

Special Article - Malnutrition: Clinical Cases & Short Reports

The Role of Thiamin in High Calorie Malnutrition

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Objective: A number of disorders have become virtual epidemics in the modern era, including Attention Deficit (ADD), with or without hyperactivity, recurrent ear infections, Autistic Spectrum Disorder (ASD) and obesity. All have male gender preponderance and obesity has been linked to cognitive dysfunction. High calorie malnutrition, defined as calorie yielding foods with insufficient non-caloric nutrients, is common in America. The objective of this review is to show that this type of malnutrition, particularly with the consumption of simple carbohydrate foods, induces thiamin deficiency, often also with magnesium deficiency, providing a common etiological component for these diseases, analogically compared with variations on a symphonic theme in music.

Conclusion: High calorie malnutrition is affecting millions of people, involving the inordinate consumption of sugar and fat as empty calories. All simple carbohydrates are metabolized in the body as glucose, with thiamin as the rate limiting factor in the three enzymes that make up pyruvic dehydrogenase and as a cofactor in transketolase. Other non-caloric nutrients are also crucial in oxidative metabolism. Thiamin has been found to be a cofactor in the enzyme 2-hydroxyacyl-CoA lyase (HACL1) in peroxisomes, indicating its role in fat metabolism and the potential clinical effects of Thiamin Deficiency (TD). The phenotype for a mutation in HACL1 has not yet been described although the gene has been mapped to chromosome 3p25. The effect of blocking phytanic acid and long chain fatty acid metabolism and the downstream effect on beta oxidation would be expected to have serious consequences in the brain.

Keywords: Attention deficit; SIDS; Oxidative metabolism; Thiamin

Introduction

An important question recently asked is why in the last decades there has been an increase in the United States of new pediatric mental illnesses and neurological dysfunctions requiring medical care, with an increase of obesity and high calorie malnutrition. Based on the hypothesis that mental illness is accompanied by autonomic dysfunction, measurements of heart rate variability in children with attention-deficit/hyperactivity disorder showed that their parasympathetic activity was reduced [1] as it was in autistic children [2]. Prevalence of childhood obesity has tripled since the 1980s and is strongly linked to the early onset of several metabolic diseases. Lower cognitive function may be a complication of childhood obesity [3]. It is hypothesized that the overwhelming preponderance of simple carbohydrates causes lower cognitive function because of the non caloric nutrient deficiency, especially thiamin and magnesium. Oxidative stress was found to be evident in 35 child or adolescent patients diagnosed with ADHD. Remarkably high levels of the nitric oxide pool and malondialdehyde oxidants together with low glutathione peroxidase activities suggested an oxidative imbalance in these patients [4]. Pre-pubertal incidence rates for depressive and anxiety disorders were higher for boys than girls, although at age 12 years the pattern reversed [5]. While the incidence of SIDS in the United States, long known to be male dominant, has declined, it currently remains the leading cause of post-neonatal mortality, highlighting an important public health priority [6]. Infantile beriberi has exactly the same epidemiology as SIDS [7] and thiamin triphosphate deficiency has been reported in the phrenic nerve of

a SIDS infant [8]. It has been hypothesized that the mechanism of SIDS, presently ill considered to be due solely to positioning of the infant, also involves genetic risk, some form of environmental stress such as a viral infection, flame retardants in the mattress, or hypoxia from the prone position, coupled with mild thiamine/magnesium deficiency, are all variable, inter-related etiological components for the final outcome of SIDS [9]. The gender ratio among children with Autistic Spectrum Disorder (ASD) of more than four boys to every girl is widely recognized. Thus the male gender appears to be a genetic risk for these common conditions [10]. The effects on the brain from hypoxia-ischemia and TD may be the same [11] and mitochondrial dysfunction has been associated with ASD [12].

The role of dysautonomia

An obesity intervention program reportedly modified the preexisting dysautonomia that existed in a group of obese children [13]. Dysautonomia and in particular, diminished parasympathetic activity, has also been questioned in the mechanism of Gastroesophageal Reflux Disease (GERD) [14]. The esophagus has no sympathetic nerve supply, so all neurological defects in it are cholinergic. Acetylcholine requires acetyl coA for its synthesis and this, in turn, reflects on efficient function of the citric acid cycle, dependent on thiamin for glucose metabolism. There are many examples of dysautonomia in the medical literature as an accompaniment or a forerunner of organic disease [15-18]. It has been hypothesized that the dysautonomia is initiated in some cases, either on genetic grounds, or by marginal high calorie malnutrition leading to dysfunction of the hypothalamic/autonomic/endocrine axis [10].

Dysautonomia was recognized in autistic children as early as 1961 [19]. Mitochondrial dysfunction is a hallmark of almost all diseases and certainly in the terminal phases of life. It is characterized by decreased cytosolic phosphorylation potential that suppresses the cell's ability to maintain its functions and control the intracellular Ca (2+) homeostasis and its redox state [20]. Recurrent ear infections and tonsillitis, constant problems for pediatricians, are associated with oxidative stress [21] and the first sign of oxidative stress may appear as neonatal hyperbilirubinemia [22]. High anxiety state individuals show an elevated reactivity to inhalations of carbon dioxide exhibited by panic disorder and increased heart rate, a form of pseudo-hypoxia. This term describes oxidation (rather than oxygen) deficiency. Since panic attacks are fragmented fight-or-flight reflexes, initiated by minor forms of stress, this indicates that oxidative inefficiency can lead to reactive hypersensitivity of brain mediated reflex action. Thus, panic attacks and perhaps other adaptive reflexes are biochemical in nature rather than ascribing them to psychosomatic etiology [23]. If oxidative stress is so common, there must be a logical explanation. The obvious place to look is the nature of the nutrition, particularly in children.

The role of thiamin deficiency (Td)

The symptoms of beriberi in its early stages of development are those of dysautonomia and can be used as a template in describing other forms of dysautonomia [24], particularly postural orthostatic hypotension syndrome [10]. Beriberi is now well recognized as due primarily to TD, though pure TD induced experimentally in human subjects produces typically diagnosed psychosomatic disease [25]. Although it is clear that thiamin is the major deficiency in beriberi, it probably involves deficiency of other members of the B complex [26]. TD in infancy can affect language development in childhood [27].

The paradox of high calorie malnutrition

Thiamin, being the rate limiting cofactor in the decarboxylating component of pyruvic dehydrogenase, stands astride the entry of glucose into the citric acid cycle and energy synthesis. The liking of sugar and fat is reportedly influenced by genotype [28].

The inordinate consumption of sweets, sweeteners and fats in many different forms as empty calories, particularly by children and adolescents, is extremely widespread throughout the United States. Refined sugars (sucrose, fructose) were absent in the diet of most people until recently in human history. Over indulgence is more decided by the pleasure of sweet taste and can be compared to drug addiction, since in animal studies intense sweetness surpasses cocaine reward [29]. Since ADHD affects nearly 10% of United States children and the prevalence has increased steadily over the past decades it is high time to study this relationship [30]. Although it has been shown that the thiamin status in adults depends on carbohydrate intake, there is no reason to suppose that this is different for children [31]. Indeed, according to our own clinical experience TD is widespread in both adults and children [10]. The term malnutrition usually conjures up a concept of starvation, the clinical situation that is entirely different than that of high calorie malnutrition. This form of malnutrition causes many different symptoms because of the thiamin deficiency effect in the limbic system and brainstem, resulting in sympathetic dominance of the resultant dysautonomia [10]. There may be enough thiamin for a normal diet, but the overload of empty carbohydrate

calories overwhelms the oxidative capacity of the cells, particularly in brain with its high metabolic rate. An overload of glucose in the presence of thiamin deficiency is extremely dangerous. Parenteral nutrition can lead to Wernicke encephalopathy, even if a high dose of thiamine is present in the administered I/V solution [32]. This may be because the concentration of glucose overwhelms oxidative capacity or because of a lack of magnesium that is also a cofactor to many of the thiamin dependent enzymes. Petechial hemorrhage in the brain of rats has been shown to be one of the results of TD [33].

In animal studies rats performed poorly on a standardized string test when subjected to a TD diet. The investigators found that TD induced an early functionally significant central muscarinic cholinergic lesion because of deficiency of acetylcholine [34]. Adrenal medullary reactivity increased substantially in rats during acute exposure to moderate hypoxia and sympathetic activity was markedly stimulated [35], suggesting that the pseudo-hypoxia of TD would do the same. There is also evidence for a central cholinergic effect from high dose thiamin [36].

The role of thiamine in fat and protein metabolism

Although thiamin deficiency has long been known to be related to carbohydrate metabolism, the pathogenesis is still unclear. However, the recent discovery of thiamine pyrophosphate as a cofactor to 2-Hydroxyacyl-Coa Lyase (HACL1) for alpha oxidation in the peroxisome [37] broadens the potential clinical effects of TD. A breakdown in alpha oxidation would have both upstream and downstream consequences in the brain [10]. We now have to accept the fact that thiamin is critical in the oxidation of simple carbohydrates and fats. Its role in the dehydrogenase of the branched chain amino acids and compromised formation of alpha-keto acids through the citric acid cycle makes it important in the reaction of transamination. This reaction uses the coenzyme pyridoxal phosphate, thus emphasizing the cooperation between vitamin B6 and thiamin. The products of transamination reactions depend on the availability of alpha-keto acids. The products usually are either alanine, aspartate or glutamate, since their corresponding alpha-keto acids are produced through metabolism of fuels. TD can result in reversal of transamination reactions [38].

Discussion

Relationship between high calorie malnutrition, metabolism and disease

A recurrence of beriberi in adolescents consuming simple carbohydrates has been reported in Japan [39]. Other non-caloric nutrient deficiencies have been described. For example, administration of coenzyme Q10 has been found to help patients with fibromyalgia [40]. An imbalance between caloric intake and non-caloric nutrients has been reported to influence the potential complications in AIDS patients [41]. Low vitamin D concentrations have been found in neonates who later developed autistic spectrum disorder [42]. Playing an "advergame" promoting energy-dense snacks contributes to increased empty calorie intake in children [43]. Early intervention with antioxidant supplementation has been suggested in the treatment of autism after studying the evidence for oxidative stress in some of these patients [44]. In spite of much skepticism that remains in attempting to approach these increasingly

common conditions with nutritional therapy, more research is being increasingly advocated [45].

This review emphasizes TD because of its known association with the oxidation of simple carbohydrates and fats. As cofactor to transketolase, occurring twice in the Hexose Monophosphate Shunt (HMPS), TD will compromise the production of reducing equivalents by the HMPS, one of its many functions and thus contributing to oxidative stress. Sweet foods and carbonated sweet beverages tend to dominate the diet of children and adolescents in particular. There is increasing evidence that TD is a major entity in the etiology of brain disease. It is the cause of Wernicke encephalopathy, generally associated with alcoholism, but has been reported in children, albeit usually with other predisposing factors [46]. TD activation of microglia is a major contributor to neurologic dysfunction [47]. The danger of glucose overloading in the presence of thiamin deficiency was shown by the original experiments of Sir Rudolph Peters in 1936 that he referred to as the cataract effect [48]. Experiments in thiamin-deficient rats showed that glucose loading precipitates acute encephalopathy [49]. Ingestion of empty calories might be compared analogically with a choked internal combustion engine, resulting in poor engine performance. Some form of stress, including viral infection, a relatively mild head injury or an inoculation initiated episodes of intermittent cerebellar ataxia in thiamin dependency [38]. Postural orthostatic tachycardia syndrome (POTS) has been reported following HPV vaccination [50]. POTS is indistinguishable from the early symptoms of beriberi, shown to be the cause of POTS in 5 adolescents in whom the symptoms were initiated immediately after HPV vaccination in 4 of them. It was hypothesized that the vaccination was a “stress factor” that precipitated POTS in the 4 individuals who were in a state of hitherto asymptomatic marginal high calorie TD, while POTS in the fifth individual was exclusively due to TD alone. All five of these individuals had been excellent students and athletes before they succumbed to POTS. They all responded partially to pharmaceutical doses of supplementary thiamin. Because of this it was hypothesized that high grade intelligence is more demanding of brain energy, thus increasing the risk from high calorie malnutrition [10]. Exercise, physical and mental work all demand cellular energy and can therefore be regarded as forms of “stress”. The collapse of elderly people shoveling snow is a possible example of cellular energy deficiency in the heart as it accelerates to meet the physical demand. Stress, defined as a physical or mental input stimulus, demands an adaptive response that requires cellular energy initiated and coordinated through the hypothalamic/autonomic/endocrine axis. The so-called reptilian system of the brain and brainstem are particularly sensitive to TD that would compromise organization of reflexive adaptation. We need to be reminded of the legacy of Hans Selye in his studies of stress and the associated evanescent changes in biochemical markers that he noted. The incidence of hypoglycemia, normoglycemia and hyperglycemia at different stages of the General Adaptation Syndrome (GAS) [51] were found to be remarkably similar, if not identical with (TD) and the GAS [52].

Oxidative stress can of course imply both too little oxidation and too much, the Yin and Yang of efficient use of oxygen. Thiamin is an oxidant, analogically to be compared with a spark plug in a car engine. Mother Nature, in her wisdom, has provided us with antioxidants like vitamins C and E, to be compared with a fireguard around an open

fire to catch the sparks of exuberant combustion. That is why Selye’s work on stress is so important because it requires energy consumption in all the cells involved in the complex adaptive mental and physical responses of the organism.

Conclusion

It is extremely difficult to get children and adolescents to understand the importance of nutrition. The entire culture inhibits it and the food industry laces everything with sugar because “sweetness” sells. Furthermore, whether we like to recognize it or not, it is addictive. Candy is encouraged from the earliest beginnings of life and used for rewards in school. There is little or no instruction or enforcement of nutritional discipline by parents. The symptoms generated by high calorie malnutrition in its early stages are not often recognized for their true etiology and are frequently referred to as psychological because of the high emotional component. Thiamin deficiency is central because of its importance in the metabolism of carbohydrates and fats, but vitamin supplementation has not yet entered the collective medical psyche. Because people believe in the taking of pills, it is easy to prescribe vitamin therapy, and it is remarkably successful in restoring function. By using this approach and making sure that the family understands the underlying mechanism, a child sometimes grows up with a better concept of his own health responsibility. He soon begins to be aware of his mental and physical improvement, a much better induction than seeing his manifest boredom from constantly being told what he needs to eat. The laboratory tests used presently will only discover the cellular effects of high calorie malnutrition. They cannot reveal the underlying biochemical lesion. Until medical thinking turns to the realization that high calorie malnutrition is a major cause of metabolic syndromes like Type 2 diabetes, affecting 29 million Americans, the status quo will remain.

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