Medical Hypotheses 84 (2015) 129–134

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Thiamine and magnesium deficiencies: Keys to disease

D. Lonsdale *

Associate Emeritus, Cleveland Clinic, Cleveland, OH, United States

ARTICLE INFO

Article history:
Received 21 September 2014
Accepted 6 December 2014

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 phytanic 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

* Address: 28575 Westlake Village Dr., Westlake, OH 44145, United States. Tel.: +1 4404714852.
E-mail address: derricklonsdale@hotmail.com

http://dx.doi.org/10.1016/j.mehy.2014.12.004
0306-9877/

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 peracute 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 affluence 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-1alpha-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 aortas 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], Freidreich'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 Sjogren'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 substrate 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

Table 1
Erythrocyte transketolase activity and thiamine pyrophosphate effect in five adolescents with postural orthostatic hypotension syndrome (POTS), four of whom had received HPV vaccine.

Subject	Sex	HPV Vacc	TKA	TPPE
1	Girl	Yes	55	49%
2	Girl	Yes	48	27%
3	Girl	Yes	66	23%
4	Boy	Yes	32	16%
5	Girl	No	61	25%

TKA *N* 42–86 mU TPPE *N* 0–18%.

Table 2
Repeated laboratory data from an 84-year old man with insomnia and stress related tenosynovitis.

Month	Cholest	Triglyc	Fibrinog	HsCRP	TKA	TPPE
February	169	206	412	7	65	35%
May	160	152	312	0.9	55	25%
August	166	124		0.3	59	0%
Sept*	169	165	220	1	62	8%

Cholest *N* < 200 mg/dL. Triglyc *N* < 150 mg/dL. Fibrinogen *N* 180–350 mg/dL. HsCRP *N* 0.1–1.0. TKA 42–86 mU. TPPE 0–18%.
* Morning after ingesting small amount of simple carbohydrates.

this small group of adolescents was an excellent student and athlete before vaccination. Perhaps their genetically determined energy requirement put them more at risk for a superimposed stress factor in the presence of marginal effects from high calorie malnutrition. A precedent for this has been set in the stress initiation of intermittent episodes of cerebellar ataxia in a patient with thiamine dependency [48] and recurrent episodes of maple-syrup-urine disease [50].

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 galactokinase 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, spasmophilia, 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

leading to particular attention to the clinical assessment of autonomic disorders in patients later affected by neurodegenerative diseases [76]. Autonomic disturbances play an important role in the symptomatology of familial amyloidotic polyneuropathy in which unmyelinated, small myelinated and large myelinated fibers tend to become impaired in that order [77], similar to the neurodegeneration that occurs in beriberi. In amyloid neuropathies, symptoms begin in the feet and ultimately progress to the proximal legs and hands, also similar to that described in the symptomatology of beriberi [78].

A 68 year old patient was reported with non-alcoholic Wernicke encephalopathy in whom 14-3-3 protein was found in the cerebrospinal fluid. This protein is typically elevated in prion disease. Unfortunately the authors did not state whether T D was present [79]. Copper toxicity has been speculatively linked to the pathogenesis of Alzheimer's and prion diseases. The addition of 1% thiamine to the drinking water of Long Evans Cinnamon rats, an animal model of Wilson's disease, markedly extended the life span [80].

Cardiac parasympathetic dysfunction has been reported in a patient with rheumatoid arthritis [81]. The connection between "mental" and "physical" is unclear, a theme that has been stated repeatedly in the many case reports where dysautonomia has been associated with organic disease. It is hypothesized here that the dysautonomia is caused by pseudo hypoxia in limbic system control mechanisms and arises as the first part of the disease combination. The ensuing organic disease might be from cellular energy failure from the same cause, or from disruption of the essential adaptive dialog between the limbic system and the organ.

Conclusion

Evidence has been presented that high calorie malnutrition, particularly involving simple carbohydrates and fats, is a major cause of functional disease by inducing relative vitamin deficiencies, mainly including members of the vitamin B group, particularly thiamine. Vitamin D deficiency is also widespread, presumably from lack of sun exposure. The loss of oxidative efficiency and brain/body signaling power causes its effects through dysfunctional limbic system and brainstem controls, resulting in variable features of dysautonomia and emotional hyper-reflexia. The ensuing symptoms are commonly diagnosed as psychosomatic disease. If these symptoms are not recognized for what they represent and the deficiency continues indefinitely, pathologic changes take place, giving rise to various brain and body dysfunctions that are regarded as individual diseases, then only minimally or non responsive to correction of the original biochemical lesion. Genetic risk, energy consumption resulting from stress, coupled with oxidative inefficiency from vitamin deficiency, all become individual components of collective etiology. Increasing knowledge and experience with epigenetic treatment should be an important development. High calorie malnutrition has been hypothesized as a potential cause of emotional change resulting in violent behavior suggesting that a mild degree of pseudo hypoxia exaggerates the activity of the limbic system and weakens the self control mechanisms of higher centers, thus imposing more primitive behavior from the affected individual, possibly even exploding in violence.

Conflict of interest

There are no conflicts of interest.

References

[1] Inouye K, Katsura E. Clinical signs and metabolism of beriberi patients. In: Shimazono N, Katsura E, editors. Thiamine and Beriberi. Tokyo: Igaku Shoin Ltd.; 1965. p. 29–63.

[2] Kollensberger M, Stampfer-Kountchev M, Seppi K, Geser F, Frick C, Del Sorbo F, et al. Progression of dysautonomia in multiple system atrophy: a prospective study of self-perceived impairment. Eur J Neurol 2007;14(1):66–72.

[3] Lonsdale D. Dysautonomia, a heuristic approach to a revised model for etiology of disease. eCAM 2009;6(1):3–10.

[4] Bannister R, editor. Autonomic failure. Oxford University Press; 1984. p. 666.

[5] Kawai C, Wakabayashi A, Matsamura T, Yui Y. Reappearance of beriberi heart disease in Japan. A study of 23 cases. Am J Med 1980;69(3):383–6.

[6] Elmadfa I, Majchrzak D, Rust P, Genser D. The thiamine status of adult humans depends on carbohydrate intake. Int J Vitam Nutr Res 2001;71(4):217–21.

[7] Williams RD, Mason HL, Marschelle HP, Russell MW. Induced thiamine (vitamin B1) deficiency in man. Arch Int Med 1943;71:38–53.

[8] Lonsdale D, Shamberger RJ. Red cell transketolase as an indicator of nutritional deficiency. Am J Clin Nutr 1980;33:206–11.

[9] Al-Attas O, Al-Daghri N, Alokail M, Abd-Alrahman S, Vinodson B, Sabico S. Metabolic benefits all of six-month thiamine supplementation in patients with and without diabetes mellitus type two. Clin Med Insights Endocrinol Diabetes 2014;7:1–6.

[10] Pacal L, Kurikova K, Kankova K. Evidence for altered thiamine metabolism in diabetes: is there a potential to oppose gluco- and liptoxicity by rational supplementation? World J Diabetes 2014;5(3):288–95.

[11] Kantor S, Prakash S, Chandwani J, Gokhale A, Sarma K, Albahrani MJ. Wernicke's encephalopathy following hyperemesis gravidarum. Indian J Crit Care Med 2014;18(3):164–6.

[12] Milone M, Di Minno MN, Lupoli R, et al. Wernicke encephalopathy in subjects undergoing restrictive weight loss surgery: a systematic review of literature data. Eur Eat Disord Rev 2014;22(4):223–9.

[13] Ramsi M, Mowbray C, Hartman G, Pageler N. Severe lactic acidosis and multiorgan failure due to thiamine deficiency during total parenteral nutrition. BMJ Case Rep 2014 [Jun 3].

[14] Gratton SM, Lam BL. Visual loss and optic nerve head swelling in thiamine deficiency without prolonged dietary deficiency. Clin Ophthalmol 2014;8:1021–4.

[15] Renthal W, Marin-Valencia I, Evans PA. Thiamin deficiency secondary to anorexia nervosa: an uncommon cause of peripheral neuropathy and wernicke encephalopathy in adolescence. Pediatr Neurol 2014;51(1):100–3.

[16] Dinicolantonio JJ, Lavie CJ, Niazi AK, O'Keefe JH, Hu T. Effects of thiamine on cardiac function in patients with systolic heart failure: systematic review and metaanalysis of randomized, double-blind, placebo-controlled trials. Ochsner J 2013;15(4):495–9.

[17] Sweet RL, Zastre JA. HIF1-alpha-mediated gene expression induced by vitamin B1 deficiency. Int J Vitam Nutr Res 2013;83(3):188–97.

[18] Vortmeyer AO, Hagel C, Laas R. Hypoxia-ischemia and thiamine deficiency. Clin Neuropathol 1993;12(4):184–90.

[19] Brahimi-Horn MC, Chiche J, Pouyssegur J. Hypoxia signaling controls metabolic demand. Curr Opin Cell Biol 2007;19(2):223–9.

[20] Peake RW, Godber IM, Maguire D. The effect of magnesium administration on erythrocyte transketolase activity in alcoholic patients treated with thiamine. Scott Med J 2013;58(3):139–42.

[21] Zhao Y, Wu Y, Hu H, et al. Downregulation of transketolase activity is related to inhibition of hippocampal progenitor cell proliferation induced by thiamine deficiency. Biomed Res Int 2014 [June 16].

[22] Gioda CR, Capettini LS, Cruz JS, Lemos VS. Thiamine deficiency leads to reduced nitric oxide production and vascular dysfunction in rats. Nutr Metab Cardiovasc Dis 2014;24(2):183–8.

[23] Szutowicz A, Bielarczyk H, Jankowska-Kulawy A, Pawelczyk T, Ronowska A. Acetyl-CoA the key factor for survival or death of cholinergic neurons in the course of neurodegenerative diseases. Neurochem Res 2013;38(8):1523–42.

[24] Costantini A, Pala MI, Tundo S, Matteucci P. High-dose thiamine improves the symptoms of fibromyalgia. BMJ Case Rep 2013 [bcr2013009019].

[25] Costantini A, Giorgi R, D'Agostino S, Pala MI. High-dose thiamine improves the symptoms of Friedreich's ataxia. BMJ Case Rep 2013 [bcr 201300 9424].

[26] Costantini A, Pala MI, Compagnoni L, Colangeli M. High-dose thiamine as initial treatment for Parkinson's disease. BMJ Case Rep 2013 [bcr 2013009289].

[27] Alfadhel M, Almuntashri M, Jadah RH, et al. Biotin-responsive basal ganglia disease should be renamed biotin-thiamine-responsive basal ganglia disease: a retrospective review of the clinical, radiologic and molecular findings of 18 new cases. Orphanet J Rare Dis 2013;8:83 [doi: 1186/1750-1172-8-83].

[28] Lonsdale D, Shamberger RJ, Obrenovich ME. Exaggerated autonomic asymmetry: a clue to nutrient deficiency dysautonomia. Webmed Cent Altern Med 2011;2(4) [WMCOO1854].

[29] Kimber J, Mitchell D, Mathias C. Chronic cough in the Holmes-Adie syndrome: association in five cases with autonomic dysfunction. J Neurol Neurosurg Psychiatry 1998;65(4):583–6.

[30] Kosztyla-Hojna B, Popko M. A rare case of Holmes-Adie syndrome in a 60-year old patient with a chronic cough cured in a laryngological way. Pol Merkuriusz Lek 2007;23(137):371–4.

[31] Rosas-Bellina M, Tracey KJ. The neurology of the immune system: neural reflexes regulate immunity. Neuron 2009;64(1):28–32.

[32] Loehri TA. Autonomic dysfunction, allergy and the upper airway. Curr Opin Otolaryngol Head Neck Surg 2007;15(4):264–7.

[33] Baraniuk JN, Kim D. Nasonasal reflexes, the nasal cycle, and sneeze. Curr Allergy Asthma Rep 2007;7(2):105–11.

[34] Urbano F, Roux F, Schindler J, Mohsenin V. Impaired cerebral autoregulation in obstructive sleep apnea. J Appl Physiol 2008;105(6):1852–7.

[35] Shao XM, Feldman JL. Central cholinergic regulation of respiration: nicotinic receptors. Acta Pharmacol Sin 2009;30(6):761–70.
[36] Melek IM, Seyfell E, Duru M, et al. Autonomic dysfunction and cardiac repolarization abnormalities in patients with migraine attacks. Med Monit Sci 2007;13(3) [RA47-49].
[37] Vermersch P, Dufourd-Delalande S, Defoort-Dhellemmes S, Stojkovic T, Launay D, De Seze J. Tonic pupils in Sjogren's syndrome. Rev Neurol (Paris) 2005; 161(10):963–6 [Article in French].
[38] Zhang Q, Gu Z, Jiang J, Bai X, Feng Y, Huang Z, et al. Orthostatic hypotension as a presenting symptom of the Guillain–Barre syndrome. Clin Auton Res 2010;20(3):209–10.
[39] Matsumoto T, Ushiroyama T, Kimura T, Hayashi T, Moritani T. Altered autonomic nervous system activity as a potential etiological factor of premenstrual syndrome and premenstrual dysphoric disorder. Biopsychosoc Med 2007;1:24. http://dx.doi.org/10.1186/1751-0759-1-24.
[40] Montagna P. Hypothalamus sleep and headaches. Neurol Sci 2006(Suppl. 2): S138–43.
[41] Casteels M, Snieckers M, Fraccasia P, Mannaerts GP, Van Veldhoven PP. The role of 2-hydroxyacyl–CoA lyase, a thiamin pyrophosphate-dependent enzyme, in the peroxisomal metabolism of 3-methyl branched fatty acids and 2-hydroxy straight chain fatty acids. Biochem Soc Trans 2007;35(5):876–80 [Six].
[42] Ollberding NJ, Aschebrook-Kilroy B, Caces DB, et al. Phytanic acid and the risk of non-Hodgkin lymphoma. Carcinogenesis 2013;34(1):170–5.
[43] Aubourg P, Wanders R. Peroxisomal disorders. Handb Clin Neurol 2013;113:1593–609.
[44] Gorgas K, Teigler A, Kokljenivic D, Just WW. The ether lipid deficient mouse: tracking down plasmalogen functions. Biochim Biophys Acta 2006; 1763(12):1511–26.
[45] Rodemer C, Thai TP, Brugger B, et al. Inactivation of ether lipid biosynthesis causes male infertility, defects in eye development and optic nerve hypoplasia in mice. Mol Genet 2003;12(15):1881–95.
[46] Oishi K, Barchi M, Au AC, Gelb BD, Diaz GA. Male infertility due to germ cell apoptosis in mice lacking the thiamin carrier, Tht1. A new insight into the critical role of thiamin in spermatogenesis. Dev Biol 2004;266(2):299–309.
[47] Bohnsack BL, Patel SS. Peripapillary nerve fiber layer thickening, telangiectasia, and retinal hemorrhages in Wernicke encephalopathy. J Neuroophthalmol 2010;30(1):54–8.
[48] Lonsdale D, Faulkner WR, Price JW, Smeby RR. Intermittent cerebellar ataxia associated with hyperpyruvic academia, hyperalaninemia, and hyperalaninuria. Pediatrics 1969;43:1025–34.
[49] Blass J. Abnormalities in pyruvate dehydrogenase and neurologic function. Int J Neurosci 1972;4:65–9.
[50] Axler O, Holmquist P. Intermittent maple syrup urine disease: two case reports. Pediatrics 2014;133(2):e458–60.
[51] Fan J, Ye J, Kamphorst JJ, Shlomi T, Thnompson CB, Rabinowitz JD. Quantitative flux analysis reveals folate-dependent NADPH production. Nature 2014; 510(7504):298–302.
[52] Yadav U, Kumar P, Yadav SK, Mishra OP, Rai V. Polymorphisms in folate metabolism genes as maternal risk factor for neural tube defects: an updated meta-analysis. Metab Brain Dis 2014 [Epub ahead of print].
[53] Platt BS. Thiamine deficiency in human beriberi and in Wernicke's encephalopathy. In: Wolstenholme GEW, O'Connor M, editors. Thiamine deficiency. Boston: Little, Brown and Company; 1967. p. 135–43.
[54] Jeyasingham MD, Pratt O, Burns A, Shaw GK, Thomson AD, Marsh A. The activation of red blood cell transketolase in groups of patients especially at risk from thiamin deficiency. Psychol Med 1987;117:311–8.
[55] Lonsdale D. Red cell transketolase studies in a private practice specializing in nutritional correction. J Am Coll Nutr 1988;7(1):61–7.
[56] Lonsdale D. Sudden infant death syndrome requires genetic predisposition, some form of stress and marginal malnutrition. Med Hypotheses 2001; 57(3):382–6.
[57] Blass JP, Gibson GE. Abnormality of a thiamine requiring enzyme in patients with Wernicke–Korsakoff syndrome. N Engl J Med 1977;297:1367–70.
[58] Blitsheyn S. Postural tachycardia syndrome following human papillomavirus vaccination. Eur J Neurol 2014;21(1):135–9.
[59] Stambolian D, Scarpino-Myers V, Eagle Jr RFC, Hodes B, Harris H. Cataracts in patients heterozygous for galactokinase deficiency. Invest Ophthalmol Vis Sci 1986;27(3):429–33.
[60] Myles IA. Fast food fever: reviewing the impacts of the Western diet on immunity. Nutr J 2014 Jun;17(13):61. http://dx.doi.org/10.1186/1475-2891-13-61.
[61] Yamada K, Miura K, Hara K, et al. A wide spectrum of clinical and brain MRI findings in patients with SLC 19A3 mutations. BMC Med Genet 2010 Dec;22(11):171. http://dx.doi.org/10.1186/1471-2350-11-171.
[62] Barichella M, Cereda E, Madio C, et al. Nutritional risk and gastrointestinal dysautonomia symptoms in Parkinson's disease outpatients hospitalized on a scheduled basis. Br J Nutr 2013;110(2):347–53.
[63] Durlach J, Bac P, Durlach V, Bara M, Guiet-Bara A. Neurotic, neuromuscular and autonomic nervous form of magnesium imbalance. Magnes Res 1997; 10(2):169–95.
[64] Lonsdale D. Hypothesis and case reports: possible thiamin deficiency. J Am Coll Nutr 1990;91(1):13–7.
[65] Lonsdale D. Thiamine tetrahydrofurfuryl disulfide: a little known therapeutic agent. Med Sci Monit 2004;10(9) [RA199-203, www.MedSci Monit.com].
[66] McCarroll KG, Robinson DJ, Coughlan A, Healy M, Kenny RA, Cunningham C. Vitamin D and orthostatic hypo tension. Age Ageing 2012;41(6):810–3.
[67] Mann MC, Exner DV, Hemmelgam BR, Sola DY, Turin TC, Ahmed SB. Vitamin D levels are associated with cardiac autonomic activity in healthy humans. Nutrients 2013;5(6):2114–7.
[68] Oner T, Guven B, Travli V, Mese T, Yilmazer MM, Demirpence S. Postural orthostatic tachycardia syndrome (POTS) and vitamin B12 deficiency in adolescents. Pediatrics 2014;133(1):e138–142.
[69] Duvall MG, Pikman Y, Kantor DB, et al. Pulmonary hypertension associated with scurvy and vitamin deficiencies in an autistic child. Pediatrics 2013; 132(6):e1699–703.
[70] Demir M, Uyan U, Keceoclu S, Demir C. The relationship between vitamin D deficiency and pulmonary hypertension. Prague Med Rep 2013; 114(3):154–61.
[71] Iodice FG, Di Chiara L, Boenzi S, et al. Cobalamin C defect presenting with isolated pulmonary hypertension. Pediatrics 2013;132(1):e248–51.
[72] Perez-Pineiro R, Bjorndahl TC, Berjanskii MV, et al. The prion protein binds thiamine. FEBS J 2011;278(21):4002–14.
[73] Pagadala NS, Bjorndahl TC, Blinov N, Kovalenko A, Wishart DS. Each Molecular docking of thiamine reveals similarity in binding properties between the prion protein and other thiamine-binding proteins. J Mol Model 2013; 19(12):5225–35.
[74] Mead S, Gandhi S, Beck J, et al. A novel prion disease associated with diarrhea and autonomic neuropathy. N Engl J Med 2013;369(20):1904–14.
[75] Frederikse PH, Zigler Jr SJ, Farnsworth PN, Carper DA. Prion protein expression in mammalian lenses. Curr Eye Res 2000;20(2):137–43.
[76] Natale G, Biagioni F, Vivacqua G, D'Este L, Fumagalli M, Fornai F. The neurobiology of dysautonomia in Parkinson's disease. Arch Ital Biol 2013;151(4):203–18.
[77] Obayashi K, Ando Y. Focus on autonomic dysfunction in familial amyloidotic polyneuropathy. Amyloid 2012;19(Suppl. 1):28–9.
[78] Shin SC, Robinson-Papp J. Amyloid neuropathies. Mt Sinai J Med 2012; 79(6):733–48.
[79] Michowitz Y, Copel L, Shiloach E, Litovchik I, Rapoport MJ. Non-alcoholic Wernicke's encephalopathy-unusual clinical findings. Eur J Intern Med 2005;16(6):443–4.
[80] Sheline CT, Choi EH, Kim-Han JS, Dugan LL, Choi DW. Cofactors of mitochondrial enzymes attenuate copper-induced death in vitro and in vivo. Ann Neurol 2002;52(2):195–204.
[81] Saraswathi PV, Neelambikai N, Mahesh A, Govindarajan K. Cardiovascular parasympathetic nervous system dysfunction in female rheumatoid arthritis patients. Indian J Physiol Pharmacol 2013;57(1):23–30.