss of ankle and knee jerks, toe and foot drop and loss of vibration and position sense ensue. The arms follow after the lower limbs are completely affected [38]. The occurrence of cerebral symptoms is most common in severe thiamine deficiency associated with alcoholism and is termed Wernicke encephalopathy.

Cardiovascular involvement in thiamine deficient patients is termed wet beriberi [56]. Wet beriberi is initially characterized by a high cardiac output state, due to peripheral vasodilation. Neurohormonal changes lead to water and salt retention, fluid overload and peripheral edema [57]. Increased heart workload leads to overuse injury and symptoms of

decompensated heart failure. If thiamine deficiency is corrected without cardiac function optimization, a state of low output heart failure can occur. Thiamine administration in this state leads to reversal of vasoconstriction and increased cardiac workload.

4.2. *Wernicke encephalopathy & Korsakoff syndrome*

Wernicke encephalopathy (WE) and Korsakoff syndrome (KS) represent different stages of thiamine deficiency. Wernicke encephalopathy is an acute and treatable disorder, whereas Korsakoff syndrome is chronic and irreversible.

4.2.1. *Wernicke encephalopathy*

WE is an acute neurophychiatric disorder presenting with the characteristic clinical triad of opthalmoplegia, ataxia, and confusion [58]. Most patients present with delirium and the presence of all three symptoms in a patient is rare; inonly 16% of patients [58-60]. The initial symptoms of WE are non-specific, such as frequent headaches, upper gastrointestinal symptoms, mood changes, and fatigue. In younger patients with WE after gastric surgery, the disorder presents with sensory motor symptoms, mainly ataxia, and the classic triad is much more common than classically described (54% vs 16%) [61].

Ocular movement abnormalities are the hallmark of Wernicke encephalopathy. Nystagmus is especially characteristic, followed by sluggish pupillary light reaction, anisocoria and gaze palsies [62, 63]. The nystagmus in patients with WE is usually of the horizontal gaze-evoked type [64], initially brief and non-sustained, later sustained without deficits in gaze-holding, and finally accompanied by gaze-holding failure. The next most common ocular abnormality is bilateral abducens palsy, followed by conjugate gaze palsy, usually horizontal and less commonly vertical [65, 66]. Complete opthalmoplegia is the last common stage of all ocular motor abnormalities in WE and, while considered a core sign, it is rare [67]. Other ocular abnormalities have also been described, such as gaze-holding failure/impairment of the vestibule-ocular reflex [68], primary position upbeat or downbeat nystagmus [62], light-near dissociation, anisocoria and blepharoptosis [69].

Gait ataxia is another common manifestation of WE. The stance of patients is broad-based, with the gait difficulty ranging from mild to gross inability to walk. The gait ataxia of WE is the consequence of combined lesions in the cerebellum, the vestibular apparatus, and the ensuing polyneuropathy [70]. As in dry beriberi, peripheral neuropathy of the symmetrical sensorimotor type involving the lower extremities can develop over time.

Symptoms of alcohol withdrawal are also common among patients with WE. Hyperactive delirium can be present and is attributed to both thiamine deficiency and alcohol withdrawal. Severe depression of consciousness can also be present in a minority of patients and in these patients, the recognition of thiamine deficiency is crucial. Concurrent hypothermia and hypotension are warning signs of thiamine deficiency [38].

The clinical presentation, as described, is commonly non-specific, making the diagnosis extremely difficult. The combination of opthalmoplegia, ataxia, and alteration of consciousness may even mimic posterior circulation ischemia [71]. WE should be considered in every patient with long term malnutrition, bariatric surgery or chronic alcohol abuse, and episodes of confusion and altered mental status. In many cases symptoms of alcohol toxicity overlap with WE, confounding the clinical presentation.

There are no specific laboratory tests and the diagnosis remains clinical and based on the physician's suspicion [72]. However, erythrocyte transketolase level and blood thiamine concentration may be used. The latter is not a valid method, since the blood concentration of thiamine represents only a minimal fraction of the total body stores. Urinary excretion is also a poor indication of thiamine stores, being dependent upon preceding thiamine ingestion. In contrast, erythrocyte transketolase activity is a sensitive assay. The method used involves an estimation of the *in vitro* activity of erythrocyte transketolase before and after thiamine addition [72]. Increase in the measured activity of this enzyme upon addition of thiamine is a sensitive sign of deficiency [73, 74]. Samples of whole blood, washed erythrocytes in EDTA or lithium heparin-containing tubes or hemolysates can be used and stored at 4 degrees C for 24h. If immediate analysis is not possible, the various samples can be kept at lower temperatures (-20 or -70 degrees) for longer periods of time. Samples of washed erythrocytes from fasting patients are preferred [75]. Pyruvate concentrations, in whole blood or plasma, have also been used as a marker of thiamine status. Elevated concentrations of pyruvate are indicative of thiamine deficiency, but the many false positives of this assay make it difficult to use in a clinical setting. Waiting for a laboratory diagnosis is not a valid option and it is imperative to initiate treatment upon suspicion of WE [38]. The response to treatment can in most cases confirm the diagnosis [73, 74].

Lumbar puncture and cerebrospinal fluid examination is sometimes performed in patients with symptoms of Wernicke encephalopathy, mainly to rule out an infectious etiology. CSF shows normal or slightly elevated protein content without pleocytosis. A case series in 2008 showed that the CSF of patients with acute WE can show elevated total tau, decreasing

after the acute stage of the disease and reflecting acute neuronal damage [76].

Magnetic resonance imaging (MRI) is usually performed in patients with symptoms of WE. While helpful in ruling out alternative diagnoses, MRI is not adequately sensitive to exclude WE. On MR imaging, patients with WE usually have evidence of symmetric T2/FLAIR hyperintensities in the dorsmedial thalami, the tectal plate, the periventricular area of the third ventricle, the periaqueductal grey matter, the floor of the fourth ventricle, and the mammillary bodies [71, 77-79]. Enhancement of the mammillary bodies after gadolinium administration is also common [80]. FLAIR weighted imaging shows signs of both vasogenic and cytotoxic edema, with DWI showing high signal with concurrent ADC hypointensity [77]. Non-alcoholic patients may have different or atypical findings and MR imaging, similar to metronidazole induced encephalopathy [78]. In this patient group, infratentorial lesions are more common, with abducens, facial, vestibular, and hypoglossal nerve nuclei and cerebellum signal-intensity alterations [78].

Electroencephalography is not particularly useful in the diagnosis of WE. EEG changes parallel the severity of the encephalopathy. Diffuse background slowing, followed by low-voltage theta and delta activity predominantly over the fronto-temporal brain regions are commonly present. Seizures and epileptiform activity is rare in adults [81].

The clinical diagnosis of WE is based on the criteria proposed by Caine et al. in 1997. If two of the following are present a diagnosis of WE can be considered: 1. history of dietary deficiency 2. oculomotor abnormalities 3. cerebellar dysfunction 4. memory impairment/altered mental state. These criteria have a sensitivity of 85% and a specificity of 100% [72]. In non-alcoholic patients the sensitivity and specificity of these criteria is not known, and a high-index of suspicion for thiamine deficiency and Wernicke-Korsakoff syndrome needs to be maintained in vulnerable populations.

4.2.2. *Korsakoff syndrome*

KS is a late neuropsychiatric manifestation of WE. It is characterized by an abnormal mental state, in which episodic memory is affected out of proportion to other cognitive functions [82, 83]. KS is a residual, largely irreversible syndrome in patients who suffered WE and did not receive treatment with thiamine supplementation [84]. In a small subset of patients, an acute episode of WE is not recognized, but characteristic WE lesions are present in their brains [85]. KS is much more common in alcohol-associated WE, reflecting the neurotoxic effects of alcohol [86].

While KS is primarily considered a disorder of memory, most patients present with a constellation of cognitive and behavioral symptoms. The severe memory impairment of KS relates to declarative memory. Episodic memory, related to events and semantic memory, related to facts are both affected, with the anterograde memory system is affected more than the retrograde one [87]. In some patients, remote memory is also affected and remote memory loss can extend back many years [88]. Executive dysfunction is also present in patients with KS, with defective planning, concept shifting, response generation and awareness of cognitive dysfunction [89, 90]. Confabulations, false memories that fill gaps in memory, are characteristic of KS [91]. Apathy, irritability, euphoria and affective instability are also considered common in KS. MRI studies of patients with KS can be normal or reveal grey and white matter atrophy, especially of the medial thalami and mammillary bodies [92].

5. Genetic associations

Genetic susceptibility in the development of symptoms of thiamine deficiency has been widely hypothesized. This hypothesis is triggered by the fact that Europeans with thiamine deficiency most commonly develop Wernicke-Korsakoff syndrome, while Asians develop symptoms of beriberi. The potential role of genes SLC19A2 and SLC19A3 has been reported, but more studies are needed to confirm this association [93].

Mutations in genes involved in thiamine metabolism result in symptoms of thiamine deficiency, despite a thiamine rich diet. These inborn errors of metabolism, caused by mutations in genes encoding proteins implicated in thiamine transport and metabolism lead to syndromes knows as thiamine metabolism dysfunction syndromes (Table 2). Currently, there are four genes implicated, SLC19A2, SLC19A3, SLC25A19, and TPK1. These gene defects produce five distinct phenotypes, termed thiamine dysfunction syndromes 1 through 5 [27].

5.1. *Thiamine metabolism dysfunction syndrome 1*

This syndrome, also known as thiamine responsive megaloblastic anemia (TRMA) or Roger's syndrome, is caused by mutations in SLC19A2. Symptoms develop in homozygotes or compound heterozygotes. SLC19A2 is a gene located in chromosome 1 and encodes thiamine transporter 1 (TTR-1), a high-affinity saturable thiamine transporter [94]. Roger's syndrome is a rare disorder, with almost all cases found in children of consanguineous partners [95].

TRMA can manifest anytime between infancy and adolescence. Affected individuals present witha clinical triad of megaloblastic anemia, non-autoimmune diabetes mellitus and sensorineural deafness [96]. Additionally, patients may experience a multitude

ΕΛΛΗΝΙΚΗ ΝΕΥΡΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ

Table 2. Inborn errors of thiamine metabolism (thiamine metabolism dysfunction syndromes)

Thiamine metabolism dysfunction syndrome	Other terms	Gene	Age at onset	General symptoms	Neurologic symptoms
1	Roger's syndrome or thiamine responsive megaloblastic anemia	SLC19A2	6 weeks to adolescence	megaloblastic anemia, diabetes mellitus, short stature, retinopathy	Sensorineural deafness, seizures, ataxia, neurodevelopmental delay, recurrent strokes
2	Biotin- or thiamine responsive encephalopathy type	SLC19A3	infancy to adulthood		Leigh syndrome: failure to thrive, respiratory distress, seizures, lethargy
					Childhood encephalopathy: confusion, dysarthria, dysphagia
					Wernicke-like encephalopathy: seizures, ataxia, nystagmus, opthamloplegia
3	Microcephaly Amish type	SLC25A19	infancy	congenital microcephaly, global developmental delay	Episodic encephalopathy with lactic acidosis, seizures
4	Bilateral striatal degeneration and progressive polyneuropathy	SLC25A19	20 months to 6,5 years-old		Episodic encephalopathy, distal weakness, dystonia, dysphagia, seizures
5	Episodic encephalopathy	TPK1	1 month to 4,5 years		Episodic encephalopathy, ataxia, dystonia, dysarthria, ataxia, seizures, opthalmoplegia

of neurologic, hematologic, endocrinologic, ophthalmologic and gastrointestinal symptoms [97]. At onset, all three characteristic findings may not be present, confounding diagnostic efforts [98]. Most patients present with diabetes and anemia in the neonatal period, requiring insulin and multiple blood transfusions. Hearing loss usually follows and requires hearing aids or cochlear implants [99].

Neurological symptoms associated with TRMA include focal or generalized epilepsy, ataxia, cognitive disorder, stroke-like episodes, spastic quadriplegia, and cerebral and optic nerve atrophy [97, 100]. Patients can present with recurrent strokes, either ischemic or hemorrhagic, usually involving the MCA territory [101, 102].

Currently, the first line treatment for TRMA is pharmacological doses of thiamine (25-75mg/d). Thiamine supplementation leads to improvements in anemia and glycemic control [99, 101]. Many children manage to discontinue insulin treatment after thiamine supplementation, but this responsivity decreases after puberty. Adults may become insulin and transfusion dependent. Hearing loss, short stature and strokes cannot be prevented by thiamine supplementation [101].

5.2. *Thiamine metabolism dysfunction syndrome 2 (biotin- or thiamine-responsive encephalopathy type)*

Thiamine metabolism dysfunction syndrome 2 is also known as biotin- or thiamine-responsive encephalopathy. It is an autosomal recessive disease caused by mutations in the SLC19A3 gene, encoding the thiamine transporter type 2 (TTR-2) protein [103, 104]. This entity was formerly known as biotin responsive basal ganglia disease and it can present with three distinct phenotypes [104]. SLC19A3 mutations most commonly present as early infantile Leigh syndrome. Infants with this phenotype present with encephalopathy, failure to thrive, feeding difficulties, lactic acidosis and respiratory distress

[105]. MRI of the brains of these patients shows either lesions limited to the basal ganglia and the perirolandic area, or diffuse brain edema and T2 hyperintensities of the cerebellum, cerebral white matter, thalami, basal ganglia and brainstem [106, 107]. Classic childhood encephalopathy is another distinct phenotype, presenting in children with initially normal psychomotor development. Mean age at onset is 3-7 years and most patients present with encephalopathy triggered by infection, trauma, vaccination or other stress. Confusion, dysarthria, and dysphagia predominate, with occasional central facial palsy or external ophthalmoplegia. If left untreated, this disorder progresses to severe cogwheel rigidity, dystonia, seizure, quadriparesis, and even death [103, 108, 109]. On the other spectrum of SLC19A3 gene mutation phenotypes lies adult onset Wernicke-like encephalopathy [110]. This disorder is characterized by acute onset of classical WE symptoms, as well as seizures, and by MRI abnormalities with diffuse leukoencephalopathy [108, 110].

Thiamine metabolism dysfunction syndrome 2 is considered a treatable disease if suspected early and biotin and thiamine supplementation starts promptly. Thiamine supplementation in these patients normalizes the metabolic abnormalities in serum (lactic acid) and urine (organic acids) by restoring thiamine levels in the cell and in the CSF [29, 30]. In some cases, radiological abnormalities are also significantly reduced by thiamine supplementation, while residual atrophy and necrosis persist in most patients [109, 111]. Biotin supplementation, on the other hand, is controversial. A recent study showed that combination therapy with biotin and thiamine was not superior to thiamine monotherapy regarding the recurrence rate, neurological sequela, or radiological abnormalities [112], as opposed to the initial description [103].

Prognosis depends on the timing of treatment initiation [27]. Infantile Leigh syndrome has a poor prognosis despite timely vitamin supplementation [107]. In the childhood and adult form, thiamine supplementation has a rapid effect on symptom control and prevents symptom recurrence [27].

5.3. *Thiamine metabolism dysfunction syndrome 3 (Microcephaly Amish type) and thiamine metabolism dysfunction syndrome 4 (bilateral striatal degeneration and progressive polyneuropathy type)*

There are two clinical phenotypes associated with SLC25A19 mutations, Amish lethal microcephaly (MCPHA) and bilateral striatal degeneration and progressive polyneuropathy [27, 113]. SLC25A19 is a gene encoding the thiamine mitochondrial carrier. The phenotype can be predicted by the mutation affecting the SLC25A19 gene. There are three missense mutations implicated, C.530G > C, which leads only to MCPHA presentations, while C.373G > A and C.580T > C4 lead to striatal necrosis and progressive polyneuropathy [27, 113, 114].

Amish lethal microcephaly is a severe autosomal recessive disorder, characterized by severe microcephaly, global developmental delay, alpha-ketoglutaric aciduria, lactic acidosis, CNS malformations (callosal dysgenesis, spinal dysraphia and lissencephaly) and encephalopathy [115, 116]. All patients reported had Amish origins and were homozygous for the same mutation (p.G177A) [117]. MRI abnormalities are present with hypoplasia of the brainstem, cerebellum and corpus callosum, as well as lissencephaly [116].

On the other hand, thiamine metabolism dysfunction syndrome 4 is a rare autosomal recessive disease, with only 5 patients reported. These patients presented with encephalopathy triggered by febrile illness, later developing polyneuropathy [27, 113]. Lactic acidosis is common in both disorders, especially during acute disease [115, 116]. Radiological studies show striatal degeneration, with bilateral symmetrical hyperintensities involving the putamen and caudate nuclei with sparing of the globus pallidum [113].

Treatment of both disorders depends on thiamine supplementation. Amish lethal encephalopathy has a poor prognosis despite treatment [116]. A mitochondrial cocktail, consisting of thiamine, co-enzyme Q10, carnitine vitamin E, vitamin C, vitamin K and riboflavin, at the same time as a high fat diet have been shown to reduce metabolic abnormalities in patients with Amish lethal microcephaly, increasing weight gain [116]. This high fat diet with concurrent low carbohydrate ingestion supports energy production through fatty acid β-oxidation and prevents lactic acidosis. Patients with thiamine metabolism dysfunction syndrome 4 treated with high dose thiamine have a better prognosis, with some improvement in weakness and prevention of further polyneuropathy progression [27, 113].

5.4. *Thiamine metabolism dysfunction syndrome 5 (episodic encephalopathy type)*

Thiamine metabolism dysfunction syndrome 5 is caused by TPK1 gene mutations, encoding thiamine phosphokinase 1 [118]. TPK1 plays an important role in thiamine metabolism, as it catalyzes the first step of the sub-pathway that synthesizes thiamine pyrophosphate from thiamine. TPK1 gene mutations lead to a defective TPK1 protein, that is either unstable or presents reduced thiamine binding, and reduced or in some patients increased enzymatic activity [119].

Patients with thiamine pyrophosphokinase deficiency present with episodic encephalopathy associated with infections or metabolic decompensation

Table 3. Treatment of thiamine deficiency disorders

Syndrome		Treatment	
Beriberi	Dry	mild: 10-20mg/day for 2 weeks severe: 20-30mg/day for 2 weeks	
	Wet	100mg/day for 2-3 weeks *heart failure treatment must precede thiamine supplementation	
Wernicke encephalopathy		Alcoholic	Non-Alcoholic
		500mg t.i.d. intravenously for 3 days followed by 250mg t.i.d. for 3 days, oral supplementation indefinitely	100-200mg/day intravenously
		* supplementation of other B vitamins and electrolytes should be considered	
Korsakoff syndrome		– alcohol discontinuation – social support/cognitive remediation – acetylcholinesterase inhibitors, memantine and methylphenidate	

Abbreviations: t.i.d: three times a day

[118]. A total of 16 patients have been reported, almost all presenting in childhood with acute encephalopathy [118-124]. Other than encephalopathy, these patients developed ataxia, dystonia, dysarthria, seizures and eye movement abnormalities. Initially, a normal psychomotor development is the norm, but after recurrent episodes of encephalopathy, psychomotor regression ensues. During the encephalopathy, elevated serum and CSF lactate, variable elevations in organic acids and low TPP levels are present [118]. Brain MRI is abnormal, with lesions developed in the cerebellum/dentate nuclei, striatum, thalamus, globus pallidus, brainstem and spinal cord [27, 123, 124].

Thiamine metabolism dysfunction syndrome 5 is a treatable disorder. When thiamine supplementation starts early, symptoms improve, normal neurodevelopment continues and MRI lesions reduce [118, 121, 123, 124]. Other treatment options like ketogenic diet showed modest or no efficacy [119, 125].

6. Treatment

Thiamine deficiency disorders, especially WE, are considered an emergency and thiamine administration should start upon diagnosis [126]. Patients with WE left untreated quickly progress to permanent neurological impairment, coma, and death [58, 127]. Undertreatment can also lead to the irreversible form of the encephalopathy, i.e. KS, in a large percentage of patients [58, 127].Treatment options for thiamine deficiency disorders are summarized in Table 3.

The ideal therapeutic regimen in patients with WE is not known. A Cochrane review by Day et al. identified only two studies regarding thiamine supplementation for WE, that fulfilled the inclusion criteria. The data from these two studies were insufficient to recommend an optimal therapeutic regimen [128]. Observational studies suggest that a dose of 100 to 200mg of intravenous thiamine per day is adequate for non-alcoholic patients with WE. In patients with alcoholic WE, thiamine supplementation should start with 500mg of intravenous thiamine three times a day [58]. If after 2-3 days no clinical response is observed, discontinuation is rational. If a clinical response is observed, continuation with a lower dose, 250mg three times a day, is recommended. Thiamine supplementation via the oral route should follow this iv regimen indefinitely. Concurrent electrolyte monitoring and supplementation is also important [129-131]. Especially magnesium, being a transketolase cofactor, potassium and other B-complex vitamins are important. Magnesium, being a transketolase cofactor, should given as 1 to 2 mL of a 50% solution of magnesium sulfate intramuscularly [38]. Other B-complex and water soluble vitamins should also be given at 5 to 10 times the recommended daily allowance for several weeks [38]. Following thiamine supplementation, recovery starts with the improvement of ocular symptoms within a few hours or days. This is followed by an improvement in gait, while delirium may take weeks to improve.Patients with KS have a less favorable prognosis, with most never recovering. Many of them need constant supervision and social support [86]. Treatment of alcoholic KS depends on abstinence [132]. Pharmacologic treatments are limited, so prevention and prompt treatment of WE before KS develops is imperative. Once KS develops, acetylcholinesterase inhibitors, memantine and methylphenidate can be tried. No controlled study is available, but anecdotal studies report efficacy [133-136]. Optimal treatment is mul-

tifaceted and incorporates medications, a balanced diet, cognitive remediation techniques and extensive psychosocial support [132].

Treatment of beriberi is also dependent on thiamine supplementation. In patients with mild polyneuropathy, 10 to 20mg/day for two weeks may be adequate to reverse the symptoms. If more severe, the neuropathy usually responds to doses of 20 to 30mg/day [39]. Treatment of wet beriberi depends first upon heart function optimization and second upon thiamine supplementation, with doses of 100mg/day recommended. Thiamine supplementation without addressing the heart failure can lead to low output states and worsening, due to reversal of vasodilation.

Inborn errors of metabolism respond to pharmacologic doses of thiamine. Their treatment has been addressed on the above passages.

In patients presenting in the ER with hypoglycemia, it is recommended that thiamine supplementation is given before or along with glucose to prevent WE. Although this is the classical teaching, this association between glucose administration and WE has not been rigorously studied, with most data coming from clinical observations and case reports [137]. Despite lack of high quality data, thiamine administration is advised before glucose in hypoglycemic patients [67]. Especially in alcoholic, malnourished and hyperemesis gravidarum patients, where thiamine deficiency is expected, 100mg of thiamine should be given concurrently. This should not delay glucose administration. Therapy with intravenous thiamine is considered safe, except for rare anaphylactic reactions [127, 138] which, however, can be prevented by proper vitamin dilutions.

Conclusions

Thiamine deficiency has a wide variety of manifestations, ranging from cardiovascular to neurologic, with often varied and non-specific presentation. Dietary thiamine deficiency was initially though exclusive to food-insecure settings, but is commonly recognized in populations of high income countries. A restrictive diet containing mainly processed food, eating disorders, alcoholism, bariatric surgery and chronic disease are common causes of thiamine deficiency. Mutations in genes implicated in thiamine metabolism also lead to symptoms of thiamine deficiency. Early identification of these disorders, as well as nutritional thiamine deficiency, is imperative. Prognosis depends on the timing of diagnosis and prompt thiamine supplementation must begin upon suspicion of thiamine deficiency. Treatment protocols differ between institutions, owning to lack of evidence-based guidelines.

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