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Is Eosinophilic Esophagitis a Sugar Sensitive Disease?

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Abstract

Eosinophilic esophagitis is an inflammatory condition, causing dysphagia, food impaction and chest pain. A minimum of 15 eosinophils per high power field by esophageal biopsy is necessary for diagnosis. It has become an increasingly important cause of gastrointestinal morbidity in the past two decades. A 14 year old boy had received a diagnosis of eosinophilic esophagitis elsewhere at the age of 8 years. His medical history had been thought for many years to be psychosomatic until endoscopy was performed. The only other positive laboratory study was eosinophilia. In spite of conventional therapy, none of which improved overall symptoms, esophagitis persisted and he had failed to gain weight and stature. Physical examination revealed many indications of autonomic dysfunction and an erythrocyte transketolase test indicated abnormal thiamine homeostasis. Treatment was started with intravenous infusions of water-soluble vitamins that included thiamine hydrochloride (THCL). Because the transketolase test became worse, THCL was replaced with thiamine tetrahydrofurfuryl disulfide (TTFD), with consequent improvement in transketolase and symptomatic response. There was a family history of alcoholism and the patient was addicted to sugar, suggesting a genetic risk to explain the abnormal thiamine homeostasis. Beriberi causes dysautonomia in its early stages. Inflammation is now known to be suppressed reflexly through the vagus nerve, itself dependent on acetylcholine. Abnormal motility of the esophagus has been reported in eosinophilic esophagitis. Failure of THCL to improve transketolase activity suggested a genetic failure in a thiamine transporter and its consequent correction with TTFD that does not require the thiamine transport system.

Keywords: Eosinophilic; Esophagitis; Inflammation; Thiamin homeostasis

Introduction

Eosinophilic esophagitis (EoE) is by far the most common form of eosinophilic gastrointestinal disease. It is a well-defined chronic atopic disease due to a T helper type 2 (Th2) inflammations, triggered often by food allergens. It is often poorly responsive to therapy and there is no commonly accepted long-term treatment [1]. It represents the most recent form of food allergy, and its control by avoiding offending foods has increasingly appeared as a therapeutic alternative to achieve and maintain remission [2]. In a town of over 700,000 inhabitants, a study showed a rapid increase of EOE in 10 years [3]. EoE has been reported with mediator complex subunit 12 (MED12) mutations [4]. Of 793 patients with EoE, 72% were male [5]. Of 173 patients with esophageal food bolus impaction, 27% were EoE [6]. Both spinal and vagal afferents of the esophagus appear to contribute to painful sensations [7] and its physiology is important in its motility [8]. The esophagus is dependent on acetylcholine for its neurological function and esophageal motor disorders have been demonstrated in EoE [9].

Case Report

A 14 year old boy had received a diagnosis of eosinophilic esophagitis elsewhere at the age of 8 years. His history began in infancy with recurrent ear infections and asthma. His many symptoms (Table 1), thought originally to be psychosomatic, confused the diagnosis until endoscopy was performed. Many laboratory studies had been consistently negative with the exception of eosinophilia and persistence of the esophageal pathology. Conventional treatments had no effect on symptomology. He had failed to gain weight and stature. Physical examination revealed severe hyperalgesia to light touch of the abdomen. Heart auscultation revealed a click suggestive of mitral valve prolapse. Patellar deep tendon reflexes were non responsive, even with the Jandrassic maneuver. Light stroking of the inner side of thigh and leg resulted in a very slow appearance of transient white dermatographia. Laboratory studies are shown in (Table 2). He was treated first with a course of intravenous infusions of water-soluble vitamins that included thiamine hydrochloride (THCl) (Table 3). Because of increasing abnormality of erythrocyte transketolase, thiamine tetrahydrofurfuryl disulfide (TTFD) was substituted for THCL with consequent improvement in transketolase and symptomology. Body weight at the beginning of treatment was 105 pounds, placing him in the 25th percentile. After one year of treatment his weight had increased to 122 pounds, placing him in the 50th percentile. His stature increased in the same time period from 64.5 inches to 68.5 inches, raising it from the 50th to the 75th percentile.

This boy was 18 years of age at the time of writing. Abdominal pain was variable and associated with visible contraction of abdominal muscles. Headaches, nausea, joint pain and fatigue appeared to be associated with food ingestion. Abdominal pain and need to urinate occurred spontaneously at night.

Discussion

Thiamine homeostasis

Thiamine Deficiency (TD) leads to the development of impaired energy metabolism and cerebral vulnerability [10]. It is only relatively recently that inherited defects in thiamine uptake, activation and the attachment of the active cofactor to target enzymes have been described [11]. Genetic variation in the SLC19A3 thiamine transporter may make a modest contribution toward genetic susceptibility to alcoholic dependence syndrome [12], possibly of importance in the family history of this patient. TD causes oxidative stress in brain mitochondria [13]. In a

Symptoms	9/6/2011	9/17/2012	Symptoms	9/6/2011	9/17/2012
Hyperalgesia	Yes	No	Dyspnea	Yes	No
Emotional instability	Yes	No	Infancy ear infections	n/a	n/a
Headaches	Yes	No	Hx/Asthma	n/a	n/a
Fatigue	Yes	No	Growth failure	Yes	Increased percentiles
Dizziness	Yes	No	Sound sensitivity	Yes	No
Panic attacks	Yes	No	Light sensitivity	Yes	No
Dysphagia	Yes	Yes	Long sleep latency	Yes	No
Chest pain	Yes	No	Awakening frequently	Yes	No
ADD/ADHD/OCD	Yes	Improved	Nightmares	Yes	No
Sleep cough	Yes	No			

Table 1: Symptoms described by a 14-year-old boy with eosinophilic esophagitis

Date	TKA	TPPE	WBC	Eosinophils	Hb	MCV	Platelets
	42-86 Mu	0-18%	4.1-13.01	15-500	12-16.9	78-98	140-400
9/6/2011	66	24%	5.2	940	14.6	87.2	254
2/3/2012	48	38%	5.9	1000	14	87.2	238
5/4/2012	53	13%	4.3	720	14.2	84.5	231

Table 2: Laboratory results from a boy with eosinophilic esophagitis

Sterile water	500 ml
Magnesium Chloride	2G
Potassium Chloride	5 meq
Dexpanthenol	500 mg
Folic acid	10 mg
Manganese Chloride	1 mg
Zinc Chloride	10 mg
Selenium	200 mcgm
Chromium	40 mcgm
Ascorbic acid	20 G
Adenosine 5' monophosphate	125 mg
Procaine 2% (pm)	100 mg
Pyridoxine Hydrochloride	100 mg
Hydroxocobalamin	1 mg
Vitamin B complex	206 mg
thiamine HCL	100 mg
riboflavin 5' phosphate Na+	2 mg
pyidoxine HCL	2 mg
dexpanthenol	2 mg
niacinamide	100 mg

Table 3: Water soluble intravenous vitamin infusion given to a boy with eosinophilic esophagitis

patient with atrophic beriberi there were 37 mutations in the SLC family of thiamine transporters [14]. TD in rats reduced acetylcholine-mediated relaxation and increased phenylephrine-mediated vasoconstriction in the aortas containing functional endothelium [15]. TD induces HIF1-alpha-mediated gene expression similar to that observed in hypoxic stress [16]. Deleting this factor in mice caused intensified hyperalgesia, suggesting its duality in pain regulation [17] and its possible bearing on the hyperalgesia/allodynia expressed by the patient. Sepsis in critically ill patients may be associated with TD and experimental TD resulted in oxidative stress and inflammatory response changes in mice [18]. In human tissues the total thiamine content is lower than in other animal species. The high sensitivity of humans to thiamine deficiency may be linked to this [19].

The Mayo Clinic has indicated that the best way of measuring thiamine deficiency is an assay of blood thiamine. Like magnesium, this may be misleading since it is its intracellular content that counts. Measuring the function of the thiamine dependent enzyme, erythrocyte transketolase activity before (TKA) and after the addition of thiamine pyrophosphate (TPPE) clearly indicates thiamine deficiency. The TKA increases within the normal range as the TPPE decreases after the administration of thiamine [20].

Empty calories

Peters was the first to recognize the relationship between thiamine and glucose. The pathology of the nervous system in thiamine deficient pigeons was similar to that in beriberi and Peters compared the respiration of TD pigeon brain cells with those that were thiamine sufficient. No difference occurred until glucose was added to the preparation when it became obvious that the production of carbon dioxide began immediately in thiamine sufficient cells whereas it did not in TD cells. Peters called this the catatorulin effect [21], thus emphasizing that ingestion of excessive simple carbohydrates, referred to as high calorie malnutrition, automatically

increases the need for this vitamin [22]. Thiamine pyrophosphate is a cofactor for 2-hydroxyacyl CoA lyase (HACL1) in the peroxisome, making alpha oxidation dependent on thiamine for fat metabolism, [23-25].

Inflammation

Action potentials originating in the vagus nerve regulate T cells that in turn produce acetylcholine, required to control innate immune responses [26]. Cholinergic neurons require acetyl-CoA, derived from pyruvate dehydrogenase, in order to synthesize acetylcholine [27], vital to the function of the esophagus [7]. It is hypothesized that TD resulted in deficiency of acetylcholine and failure of vagal suppression of inflammation as well as affecting esophageal motility in this patient.

Dysautonomia

Dysautonomia does not produce unique symptoms. It is the set of symptoms, taken together, that suggests that a dysautonomic state is present. Familial Dysautonomia (FD) was described in 1949, but Riley and Moore later went on to notice other dysautonomic syndromes [28,29]. Considering the critical dependence of the brain on glucose, it is capable of controlling its metabolism through the neuroendocrine axis. As a result, our understanding of diseases should be expanded to consideration of neural inputs in a concept of the pathophysiological process [30]. This patient exhibited a number of clinical phenomena that indicated autonomic dysfunction. Examination revealed the unmistakable mid systolic click of Mitral Valve Prolapse (MVP), associated with dysautonomia in 1979 [31]. Ninety-four patients were identified with MVP and 59 of them had low concentrations of red cell magnesium in erythrocytes [32]. Thiamin and magnesium work together as cofactors for thiamin dependent enzymes. Inhalation of carbon dioxide can induce in humans an emotion closely replicating spontaneous panic attacks [33], one of the symptoms recorded in the history of this patient. Since hypoxia results in sympathetic overdrive in animal studies [34] and TD causes oxidative imbalance described as pseudo-hypoxia, it is hypothesized that panic attacks are fragmented fight-or-flight reflexes, initiated by TD in this patient. His history of ADD/OCD, that had caused some diagnostic confusion before the diagnosis of EoE showed some clinical improvement as a result of his vitamin treatment. Oxidative stress has been reported in ADD/ADHD) [35]. In his early history, this patient had recurrent otitis media, a frequent disorder attributed to oxidative stress [36]. He also had experienced recurrent asthma, a disease that occurred in the history of a child with intermittent cerebellar ataxia due to thiamin dependency [37]. Of 1,180 patients with EoE, 160 (14%) were suspected of having aeroallergen-associated triggers by history and 32 (20%) had biopsy confirmation of this. Most of them were boys (84%). All had a history or examination consistent with allergic rhinitis and 75% had a history of asthma [38]. Several pathogenic mechanisms related to the nervous system have been reported in non allergic rhinitis, including dysautonomia [39]. Riley noted that failure of general body growth in Familial Dysautonomia appears to be a regular feature despite normal growth hormone [29]. Perhaps the delay in growth would not have been noticed in this patient if he had not had a phenomenal growth acceleration of 4 inches in height and a weight increase of 17 pounds in one year of treatment. The higher percentiles for both showed that this was an unusual acceleration of growth. It is unknown whether the mechanism for growth failure in FD is directly related to the genetic cause of the disease or because of the resulting dysautonomia. Since the dysautonomia in this patient appears to have been acquired in relationship to thiamine metabolism, it suggests that growth failure was related to the dysautonomia.

The role of thiamine derivatives

If TD was the primary biochemical lesion in this patient and its clinical effects started in infancy, an explanation is needed for the adverse response of erythrocyte transketolase to the administration of thiamine hydrochloride. The mechanism is unknown, but the clinical and laboratory response to thiamin tetrahydrofurfuryl disulfide (TTFD) suggests a genetically determined thiamin transporter problem. TTFD, an open ring form of thiamin, is reduced at the cell membrane non enzymatically. The thiazolium ring closes and an intact form of thiamin is introduced into the cell [40]. The early symptoms of TD are due to dysautonomia, frequently diagnosed as psychosomatic and easily reversible at this stage. It has been hypothesized that if these symptoms are not recognized and the biochemical lesion is allowed to continue because of failure to correct the TD, unpredictable complications may follow [41]. The role of genetic risk is expanding: for example, deficiency or dependency of thiamine pyrophosphate can cause a defect in pyruvic dehydrogenase [41], the dehydrogenase of branched-chain amino acids [42], or thiamine pyrophosphate kinase [43], although the clinical effects vary. All of these genetically determined conditions are treatable with pharmacologic doses of thiamine. Therefore the phenol typical expression of the disease is much less important than spotting the biochemical lesion. Due to genetic defects of this type, there may be many individuals who require higher amounts of thiamine, not typically provided by the diet. Thiamine precursor drugs can achieve these high blood levels and result in increased concentrations in the central nervous system [44,45]. An experiment in DBA/J2 mice suggested also that TTFD had a cholinergic effect [46]. An S-alkyl derivative of thiamine (benfotiamine) has had a beneficial effect on peripheral nerve function and inflammatory markers in type I diabetes [47] and significantly decreased pro-inflammatory mediators in liposaccharide-stimulated murine BV-2 microglia [48]. It has been shown, however, that this derivative is practically insoluble in water, organic solvents or oil, making it unsuitable for intravenous use. When solubilized in hydroxypropyl-beta-cyclodextrxin and given to mice, thiamine levels rapidly increased in blood and liver but there was no significant increase observed in the brain. These investigators proposed that benfotiamine only penetrates the cells after dephosphorylation by intestinal alkaline phosphatases, entering the bloodstream as S-benzoylthiamine that is converted to thiamine in erythrocytes and in the liver. This derivative should therefore be differentiated from true lipid-soluble thiamine disulfide derivatives and used appropriately [49]. It has been shown that TTFD inhibits the arachidonic acid cascade-line activation that would make it potentially more suitable for brain inflammation [50]. Thiamine pyrophosphate prevented cisplatin-associated oxidative stress, whereas thiamine did not prevent this [51]. TTFD rapidly increased thiamine activity in whole blood, erythrocytes, CSF and urine in normal and thiamine-deficient subjects. Such repletion was equal to that produced by parenteral, water-soluble thiamine hydrochloride or thiamine pyrophosphate [52], suggesting that this derivative might be useful in the correction of TD in the peroxisome where thiamine pyrophosphate is the cofactor required [23]. It is very unlikely that thiamine deficiency or abnormal homeostasis is the ultimate biochemical lesion in causing EoE. For example vitamin D deficiency has been associated with increased risk for severe asthma, challenge proven food allergy, severe atopic dermatitis and EoE [53]. It is hypothesized therefore that the biochemical lesion, whether it be genetically determined, nutritional in origin, or a combination of the two, represents the etiology for EoE that might be applicable to the etiology of other diseases.

Conclusion

Evidence has been presented that a single patient with EoE had abnormal thiamine metabolism as the underlying ultimate etiology. It has been hypothesized that acetylcholine deficiency, resulting from inefficient citric acid cycle function, interfered with the motility of the esophagus and failed to suppress the inflammatory reaction arising from food allergens. Since the vagus nerve supplies the intestine, it might explain the incidence

of eosinophilic enteritis as well as esophagitis. The incidence of TD related EoE might be differentiated from other cases by measuring the activity of erythrocyte transketolase (TKA) and the effect on this enzyme by the addition of thiamin pyrophosphate (TPPE).

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