Thiamine and magnesium deficiencies: Keys to disease

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Abstract

Thiamine deficiency (TD) is accepted as the cause of beriberi because of its action in the metabolism of simple carbohydrates, mainly as the rate limiting cofactor for the dehydrogenases of pyruvate and alpha-ketoglutarate, both being critical to the action of the citric acid cycle. Transketolase, dependent on thiamine and magnesium, occurs twice in the oxidative pentose pathway, important in production of reducing equivalents. Thiamine is also a cofactor in the dehydrogenase complex in the degradation of the branched chain amino acids, leucine, isoleucine and valine. In spite of these well accepted facts, the overall clinical effects of TD are still poorly understood. Because of the discovery of 2-hydroxyacyl-CoA lyase (HACL1) as the first peroxisomal enzyme in mammals found to be dependent on thiamine pyrophosphate (TPP) and the ability of thiamine to bind with prion protein, these factors should improve our clinical approach to TD. HACL1 has two important roles in alpha oxidation, the degradation of phy-tanic acid and shortening of 2-hydroxy long-chain fatty acids so that they can be degraded further by beta oxidation. The downstream effects of a lack of efficiency in this enzyme would be expected to be critical in normal brain metabolism. Although TD has been shown experimentally to produce reversible damage to mitochondria and there are many other causes of mitochondrial dysfunction, finding TD as the potential biochemical lesion would help in differential diagnosis. Stresses imposed by infection, head injury or inoculation can initiate intermittent cerebellar ataxia in thiamine deficiency/dependency. Medication or vaccine reactions appear to be more easily initiated in the more intelligent individuals when asymptomatic marginal malnutrition exists. Erythrocyte transketolase testing has shown that thiamine deficiency is widespread. It is hypothesized that the massive consumption of empty calories, particularly those derived from carbohydrate and fat, results in a high calorie/thiamine ratio as a major cause of disease. Because mild to moderate TD results in pseudo hypoxia in the limbic system and brainstem, emotional and stress reflexes of the autonomic nervous system are stimulated and exaggerated, producing symptoms often diagnosed as psychosomatic disease. If the biochemical lesion is recognized at this stage, the symptoms are easily reversible. If not, and the malnutrition continues, neurodegeneration follows and results in a variety of chronic brain diseases. Results from acceptance of the hypothesis could be tested by performing erythrocyte transketolase tests to pick out those with TD and supplementing the affected individuals with the appropriate dietary supplements.

Introduction

The initial symptoms of thiamine deficiency beriberi are those of dysautonomia [1], a broad term that describes any disease or malfunction of the autonomic nervous system. This includes postural orthostatic tachycardia syndrome (POTS), inappropriate sinus tachycardia (IST), vasovagal syncope, mitral valve prolapse dysautonomia, pure autonomic failure, neurocardiogenic syncope (NCS), neurally mediated hypotension (NMH), autonomic instability and a number of lesser-known disorders such as cerebral salt-wasting syndrome. Dysautonomia is associated with Lyme disease, primary biliary cirrhosis, multiple system atrophy (Shy–Drager syndrome) Ehlers–Danlos syndrome and Marfan syndrome for reasons that are not fully understood [2]. It has been hypothesized that the association of dysautonomia with so many different diagnoses is because a common form of dysautonomia originates from high calorie malnutrition. This leads to loss of oxidative efficiency (pseudo hypoxia) and subsequent disorganization of ANS controls that are mediated through the limbic system and brainstem. Perhaps the associated organic disease is a result of years of “maladaptive wear and tear” or is itself a result of loss of oxidative efficiency in target organs [3]. The most definitive publication on autonomic failure was published in a comprehensive book in 1983. It covered the various syndromes recognized at that time. Classification was
presented as primary, secondary (associated with a number of diseases) and that caused by drugs. Although much discussion was given to symptomology, pathology and meticulous examination of histopathology, nowhere was there any reference to malnutrition as a potential cause, although much has been written about it since [4].

**Oxidative stress**

**The role of thiamine**

Although it is obvious that thiamine deficiency is not the only cofactor to be implicated in oxidative function, its vital importance in many aspects of energy metabolism can be used as a model for discussion of oxidative inefficiency. Our experience is that dysautonomia is common and the prototype is beriberi in its early stages when it is treatable with large doses of thiamine. In its later stages the autonomic ganglia and the nerves that flow from them degenerate and the condition is irreversible. The disease is clearly related to metabolic rate since the acuity of symptoms is greatest in infants, in whom sudden death is a common disaster [1]. It may not be a coincidence that modern Sudden Infant Death Syndrome (SIDS) has its maximum incidence at 3–4 months of age, precisely the same timing as infantile beriberi. Beriberi is less acute in older children and is usually most chronic in adults, although a peracetic form was recognized in Japan and called Shoshin. The extraordinary multiplicity of symptoms recorded in beriberi [1] should be known by physicians since they are occurring in the modern era and usually ascribed to other “more modern” causes. There is an outstanding collective psychological problem in the medicine of today for we have assumed that the diseases associated with vitamin deficiency have been eradicated and that they are only of historical interest. When patients today have some of the symptoms that would have been readily recognized 70 years ago for what they represent, the potential underlying cause of malnutrition is not even considered in the differential diagnosis. Unfortunately malnutrition is often conceived of only in the world-wide incidence of starvation and its typical clinical presentation. People suffering from the early effects of high calorie malnutrition are frequently obese, look relatively robust, often have symptoms that are considered to be minor in nature and whose laboratory data are confusing or noncontributory to diagnosis. Little thought has been given to an excess of “empty calories” that result in relative vitamin deficiency, in spite of artificial vitamin enrichment of many foods. Even a rough estimate of dietary habits often reveals nutritional mayhem, particularly in the young and perhaps more surprisingly, pregnant women, where there is potential damage to the fetus. Beriberi is now well accepted as a thiamine deficiency disease. Symptoms of the disease arise from pseudo hypoxia primarily affecting brain, heart and nervous systems, particularly the ANS, the most metabolically active tissues in the body. Most importantly, beriberi reflects a high carbohydrate diet, for centuries represented in Eastern cultures by the consumption of polished rice. Epidemics were related to increased afluen in conditions when peasants were able to afford milling of their rice crops. Some factory workers would take their lunch in the corridors between factory buildings in the summer months. Initially in the shade, as the sun began to shine into the corridor, some of them would develop their first symptoms of beriberi. This observation, together with the appearance of epidemics, commonly in the summer months, misled investigators at that time into believing that the cause of beriberi was an infection [1]. We now have reason to believe that this represented the stress of exposure to ultraviolet light on individuals in a marginal state of high calorie malnutrition who were either asymptomatic or whose symptoms before exposure to sunlight were regarded as minor. In spite of this, the disease made its reappearance recently in 23 Japanese patients, 17 of whom were teenagers consuming sweet carbonated soft drinks, instant noodles and polished rice [5]. We have compared the disease to a “choked engine” in a car where there is an excess of fuel that cannot be efficiently oxidized, resulting in increased carbon from the exhaust. Relative thiamine deficiency is easily induced by an excess of simple carbohydrates [6]. Experimental thiamine deficiency was carried out in human subjects in 1943. Symptomatic results were those that are typically described as psychosomatic and were easily reversed when thiamine adequacy was restored [7]. Symptoms, generally conceived as being psychosomatic in nature, were reported in 20 adolescents in whom thiamine deficiency was proved by abnormal transketolase activity. Symptoms were easily reversed by the administration of dietary supplements that included thiamine [8]. Thiamine supplementation is a promising adjuvant therapy for patients with diabetes [9], a disease in which there is evidence for altered thiamine metabolism [10]. Thiamine deficiency has been implicated in hyperemesis gravidarum [11], restrictive weight loss surgery [12], in the use of total parenteral nutrition [13], optic neuropathy [14], anorexia nervosa [15], congestive heart failure [16] and induces HIF-1-alpha-mediated gene expression similar to that observed in hypoxic stress [17]. The morphological changes in the mamillary bodies due to TD and those due to hypoxia–ischemia may be identical [18], perhaps throwing some light on the mystery behind the molecular mechanisms of the Warburg effect in cancer cells [19].

Magnesium is a cofactor to transketolase and its administration to chronic alcoholic patients being treated with thiamine demonstrated a positive effect on erythrocyte transketolase activity [20]. In animal experiments, hippocampal neurogenesis and the activity of transketolase decreased markedly under conditions of TD [21]. Thiamine deficiency induced in rats caused a reduction of acetylcholine-mediated relaxation and an increased phenylephrine-mediated vasoconstriction in the aorta containing functional endothelium, by modulating nitric oxide production [22]. Acetyl-CoA is the key factor for survival or death of cholinergic neurons in the course of neurodegenerative diseases [23]. High-dose thiamine improves symptoms of fibromyalgia [24], Friedreich's ataxia [25], Parkinson's disease [26] and in biotin-thiamin responsive basal ganglia disease [27], suggesting the expanding role of epigenetics.

**Dysautonomia associated with other diseases**

Acquired dysautonomia in 17 patients [28] included insomnia, bruxism, night cough, sleep eating and sleep apnea. Chronic cough has been reported in 5 patients with the Holmes–Adie syndrome, associated with autonomic disturbances. The authors suggested that chronic cough may be part of the autonomic dysfunction [29]. An article in Polish recorded a 60-year old woman with this syndrome who had experienced chronic dry cough for 4 years [30]. The concept of organic disease as a separate entity divorced from brain action is changing. Studies have shown that the cholinergic anti-inflammatory pathway that inhibits innate immune responses provides evidence that innate immunity is reflexive [31]. Thus, in patients with recurrent infections, the fitness of this reflex mechanism must be taken into account as, for example, the virtual epidemic of recurrent ear infections in hosts of children seen by pediatricians today. Autonomic nervous system dysfunction may play a role in chronic upper airway inflammatory disease [32,33]. Obstructive sleep apnea events are associated with surges in blood pressure, hypercapnia, and fluctuations in cerebral blood flow. Impaired cerebral autoregulation appears to be an important part of either the etiology or the consequences [34]. Nicotinic acetylcholine receptors are expressed in brainstem and spinal cord regions involved in the control of breathing. Impairment of these
mechanisms should be considered in neural control of automatic breathing such as sleep apnea and SIDS [35]. Disturbances in the ANS are widely accepted in migraine that may also affect atrial and ventricular repolarization [36]. Adie syndrome, isolated or accompanied by other dysautonomic disorders, may reveal or precede the diagnosis of Sjögren's syndrome [37]. Dysautonomia is commonly observed in Guillain–Barre syndrome [38]. Several theories have been proposed to explain the underlying mechanisms of pre menstrual syndrome (PMS), but it has been found that there is altered functioning of the ANS in the late luteal phase [39]. We have repeatedly found that PMS responds readily to dietary correction, particularly with removal of sugar and caffeine and with the aid of nutritional supplements. The role of the hypothalamus is sometimes neglected in disease and it seems that this overlook is related to the present disease model in which organic disease is separated from brain disease. It is presently conventional to label a large number of seemingly unconnected symptoms as psychosomatic. This is particularly true if the laboratory studies and technological imaging do not support an organic disease. Laboratory studies can be superficially compared with a fishing expedition where the “net” has to be “where the fish are”. The screening laboratory tests mainly used to support a clinical diagnosis seldom look for nutritional deficiency as the underlying cause. The right laboratory test can and will reveal the true etiology. Such tests as erythrocyte transketolase need to be broadly expanded. Montagna [40] noted that the hypothalamus is a key neural region in the regulation of sleep. It forms part of the so-called central autonomic network, regulating body homeostasis by which we are able to adapt to the many physical and mental stresses encountered in the modern era. Our experience is that these adaptive mechanisms are commonly failing and we have hypothesized that an easy way to produce this is through the dietary mayhem that flourishes worldwide, particularly in Western society.

**The newly discovered role of thiamine in fat metabolism**

The recent discovery of the peroxisomal thiamine pyrophosphate-dependent enzyme 2-hydroxyacyl-CoA lyase (HACL1) may alter our views on the clinical presentation of TD considerably. This enzyme is involved in the alpha oxidation of phytanic acid and 2-hydroxy straight-chain fatty acids. The effect of TD on HACL1 in cells cultured under low thiamine conditions pointed to a clear thiamine dependence of total alpha oxidation. Although the HACL1 gene has been mapped to chromosome 3p25, no diseases have been linked to this gene locus so the phenotype is unknown. These authors note that it can be expected that under clinical conditions, when dietary thiamine is restricted, alpha oxidation would be impaired, leading to the accumulation of phytanic acid and 2-hydroxy straight chain fatty acids [41]. Milk and meat are the major sources of phytol, the precursor of phytanic acid, accumulation of which has been associated with risk for some malignancies [42]. Peroxisomal disorders represent a group of genetic diseases in which there is an impairment of one or more peroxisomal functions. These include the peroxisome biogenesis disorders, seven different enzyme deficiencies, the best known of which causes Refsum's disease and the subtype transport deficiency disease, adrenoleukodystrophy [43]. Compromised alpha oxidation from TD would result in the accumulation of phytanic acid and 2-hydroxy straight chain fatty acids, an upstream effect. The downstream effects might be multiple, including the synthesis of plasmalogens, essential to the construction of cell membranes [44] and clinical effects that might include male infertility, defects in eye development and optic nerve hypoplasia [45], also offering an additional explanation for male infertility from TD [46] and optic neuritis, described in a case of Wernicke encephalopathy [47].

**Brain disease, nutritional deficiency and stress**

A 6 year old boy with intermittent episodes of cerebellar ataxia [48] was shown to be thiamine dependent [49]. Each episode was initiated by a mild infection, slight head injury, inoculation or even by sudden changes of environmental temperature such as turning the air conditioning on in a car. This suggested the combination of genetic risk, some form of environmental factor defined as stress, and an unstable cellular energy requirement in triggering each episode of ataxia. A similar situation has been described in intermittent maple syrup urine disease [50].

It has been hypothesized that all three components may have to be present for clinical presentation of a disease process, represented as “the three circles of health”. The proportion of etiology provided by each component would be decided by the degree of overlap and the relative size of each circle, a mathematical concept known as Boolean algebra [3].

**Oxidative pentose phosphate pathway and one-carbon metabolism**

The most direct route to produce NADPH from glucose is the oxidative pentose phosphate pathway. Since the enzyme transketolase occurs twice in this pathway, deficiency of thiamine as its cofactor would be expected to have some effect on the production of reducing equivalents. Surprisingly, however, a nearly comparable contribution comes from serine-driven one-carbon metabolism, implicating folate that has not previously been considered as an NADPH producer. Tracing of mitochondrial one-carbon metabolism revealed complete oxidation of 10-formyl-tetrahydrofolate to make NADPH [51]. Polymorphisms in folate metabolism genes, associated with neural tube defects developing in the fetus during pregnancy [52] are more likely to occur with dietary deficiency of folate in the mother. Platt emphasized that the clinical manifestations of beriberi are different from those that would be acquired by pure TD [53], suggesting that other members of the vitamin B complex might be involved in beriberi. Since transketolase occurs in erythrocytes, the measurement of its baseline activity (TKA), followed by the acceleration of this activity after addition of thiamine pyrophosphate to the reaction (TPPE) is by far and away the best test for evidence of TD [54,55].

The potential importance of the interrelationship of genetics, stress and energy was illustrated by hypothesising that Sudden Infant Death Syndrome (SIDS) may require a variable combination of all three components [56]. This was again emphasized in 2013 when an 18-year old girl was brought to our notice because she had developed Postural Orthostatic Hypotension Syndrome (POTS) after receiving human papilloma virus vaccination (HPV). Erythrocyte transketolase testing proved TD. As a result of this, two other girls and a boy suffering from post HPV vaccination POTS were tested by erythrocyte transketolase, all of whom demonstrated TD (Table 1). Further inquiry into the case of the boy revealed that his father had Wernicke encephalopathy and there was a strong paternal family history of alcoholism, suggesting a genetic component [57]. Post HPV vaccination POTS was reported in six patients [58]. Another girl who was suffering from POTS, although she had not received the HPV vaccine, was tested with the erythrocyte transketolase that showed TD.

Although a small number of cases of this nature makes it impossible to draw any final conclusions, it is worth repeating the statement that beriberi is the prototype of dysautonomia [1] and cannot be distinguished clinically from POTS without proving TD as the etiology. We further hypothesize here that, in the case of the post-vaccination POTS patients, the vaccination represented a non specific stress factor imposed on individuals who were at risk as a result of high calorie malnutrition. Each of the individuals in
Clinical support for the three circles of health

Some years ago, a 6 year old boy, who came to our attention, experienced a head injury involving a skull fracture. After treatment he returned to school and was instructed by the school nurse to report every 2 weeks to her office for visual testing. Three months later there was a marked visual change and he was referred to an ophthalmologist who found bilateral cataracts. Genetic screening revealed that he was a carrier of the galactokinese deficiency allele. He had also been consuming a large amount of milk as a “health drink”. Three of 39 patients with presenile cataracts, developing between the ages of 20 and 55 years, were found to be carriers of the galactokinase deficiency allele, two of whom had high dietary galactose intake [59]. It is hypothesized here that the combination of head injury (stress), the marked visual change that occurred 3 months after the injury (genetics) and the consumption of milk (energy) were collectively responsible for advancing the formation of cataracts in my patient from adulthood to childhood.

An 84 year old gentleman came to our attention. He had developed inflammatory tenosynovitis in one finger from ringing a heavy bass bell in a hand-bell choir (stress). Laboratory testing revealed several inflammatory markers and an erythrocyte transketolase that proved TD (energy). Although his sugar intake was, by conventional standards modest, he was instructed to discontinue sugar in all its forms. No other treatment was offered. Serial laboratory tests (Table 2) showed a gradual improvement of all parameters over a period of 6 months. The rise in triglycerides and slight increase in the thiamine pyrophosphate effect (TPPE) is to be noted one day after ingesting a small amount of simple carbohydrate [6]. It is hypothesized that this man was inordinately sensitive to sugar ingestion (?genetic).

Genetic risk coupled with malnutrition

There is no doubt that the Western diet has an impact on immune function [60] and brain disease in reference to genetic mutations [61]. Dysautonomia symptoms of nutritional interest may often occur in Parkinson’s disease but the role played in affecting the risk of malnutrition still needs to be clarified [62]. Nervous hyperexcitability due to chronic magnesium deficiency in the adult results in a non-specific clinical pattern with associated central and peripheral neuromuscular symptoms, analogous to the symptomatology previously described in medical literature as latent tetany, hypoventilation syndrome, spasmodhia, chronic fatigue syndrome, neurocirculatory asthenia and idiopathic Barlow’s disease [63]. Three family members were reported with functional symptoms. Desaturation of erythrocyte transketolase indicated that TD was common to all three individuals. Although they failed to respond clinically and biochemically to large doses of thiamine hydrochloride, they did respond to thiamine tetrahydrofurfuryl disulfide [64], a little known therapeutic agent, known to have significant merit in conditions where thiamine metabolism is implicated [65]. Subjects with orthostatic hypotension had lower serum 25 (OH)D than age and gender-matched subjects who had no history of blackouts [66]. Vitamin D deficiency is a cardiovascular risk factor with unfavorable cardiac autonomic activity [67]. Vitamin B12 deficiency in patients with postural orthostatic tachycardia syndrome (POTS) may lead to sympathetic nervous system baroreceptor dysfunction [68]. Although restricted dietary intake was considered to be responsible for multiple vitamin deficiencies in a severely autistic child, the authors did not consider the possibility of it being the etiology rather than the effect. Pulmonary hypertension, found in this child [69], was found to be related to vitamin D deficiency by other authors [70] and a child with an inborn error of vitamin B12 metabolism presented with isolated pulmonary hypertension [71]. Hypoxia–ischemia produces similar, if not identical pathology in brain [18] and it was shown that both acute and chronic hypoxia in animal experiments produced sympathoadrenal responses that might be responsible for aggressive behavior in humans if a similar response were to be elicited by pseudo hypoxia as in TD [72].

Prion disease

The exact biological function of the prion protein is still unclear but it has recently been found that it binds thiamine [72]. Prion-induced diseases are a global health concern and molecular docking of thiamine reveals similarity in binding properties between the prion protein and other thiamine-binding proteins [73]. Human prion diseases present as neurologic conditions associated with rapid multi focal central nervous system degeneration, usually dominated by dementia and cerebellar ataxia. A novel prion disease was identified in a large British kindred in which the consistent phenotype of chronic diarrhea and neuropathy was associated with autonomic failure [74]. Dementia and cerebellar ataxia were clinical manifestations of thiamine dependency [48]. Aging and oxidative stress resulting from over-expression of Alzheimer precursor protein (beta APP) have been studied as important factors contributing to the major age-related (sporadic), and minor (hereditary) forms of Alzheimer’s disease and muscle inclusion body myositis. In lens betaAPP and Abeta, increase occurs in cultured lenses exposed to oxidative stress and in areas of lens fiber cell degeneration in thiamine deprived mice, a classic model of systemic oxidative stress [75]. In a variety of neurodegenerative diseases a common feature is the accumulation of misfolded protein aggregates, an example being prion protein in prion diseases. These often precede the onset of motor symptoms by several years.

Table 1

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>HPV Vacc</th>
<th>TKA</th>
<th>TPPE</th>
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<tbody>
<tr>
<td>1</td>
<td>Girl</td>
<td>Yes</td>
<td>55</td>
<td>49%</td>
</tr>
<tr>
<td>2</td>
<td>Girl</td>
<td>Yes</td>
<td>48</td>
<td>27%</td>
</tr>
<tr>
<td>3</td>
<td>Girl</td>
<td>Yes</td>
<td>66</td>
<td>23%</td>
</tr>
<tr>
<td>4</td>
<td>Boy</td>
<td>Yes</td>
<td>32</td>
<td>16%</td>
</tr>
<tr>
<td>5</td>
<td>Girl</td>
<td>No</td>
<td>61</td>
<td>25%</td>
</tr>
</tbody>
</table>

*TKA N 42–86 mU TPPE N 0–18%.

Table 2

<table>
<thead>
<tr>
<th>Month</th>
<th>Cholest</th>
<th>Triglycer</th>
<th>Fibrinogen</th>
<th>HsCRP</th>
<th>TKA</th>
<th>TPPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>February</td>
<td>169</td>
<td>206</td>
<td>412</td>
<td>7</td>
<td>65</td>
<td>35%</td>
</tr>
<tr>
<td>May</td>
<td>160</td>
<td>152</td>
<td>312</td>
<td>0.9</td>
<td>55</td>
<td>25%</td>
</tr>
<tr>
<td>August</td>
<td>166</td>
<td>124</td>
<td>0.3</td>
<td>0.9</td>
<td>59</td>
<td>0%</td>
</tr>
<tr>
<td>Sept</td>
<td>169</td>
<td>165</td>
<td>220</td>
<td>1</td>
<td>62</td>
<td>8%</td>
</tr>
</tbody>
</table>

*Morning after ingesting small amount of simple carbohydrates.

Cholest N < 200 mg/dL. Triglycer N < 150 mg/dL. Fibrinogen N 180–350 mg/dL. HsCRP N 0.1–1.0. TKA 42–86 mU. TPPE 0–18%.


Montagnac P. Hypothalamic sleep and headaches. Neurol Sci 2006 Suppl 2; S138–43.


