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Research Article

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Functional Vitamin B12 Deficiency in Sleep Disorders in Children

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Abstract

It has been known for some time that an absolute deficiency in vitamin B12 is often associated with sleep disorders in children. The mechanism for the sleep disorders, though, is not generally stated. We have identified a cohort of children, who suffered from long term sleep disorders, who were characterized by elevated serum vitamin B12 levels. Retrospective Organic Acid Analysis of the urine of the children identified many markers of functional vitamin B12 deficiency, despite the elevated serum B12. As such the children may have paradoxical B12 in which serum levels of vitamin B12 were normal or elevated, however they had elevated markers of functional vitamin B12 deficiency. This functional vitamin B12 deficiency appeared to be the result of functional vitamin B2 deficiency. The mechanism is discussed. Effective treatment required resolution of the functional vitamin B2 deficiency as well as high dose vitamin B12 administration.

Keywords: Autism; Organic Acids Test; Sleep Deficiency, Vitamin B12; Cobalamin; Paradoxical B12 Deficiency.

Introduction

Sleep problems are a common complaint in young children and adolescents, and are more frequent in those with autism spectrum disorder (ASD) [1-5]. Correctly diagnosing and treating sleep problems in children is very important as without treatment it can lead to other problems such as such as inattention or irritability and reduced cognitive performance and neurodevelopmental problems in children [6-11]. Several studies have suggested that overt vitamin B12 deficiency may have a role in those with poor sleep habits [12, 13]. The mechanism for this, is not though well described.

Melatonin is the main biochronologic molecular mediator of circadian rhythm and sleep. Melatonin deficiency is associated with disordered sleep, and several studies have shown that sleep patterns can be improved through treatment with melatonin [1,14-17]. Biochemically there is an essential link between levels of functional vitamin B12 and the production of melatonin. The last step in production of melatonin is the methylation of the melatonin precursor N-Acetyl-serotonin by the S-Adenosyl-methionine-dependent enzyme, Hydroxy-indole-O-methyl-transferase (HIOMT), as such the reaction is one of the 200 or so methylation reactions in the body that are critically dependent upon the methylation cycle, in which MethylCo (III)B12 plays an essential role. Hence, in either an absolute deficiency of vitamin B12, or a functional deficiency of vitamin B12, the rate of methylation goes down and so the production of melatonin would be expected to be reduced.

We have used the Urinary Organic Acids test to examine the functional vitamin B12 status of a group of 10 children with clinically defined sleep disorders, Individual data is plotted.

Results

Retrospective data analysis of OAT data from a cohort of 10 children who had a history of sleeping disorders, was performed in which specific markers of vitamin B12 deficiency revealed anomalously high markers of functional vitamin B12 deficiency. Representative data is presented below for this cohort and is compared to a cohort of normal individuals (n=45, Control). These individuals also had elevated organic acids typical of those found in functional vitamin B2 deficiency, suggesting that the observed functional B12 deficiency may be a consequence of the reduced levels of functional vitamin B2. Hence, there were increased levels of glutaric acid, adipic acid and suberic acid. In addition, these individuals had a functional deficiency in vitamin B12 (see Figures 1 to 3; Table 1). Thus, there were increased levels of MMA, a marker of Adenosylcobalamin (Adenosyl B12) deficiency (See Figure 1), as well as greatly increased levels of the neurotransmitter metabolites, HVA, VMA, 5HIAA, QA and KA (Table 1), and pyroglutamic acid, which are characteristic of Methylcobalamin (Methyl B12} deficiency. Increased levels of metabolites, appeared to be correlated with levels of glutaric acid, a marker of functional B2 deficiency (Figures 1, table 1, 2)

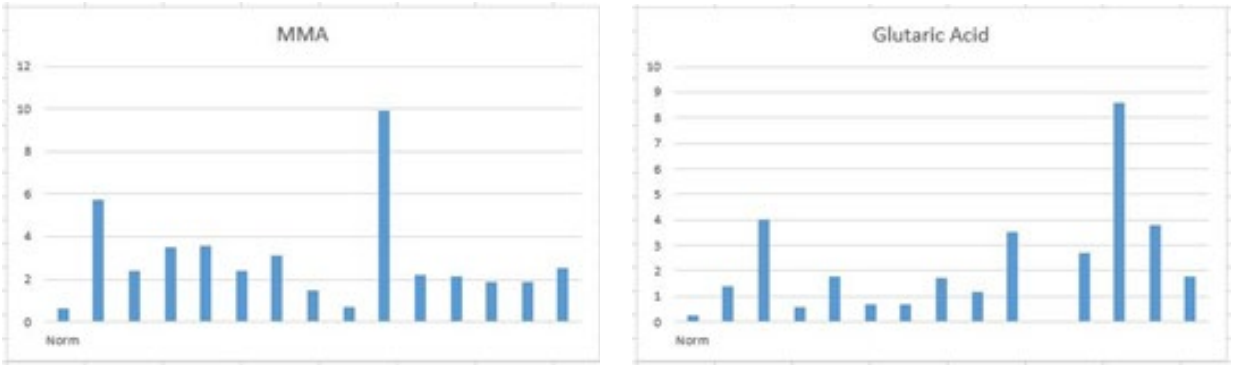

Figure 1: Individual Methylmalonic acid (Left) and Glutaric acid (Right)

Table 1: Functional Differences in Vitamin B12 -deficiency related markers between Healthy individuals (Control) and those with Chronic Sleep Disorders (CSD). Data is presented as Mean ± STD

Marker	Control	CSD
Methyl Malonic Acid	0.66 +/- 0.21	3.1 ± 2.28
Homovannilic Acid	1.5 ± 1.07	7.86 ± 2.45
Vanillyl Mandelic Acid	1.01 ± 0.46	4.19 ± 1.65
5HIAA	0.52 ± 0.55	4.16 ± 1.83
Quinolinic Acid	1.12 ± 0.65	11.25 ± 4.35
Kynurenic Acid	0.45 ± 0.27	1.71 ± 1.13
QA:KA	3.12 ± 2.05	11.1 ± 9.6
Pyroglutamate	17.04 ± 9.93	60.1 ± 30.1

Table 2: Functional Differences vitamin B2 – deficiency associated OAT markers in normal individuals and those with Chronic Sleep Disorders (CSD). Data is presented as Mean ± STD Apart from the increased level of glutaric acid observed in the children with Chronic Sleep Disorders, many other markers typical of functional vitamin B2 deficiency were also elevated, including lactic acid, ethylmalonic acid, methylsuccinic acid, adipic acid, suberic acid, and succinic acid.

Marker	Control	CSD
Lactic Acid	14.3 ± 16	97.4 ± 155.5
Ethylmalonic Acid	2.09 ± 1.21	4.93 ± 2.84
Methylsuccinic Acid	1.31 ± 1.1	3.3 ± 1.4
Adipic Acid	1.28 ± 1.18	4.95 ± 3.46
Suberic Acid	1.68 ± 2.11	7.78 ± 6.84
Glutaric Acid	0.218 ± 0.13	2.31 ± 2.2
Succinic Acid	0.218 ± 0.13	57.5 ± 59.7
Pyroglutamate	17.04 ± 9.93	60.1 ± 30.1

Discussion

Melatonin produced in the pineal gland is the primary regulator of sleep patterns as part of the normal circadian cycle [18-20]. Lack of production of pineal melatonin has been associated with circadian rhythm-related sleep disorders, insomnia in children, particularly those with neurodevelopmental disorders, and those with poor (non-restorative) sleep quality. Production of melatonin in body, involves a multi-step synthesis initiated by the uptake of tryptophan into the cell followed by its conversion to 5HTP, then serotonin, and then N-Acetyl-Serotonin. The final step in the synthesis of melatonin involves the methylation of N-Acetyl-Serotonin by the S-Adenosylmethionine dependent enzyme, Hydroxy-indole-O-MethylTransferase (HIOMT) (Figure 2.).

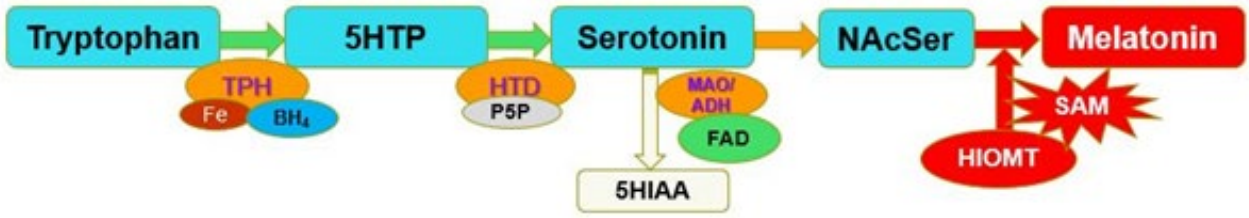

Figure 2: Synthesis of Melatonin from imported Tryptophan. TPH – Tryptophan hydroxylase, 5TP- 5-hydroxytryptophan, HTD – 5-hydroxytryptophan decarboxylase, 5HIAA – 5-hydroxyindole acetic acid, MAO – Monoamine oxidase, NAcSer – N-acetylserotonin, HIOMT – Hydroxyindole – 0- Methyltransferase, SAM – S-adenosylmethionine, FAD – Flavin-adenine dinucleotide, P5P pyridoxyl-5-phosphate.

In situations of low functional methyl B12, production of S-Adenosylmethionine (SAM) is reduced, with the result that levels of melatonin drop, which is accompanied by an increase in the levels of serotonin, and its break-down product 5-hydroxy-indoleacetic acid (5HIAA). In order to increase the likelihood of melatonin production the cell imports more tryptophan, which is then broken down into Quinolinic Acid (QA) and Kynurenic Acid (KA) (Figure 3). (See Table 1.)

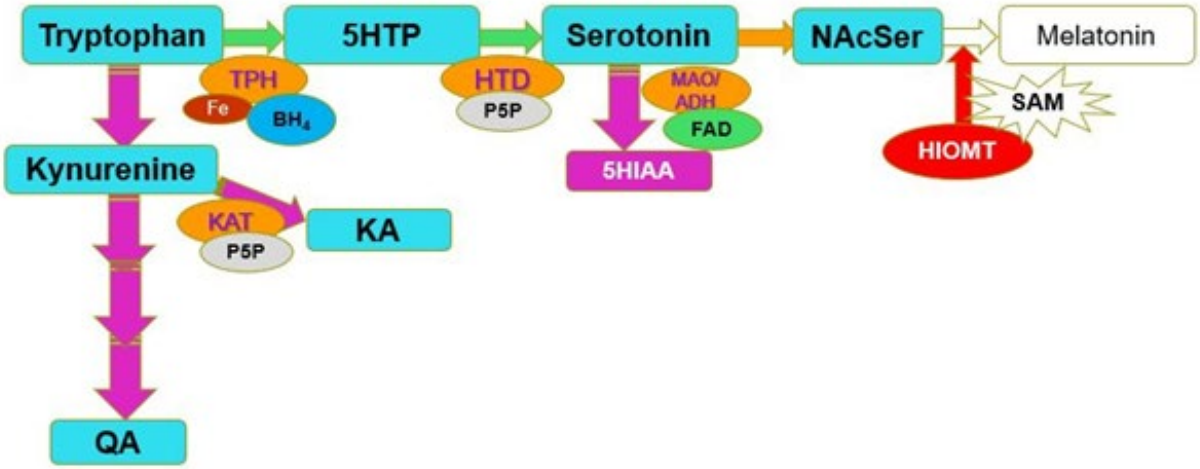

Figure 3: Alteration in the Kynurenine Pathway in functional Methyl B12 deficiency. KAT – kynurenine-aminotransferase, KA – Kynurenic acid, QA – Quinolinic Acid

In individuals who have reduced levels of vitamin B12 in serum, the mechanism of sleep disorders should be relatively easy to ascertain, however in functional vitamin B2 deficiency, serum B12 levels may be normal to high, a condition of "Paradoxical B12 deficiency" and as such functional B12 deficiency is harder to ascertain [21].

Measurement of many markers in OAT indicated moderate to severe vitamin B12 deficiency in all individuals with a diagnosis of chronic sleep disorders, as analysed in the current study.
Levels of MMA, the "traditional" marker of Adenosyl B12 deficiency, were increased to as much as five times that of healthy individuals (Figure 1. Table 2). Similarly, many less "traditional" markers associated with Methyl B12 deficiency were also elevated including KA, QA, 5HIAA, VMA, and HVA (Table 1). In addition, pyroglutamate, a standard marker of intracellular methyl B12 deficiency was also. The primary role of Methyl B12 inside the cell is the maintenance of the methylation cycle and the continued production/regeneration of methionine for the subsequent production of S-Adenosylmethionine, the ubiquitous methyl-donor for methylation. Functional methyl B12 deficiency through the reduced production of S-Adenosylmethionine, has particular relevance to two methylation reactions in the body, the production of Epinephrine (Adrenalin) through the methylation of Norepinephrine by the enzyme Phenylethanolamine-N-Methyl transferase (PNMT) viz: Norepinephrine + SAM (PNMT) => Epinephrine and the production of Melatonin by the methylation of N-Acetylserotonin by the enzyme Hydroxy-Indole-O-methyl transferase (HIOMT). Accompanying the reduced methylation inside the cell, overproduction of serotonin in Chronic Sleep Disorders would occur due to lower production of SAM, and thereby result in reduced synthesis of melatonin.

It is intriguing to speculate that it is the original functional vitamin B2 deficiency that subsequently caused the functional vitamin B12 deficiency. In this case, the effect would be indistinguishable from absolute B12 deficiency in symptoms, but would be dismissed by the clinician due to there being normal or elevated serum vitamin B12 levels.

The current study supports the notion that the functional deficiency in vitamin B2, observed in the test cohort, leads to an expected deficiency in functional vitamin B12, which would then result in reduced melatonin and poor sleep patterns in the children.

The current studies fill a critical gap in the understanding of the mechanism behind the factors involved in chronic sleep disorders and therefore provide a potential mechanism for the treatment of the condition.

Methods

Study Sample

Data analysis was carried out under the Australian National Health and Medical Research Council guidelines (NHMRC). Under these guidelines, all data was deidentified and steps were taken to ensure the anonymity and confidentiality of the data. Deidentification has consisted of absolute anonymity and confidentiality of the data, such that no specifics such as gender, ethnicity, Country of Origin, etc is associated with any data point in the study.

A retrospective data analysis was performed upon data submitted to us for analysis from a cohort of 10 children aged between 10 and 30 months of age who attended a sleep clinic in Adelaide South Australia. No selection was made in the acceptance of data, with no data being rejected. Metabolic analysis was performed on Organic Acid Test Data (316 sets, Great Plains Laboratories, Lenexa, KS, USA), which had been submitted to us for interpretation. This data, (that from those with CSD) was compared to that from persons who were healthy, and who had no previously identified health condition (Control). Data was tabulated in an Excel spreadsheet, and processed using the standard plotting functions in the program. Individual data is plotted in bar graphs and tabulated (see Figure 1 and Table 1 and 2) [22].

Conclusions

Retrospective analysis of urinary Organic Acids in young children with prolonged sleeping disorders have identified two main areas of metabolic insufficiency, functional vitamin B2 deficiency and functional vitamin B12 deficiency. Initiation of the functional vitamin B2 deficiency with resultant vitamin B12 deficiency appears to have occurred due to inadequate intake of Iodine, Selenium, and/or Molybdenum in the mothers during pregnancy. The subsequent functional vitamin B2, then results in functional B12 deficiency, in the mothers and newborn children. Examination of neurotransmitter metabolites in the urine of the children suggest that the functional B12 deficiency particularly in methyl B12, thereby results in reduced production of the sleep-inducing hormone, melatonin. The functional B12 deficiency can often be missed as paradoxically serum B12 may be normal or higher than normal and as such is over-looked by the clinician. Resolution of the condition involves establishment of functional vitamin B2 sufficiency as well as high dose parenteral administration of vitamin B12.

Compliance with Ethical Standards

We declare that there are no potential conflicts of interest

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