

Recent Advances in Autism

Chapter 1

Etiology of Autism: Connecting the Dots

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Abstract

Although much has been written concerning the etiology of autism, now considered to be in epidemic form, none have yet been proven. If abnormal thiamin metabolism is represented as an outlay of manuscripts, a strong case for it as a common cause can be made by “connecting the dots”. It is hypothesized here that the legacy for its etiology may begin in pregnancy. Thiamin supplementation as a routine during pregnancy has been shown to virtually abolish the well-known pregnancy complications that affect both mother and fetus. Hyperemesis gravidarum has been shown to lead to the clinical and magnetic resonance imaging characteristics of Wernicke encephalopathy, a classical expression of brain thiamin deficiency. Autism rates have been established for each state. The percentage of infants who participate in the Women, Infants and Children (WIC) program for low-income families have significantly lower autism rates. Infants who were solely breast-fed had diets that contained less thiamin, riboflavin, and vitamin D than the minimum daily requirements. In a case-control study, 20 children who were fed thiamin-deficient formula in infancy had their language development in childhood affected. Evidence for abnormal thiamin metabolism in the etiology of SIDS has been published. Thiamin pyrophosphate was shown to be decreased in 24% of autistic children compared to healthy controls. Dysautonomia has been reported in autistic spectrum disorder (ASD) and is the clinical presentation of thiamin deficiency disease in its early stages. Thiamin triphosphate, still a largely unknown entity in normal physiology, occurs in rat brain mitochondria and is coupled to the respiratory chain. A paradoxical increase in vitamin B12 and folate has been reported in maternal plasma at birth, with an increased risk of ASD in the infant. This paradoxical increase has also been reported in anorexia nervosa, itself associated with thiamin deficiency. Two children, who had recurrent episodes of febrile cervical lymphadenopathy that were prevented by thiamin supplementation, also had elevated concentrations of

blood folate and B12 that fell into the normal range after thiamin ingestion. Autistic children excreted higher levels of sulfate, sulphite and thiosulphate, but reduced levels of thiocyanate, indicating decreased rhodanese activity and cyanide toxicity. Low expression of rhodanese predicts mortality in hemodialysis patients, known to be at risk for thiamin deficiency. Japanese researchers showed that pretreatment of mice with thiamin propyl disulfide (TPD) gave some protection from cyanide toxicity. An uncontrolled pilot study has been reported in which some clinical benefit accrued from treatment of a small group of ASD children with thiamin tetrahydrofurfuryl disulfide.

Keywords: Autism; Sulfur metabolism; Cyanide; Thiamin

1. Introduction

Supplementary thiamin, starting as early as three months of gestation, virtually abolishes the complications of pregnancy including hyperemesis and toxemia [1]. The author, an American practicing OB/gynecologist, relates a few cases “that demonstrate how thiamin very rapidly removed mothers and their infants from the jaws of almost certain death, achieving astounding beneficial effects never before obtained in the United States”. He also describes his failure to find a university physician who would take him seriously in order to prove the issue as a research objective. A nutritional epidemiology in hyperemesis gravidarum-induced Wernicke’s encephalopathy is an underestimated condition. Five cases were recently reported with a classic triad of encephalopathy, ataxia and ocular signs in four of them. Magnetic resonance imaging was abnormal in all five patients [2]. One would expect thiamin deficiency (TD) in the mother to affect the development of the fetus. It has been published that TD is surprisingly common in pregnancy. An ecologic study design linked the possible cause of autism to nutrition by creating autism rates for the 50 states of America and comparing them with published measures of infant nutrition such as duration of exclusive breast-feeding and participation in the Women, Infants and Children (WIC) program. The states with the highest WIC participation have significantly lower autism rates ($p < 0.02$). Infants who were solely breast-fed had diets containing less thiamin, riboflavin and vitamin D than the minimum daily requirements and there was a direct positive correlation with the increasing percentage of women exclusively breast-feeding from 2000-2004 ($p < 0.001$) [3]. Twenty children who had been exposed to TD in infancy, due to feeding a soy-based formula that was accidentally deficient in thiamin, were compared with 20 children fed with a thiamin sufficient formula. Study and control groups differed significantly in expressive communication, auditory comprehension, language subscales and evaluation for autistic spectrum disorders (ASD). The authors concluded that TD in infancy could produce a legacy of failed development in early childhood [4]. Although the cause of sudden infant death (SIDS) has been explained by positioning of the infant in the crib, it has not by any means fully explained all causes. Evidence for abnormal thiamin metabolism has been published [5] and the finding of vitamin deficiency in breast milk [3] suggests the possibility of TD as an important source of etiology. Twenty-seven children with

autism were compared with 21 age-matched healthy control children. Plasma thiamin and thiamin monophosphate concentrations were similar in both groups. Thiamin pyrophosphate, the active cofactor form of the vitamin, was decreased 24% in the autistic children compared with healthy controls [6]. In the case histories of a mother and her two children, the mother was a recovered alcoholic. Both children had symptoms of ASD. All three individuals had intermittently abnormal erythrocyte transketolase studies that correlated with symptoms of TD dysautonomia. Symptoms improved with diet restriction and supplementary vitamin therapy, but relapse occurred with ingestion of sugar, milk or wheat [7].

A three-year-old girl with ASD has been reported in whom the etiology was considered to be from the maternal use of a thiaminase containing herbal remedy and ethanol during pregnancy. The mother reported a significant weight loss during the pregnancy and a deficiency of B-complex vitamins. The authors suggest that TD could have been potentiated by thiaminase activity compounding the TD effect of ethanol [8].

2. Paradoxical Increase of B12 and Folate

Extremely high maternal plasma folate and B 12 levels at birth were associated with ASD risk [9]. A paradoxical increase of plasma vitamin B12 and folate with disease severity was reported in anorexia nervosa [10], itself associated with thiamin deficiency [11]. An unusual clinical situation was reported in 1980. Each of two boys had recurrent episodes of febrile lymphadenopathy that had been treated for several years as infections. One had an abnormal erythrocyte transketolase test. The other had a test that had been reported as depicting thiamin triphosphate deficiency [12]. Both of these boys had a paradoxical increase of blood folate and B 12 and both responded clinically to therapy with thiamin that prevented their recurrent lymphadenopathy episodes. The concentrations of folate and B 12 fell into the normal range after thiamin therapy. In one child, after discussion with his reluctant mother, the thiamin was withdrawn. Several weeks later he had another episode of febrile lymphadenopathy. The blood folate and B 12 were increased. They decreased to normal again with thiamin restoration [13].

3. Sulfur Metabolism in Autism

In a controlled study, autistic children excreted higher levels of sulfate, sulfite and thio-sulfate, but reduced levels of thiocyanate [14]. This indicates deficient activity of the enzyme rhodanese that catalyzes the detoxification of cyanide to thiocyanate [15]. Experiments in mice have stressed the importance of the rhodanese reaction for cyanide detoxification [16]. Silencing of the rhodanese gene caused not only a proportional decrease of 5S rRNA import but also a general inhibition of mitochondrial translation, indicating the functional importance of the imported 5S rRNA inside the organelle [17]. Fujiwara and associates predicted that al-lithiamin, a naturally occurring disulfide derivative of thiamin in garlic, might prove to be ef-

fective in the prevention of potassium cyanide intoxication. He and his associates performed a series of experiments using thiamin propyl disulfide (TPD), a synthetic derivative of thiamin. After mice had been treated with 1 mg of TPD intravenously, they were administered potassium cyanide in a dose of 150 μg per 10 g body weight by stomach tube. In 51 mice treated with both KCN and TPD, only six died (11.7%), whereas the death rate in 51 mice treated only with KCN was 36 (70.6%). Further experimentation proved that TPD increased the activity of rhodanese [18].

4. Cyanide Intoxication

In Mozambique, large epidemics of the cassava-associated paralytic disease, Konzo have occurred at times of agricultural crisis during the cassava harvest. When measured, serum or urinary thiocyanate concentrations, indicative of cyanide poisoning, have been high [19]. Thiamin is known to be rendered inactive when the sulfur in its thiazole moiety is combined with hydrogen cyanide, thus stimulating a hypothesis that thiamin deficiency represents part of the etiology in this disease [20]. Leber described a particular type of hereditary optic atrophy in 1871. In many cases the severity of the disease is related to tobacco smoking. Increased cyanocobalamin blood levels in patients and increase cyanide blood levels support this hypothesis [21]. The disease presented in a patient as the retinal phenotype, together with a novel point mutation in the SLC 19 A2 gene that co-segregated with thiamin responsive megaloblastic anemia syndrome [22]. Dialysis patients are at risk for thiamin deficiency. Of 30 dialysis patients with altered mental status, 10 patients had thiamin deficiency, nine of whom recovered with thiamin treatment [23]. Compared to healthy subjects, hemodialysis patients showed significantly lower rhodanese mRNA and protein expression [24]. Abnormal cyanide metabolism is involved in the development of uremic neuropathy [25]. Although far removed from the diagnostic category of autism, this illustrates the unpredictable nature of the biochemical lesion caused by TD, represented in many different disease conditions.

5. Conclusions

Evidence has been produced that thiamin deficiency plays a large part in diseases associated with pregnancy, birth and the early development of the infant. One has only to look at the head circumference growth chart of the infant in the first six months of life to see the incredible growth which reflects the rapidly increasing size of brain. The energy requirement for this is huge and the position of thiamin as cofactor to the first enzyme in the pyruvic dehydrogenase complex emphasizes its vital importance in energy metabolism. Together with magnesium and other members of the B complex, their role is the production of ATP. The role of thiamin triphosphate is also still not well defined, but is important in energy metabolism [26]. All other biochemical pathways that result in total function consume energy in relationship to genetically determined structure. There is also increasing evidence pointing to the possibility

that gestational and early childhood vitamin D deficiency causes some cases of autism [27]. The author reported that high-dose vitamin D improved the core symptoms of autism in about 75% of autistic children. A few of the improvements were said to be remarkable. An uncontrolled pilot study showed that eight of 10 autistic children improved clinically by administration of thiamin tetrahydrofurfuryl disulfide [28]. Whether other nutritional deficiencies have a part to play is questionable, depending on changes in research perspective that accentuates the part played by epigenetic mechanisms rather than an almost exclusive approach to fixed gene structure. Nutritional research would lead to a consideration of gene/nutrient interaction that could result in prevention.

6. References

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