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Sudden infant death syndrome and abnormal metabolism of thiamin

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ABSTRACT

Although it has been generally accepted that moving the infant from the prone to the supine position has solved the problem of sudden infant death syndrome (SIDS), it has been hypothesized that this is an insufficient explanation and that a mixture of genetic risk, some form of stressful incident and marginal brain metabolism is proportionately required. It is suggested that each of these three variables, with dominance in one or more of them, act together in the common etiology. Much has been written about the association of thiamin and magnesium but the finding of extremely high concentrations of serum thiamin in SIDs victims has largely caused rejection of thiamin as being involved in the etiology. The publication of abnormal brainstem auditory evoked potentials strongly suggests that there are electrochemical changes in the brainstem affecting the mechanisms of automatic breathing and the control of cardiac rhythm. The brainstem, cerebellum and limbic system of the brain are known to be highly sensitive to thiamin deficiency (pseudo-hypoxia) and the pathophysiology is similar to a mild continued deprivation of oxygen. Little attention has been paid to the complex metabolism of thiamin. Dietary thiamin requires the cooperation of the SLC19 family of thiamin transporters for its absorption into cells and recent information has shown that transporter SNPs may be relatively common and can be expected to increase genetic risk. Thiamin must be phosphorylated to synthesize thiamin pyrophosphate (TPP), well established in its vital action in glucose metabolism. TPP is also a cofactor for the enzyme 2-hydroxyacyl-CoA lyase (HACL1) in the peroxisome, emphasizing its importance in alpha oxidation and plasmalogen synthesis in cell membrane physiology. The importance of thiamine triphosphate (TTP) in energy metabolism is still largely unknown. Thiamin metabolism has been implicated in hyperemesis gravidarum and iatrogenic Wernicke encephalopathy has been reported when the patient is treated with hyperalimentation, in spite of the pharmaceutical doses of thiamin in the intravenous fluid. Defective glucose metabolism, the vital fuel for energy synthesis, particularly in brain, must affect the developing fetus and the pattern of subsequent neonatal health. Sudden death in an apparently healthy infant, occurring at 3–4 months, has long been known to result from feeding the infant with thiamin deficient breast milk. The early investigators of the cause of beriberi considered that this form of sudden death was pathognomonic of the infantile form of the disease.

Introduction

Many theories have been proposed for the etiology of the sudden infant death syndrome (SIDS). Severely premature infants are at risk because of incomplete development of life supporting systems [1]. The neurotrophin brain-derived neurotrophic factor, required for the appropriate development of the central respiratory network, has been implicated [2]. Laryngeal inflammation has been found in some cases of SIDS [3]. Neuroanatomical and functional changes in the inferior colliculus have been reported [4]. Guidelines for preventive care have been published [5–7]. The underlying mechanism has still not been described.

Thiamin deficiency

As long ago as 1944, the clinical description of sudden death in breastfed infants of thiamin deficient Chinese mothers was reported as infantile beriberi. During the Japanese invasion of Hong Kong the rice ration to the mothers was severely restricted and this form of sudden death disappeared, only to reappear again when *ad lib* rice was restored after the Japanese left the colony. The epidemiology of this kind of sudden death in 3–4 month old infants, often considered to be the healthiest in the family, was so similar to "cot death" as it was then described in England, that Fehily proposed thiamin deficiency as its cause [8]. A very important

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etiological clue lies in the fact that sudden infant death disappeared when rice rationing was instituted in the mothers. Beriberi still occurred in infants breast fed by their starving mothers but it was less acute and the clinical presentation was completely different.

It was this kind of information that led Read and his group in Australia to study the relationship of thiamin deficiency as the underlying cause of SIDS [9]. These investigators had found an unexpectedly high incidence of thiamin deficiency in groups of mothers and infants by the measurement of erythrocyte transketolase, selected for apparent health. The incidence of thiamin deficiency was high in "near-miss" SIDS infants and their mothers and in siblings of SIDS. The thiamin deficient infants had a high familial incidence of SIDS deaths. They stated that apparently thriving infants with thiamin deficiency can sometimes die unexpectedly and that thiamin status deserved more attention in clinical practice and research [10]. They also reported a wide range of clinical findings in 58 near-miss SIDS infants [11].

Interest arising from these studies was quickly refuted. Post mortem heart blood aspirates from 24 consecutive SIDS victims revealed no differences in an erythrocyte transketolase activity with those in infants dying from other causes [12]. In 1982 it was reported that serum thiamin concentrations in 233 infants dying from SIDS were significantly higher than those found in 46 infants dying from other explicable causes [13]. Subsequently thiamin serum levels from 12,613 infants showed a fivefold increase in SIDS victims as compared with controls. The author stated that the interpretation of thiamin screening data required further detailed investigation [14]. Thiamin deficiency and sudden death again received some comment in 1990 [15] and infantile beriberi was recognized as the main cause of death, accounting for 40% of all infant mortality in a refugee population in Thailand [16].

Magnesium dependent metabolism in SIDS

The biochemical relationship between thiamin and magnesium is well known and the clinical effects of deficiency of one overlaps the other, each or both collectively being responsible for many symptoms [17]. Even though magnesium is by far the least abundant electrolyte in serum, it is extremely important, together with thiamin for the metabolism of many enzymes that govern energy metabolism. Its absorption into cells depends on a large number of variables, absence of even one leading to its deficiency [18]. In 1992 it was hypothesized that SIDS occurred as a shock-like event in a stressed infant with congenital or acquired magnesium deficiency with respect to calcium or with genetically determined high magnesium requirements [19]. The same author cited cases linking respiratory distress syndrome and SIDS with magnesium deficiency shock [20]. At peak incidence of SIDS between two and four months the vitreous magnesium concentration is high and there is little change despite the extremes in dietary magnesium [21]. It was concluded that magnesium deficiency was at least one major unifying factor that explained increased SIDS in the prone sleeping infants, a position that stressed the infant [22]. Gestational magnesium deficiency results in suboptimal growth and development of the fetus and reduced survival in the infant [23]. Durlach and associates also claimed magnesium deficiency in the etiology of SIDS [24–26] and it has been shown to produce an inflammatory lung reaction in mice that suggested a similar mechanism in SIDS [27].

Brainstem auditory evoked potential (BAEP)

Although a number of papers were published more than 30 years ago on BAEP studies in SIDS, there has been little interest in recent years. Fifteen infants at risk for sudden infant death syndrome by clinical criteria were tested by BAEP. All of them demonstrated abnormalities on two or more of the seven criteria employed to assess results [28]. Thirty-six infants identified as infant apnea syndrome (IAS) and 25 controls with comparable age distribution were evaluated by BAEP. Fifteen IAS patients had bilateral abnormalities. Of 21 IAS patients with unilateral abnormalities, 17 of them had abnormalities on the left side. Significant differences between normal controls and IAS infants were found for peak latencies I, III and V and amplitude III [29]. BAEP responses were recorded from 63 near-miss SIDS infants, 26 siblings of SIDS and 67 control infants between 0 and 30 weeks post-term. The majority of BAEP records from both groups of infants had normal form and inter-peak intervals. The distributions of VIIn intervals for both groups of at risk infants were significantly different compared with those of control infants. The authors concluded that although BAEP is not suitable for identifying infants at risk of SIDS, they suggested that maturation of the overall neural processing in the brainstem may be delayed [30].

The three circles of health [17]

It has been hypothesized that SIDS requires a genetic risk factor, coupled with some form of stress and marginal malnutrition, either in the infant, the mother, or both [31].

Genetics

Table 1 presents the results of genomic analysis on six adolescent subjects, all of whom were suffering from postural orthostatic hypotension syndrome (POTS). Subjects 1 and 2 acquired POTS immediately after receiving HPV vaccine and were then found to have an abnormal erythrocyte transketolase thiamin pyrophosphate effect (TPPE), proving thiamin deficiency. Subject 3 also had thiamine deficient POTS but had not received the vaccine. Subjects 4–6 had the genomic analysis, but had not been tested with the erythrocyte transketolase test. The interest lies in the fact that the SNPs were found in the SLC family of thiamin transporters. This small number of cases suggests that POTS is early beriberi from dietary thiamin deficiency or that a stress factor such as a vaccine can precipitate the symptoms in an individual who is in a state of asymptomatic marginal malnutrition prior to the vaccination [17].

It is only relatively recently that inherited defects in thiamin uptake, activation and the attachment of the active cofactor to target enzymes have been described [32]. Despite normal thiamin serum levels, a patient with atrophic beriberi responded quickly to intramuscular thiamin treatment. He was found to have 37 mutations, 29 in SLC19A2, 6 in SLC19A3, and 2 in SLC25A19 [33].

Genotyping of two single-nucleotide polymorphisms (SNPs) in genes of importance for respiratory control was studied in SIDS. For rs701265 in P2RY1, homozygous G carriers were significantly more frequent in the control group. The authors concluded that allele G provides a protective effect in events of ventilatory stress and recommended further studies to further investigate functional polymorphisms in the genes involved in respiratory control [34].

Table 1
SNPs recorded from six adolescents, all of whom had postural orthostatic hypotension syndrome (POTS) (see text).

Subject	Gardasil	POTS	TPPE (%)	SLC19A2	SLC19A3	SLC25A19
1	Yes	Yes	49	5	14	1
2	Yes	Yes	48	9	16	6
3	No	Yes	25	9	16	6
4	Yes	Yes	–	5	17	0
5	Yes	Yes	–	5	8	0
6	Yes	Yes	–	9	15	6