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Research Article

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Functional Vitamin B12 deficiency in Chronic Fatigue Syndrome

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Abstract

Chronic Fatigue Syndrome/Myalgic encephalomyelitis (CFS/ME) is a complex chronic condition, characterized by periods of extreme fatigue, for which an underlying medical condition has previously not been identified. Many of the symptoms of CFS/ME, are, though, similar to those with vitamin B12 deficiency. In contrast to nutritional vitamin B12 deficiency, the majority of individuals with CFS have been shown to have functional vitamin B12 deficiency as well as functional vitamin B2 deficiency. This functional B12 deficiency occurred despite elevated serum B12 being found, and hence presents as Paradoxical vitamin B12 deficiency. As such, CFS due to functional B2 deficiency presents as Paradoxical B12 deficiency. Maintenance of vitamin B12 functional activity is critically dependent upon functional B2 sufficiency, and hence resolution of CFS there must first be resolution of functional B2 deficiency before treatment with vitamin B12 can be effective.

Keywords: Chronic Fatigue Syndrome; Organic Acids Test; Vitamin B12; Cobalamin; Paradoxical B12 Deficiency.

Introduction

Chronic Fatigue Syndrome is a condition, of varying complexity, with the most common symptom being severe fatigue lasting longer than six months, which is accompanied by a range of additional physical symptoms including post-exertional malaise; muscle pain, polyarthralgia, unrefreshing sleep, headaches, impaired memory or concentration, “brain fog”, and depression [1]. Many people also complain of digestive disturbances, increased sensitivity to food and multiple chemical sensitivities, orthostatic intolerance and many people become so exhausted that they can no longer maintain a normal standard of life. Characteristic of the condition is that the symptoms must persist for longer than six months, but many people have the condition for 10 to 20 years. The extent/severity of the condition is highly varied and around 25% of affected individuals have a mild form of the condition and can work either full or part-time, whilst reducing other activities. Around half of the individuals have a moderate to severe form of the condition and may not be able to work, whilst the remaining 25% may remain housebound or may even be bed-bound. It has been estimated that the frequency of CFS/ME is around 0.2% -0.8% of the population with between 836,000 to 2.5 million Americans suffering from the condition. The annual health care cost is estimated to be between US$17-24 billion [2].

The condition is much higher in females (78%) than males (22%) [3]. The cause of chronic fatigue syndrome is unknown, although there are many theories - ranging from viral infections to psychological stress, many experts believe chronic fatigue syndrome might be triggered by a combination of factors [4-6].

Regland and co-workers examined the levels of homocysteine in the cerebrospinal fluid (CSF) of CFS/ME patients and found that the levels of homocysteine were higher than in matched control individuals [7]. The extent of homocysteine elevation was inversely proportional to the level of vitamin B12 in the CSF, thereby suggesting that vitamin B12 deficiency in the CSF caused a reduction in the remethylation of homocysteine by methionine synthase and methylcobalamin. In a later study, the same workers found some improvement of symptoms in some individuals who had CFS and who were given repeated high dose treatment with methyl vitamin B12 and folic acid [8, 9]. Treatment response was found to be dependent upon adequate thyroid hormone, suggesting a role for active vitamin B2 in the response to folate and methyl vitamin B12, which could potentially be due to the absolute necessity of functional vitamin B2 for the integrity of function of the methylation cycle. In contrast, Kaslow and co-workers and Wiebe found no response to the injection of cyanocobalamin for treatment of CFS [10, 11]. It should be noted, however, that in functional vitamin B2 deficiency, it is not possible to convert cyanocobalamin to Adenosyl and Methyl cobalamin. Persons with CFS and Fibromyalgia (FM) have been shown to have perturbations of the tryptophan-kynurenine pathway [12, 13]. Despite the above findings,

it is curious that there has been no explanation on what causes the chronic fatigue, which typifies the condition [4-9, 13-15].

Since the primary symptom in CFS is fatigue, or a constant lack of energy, it seemed logical to examine the energy systems of those with the condition and compare them to those who had no underlying health condition (s). To do this, the Urinary Organic Acids test (OAT) was used to measure the metabolites of glycolysis, lipolysis and break-down products associated with the use of amino acids for energy. In addition, the OAT was also used to quantitate neurotransmitter markers associated with processing of dopamine, nor-adrenalin, adrenalin and serotonin, which are often altered in depression and insomnia. A comparison was made between 316 individuals previously diagnosed with CFS, between the ages of 21 to 65, and a cohort of 25 individuals with no known health condition.

Results

Analysis of OAT data from the cohort of 316 individuals diagnosed with CFS revealed that every individual within the cohort had a reduced efficiency to gain energy from fats, carbohydrates and protein, due to a functional deficiency in vitamin B2. This was reflected in elevated levels of the Organic Acids, glyceric acid, glycolic acid, oxalic acid, lactic acid, glutaric acid, and succinic acid. There was also evidence of iron insufficiency, which results in the reduced activity of the enzyme, aconitase, and results in elevated levels of citric 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 methylmalonic acid (MMA), a marker of Adenosylcobalamin (Adenosyl B12) deficiency (See Fig 1), as well as greatly increased levels of the neurotransmitter metabolites, HVA, VMA, 5HIAA, QA and KA (see Fig 2-3, Table 2), pyroglutamic acid and the intermediate metabolite, 3-hydroxymethylglutarate, which are characteristic of Methylcobalamin deficiency (Methyl B12 deficiency). Increased levels of metabolites, appeared to be correlated with levels of glutaric acid, a marker of functional B2 deficiency (Figures 1,2, 3)

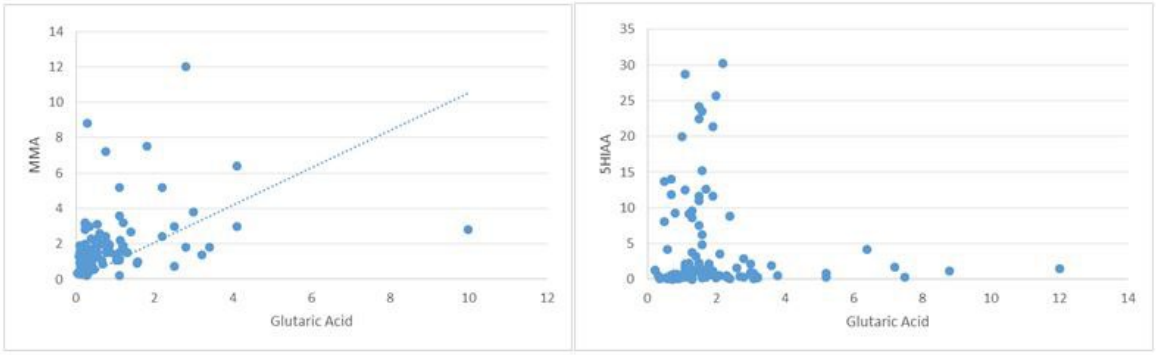

Figure 1: Methylmalonic acid (Left) and 5-hydroxyindole acetic acid (5HIAA) (Right) plotted against glutaric acid

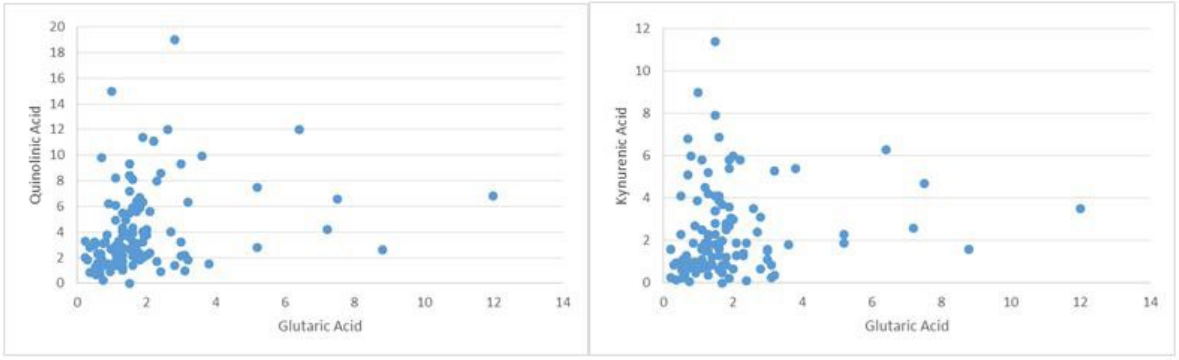

Figure 2: Quinolinic acid (Left) and Kynurenic acid (Right) plotted against glutaric acid

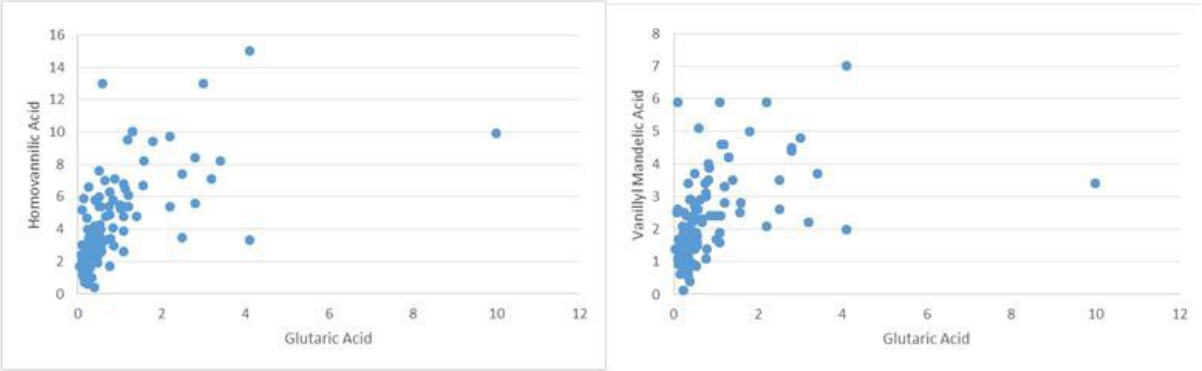

Figure 3: Comparison of HVA acid (Left Panel) and VMA (Right Panel) with glutaric acid

The degree of functional B12 deficiency was highly variable between CFS individuals as is reflected in the high standard deviation from the mean values (Table 1.)

Table 1: Functional Differences in processing of glucose, fats, and proteins between Healthy individuals and those with Chronic Fatigue Syndrome (CFS). Data is presented as Mean ± STD

Marker	Control	CFS
Glyceric Acid	2.48 +/- 1.48	4.94 ± 4.94
Glycolic Acid	45.8 ± 25.7	81.9 ± 69.1
Oxalic Acid	71.8 ± 47.3	115.3 ± 80.2
Lactic Acid	14.3 ± 16	19.7 ± 27.4
Pyruvic Acid	2.09 ± 1.21	6.25 ± 8.56
Citric Acid	145.42 ± 126	283.7 ± 184.5
Adipic Acid	1.28 ± 1.18	4.45 ± 11.68
Suberic Acid	1.68 ± 2.11	2.56 ± 3.28

Table 2: Functional Differences in Vitamin B12 -deficiency related markers between Healthy individuals and those with Chronic Fatigue Syndrome (CFS). Data is presented as Mean ± STD

Marker	Control	CFS
Methyl Malonic Acid	0.66 +/- 0.21	1.34 ± 0.85
Homovannilic Acid	1.5 ± 1.07	2.88 ± 4.12
Vanillyl Mandelic Acid	1.01 ± 0.46	1.83 ± 1.04
5HIAA	0.52 ± 0.55	7.87 ± 16.04
Quinolinic Acid	1.12 ± 0.65	2.58 ± 1.05
Kynurenic Acid	0.45 ± 0.27	2.05 ± 2.68
QA:KA	3.12 ± 2.05	6.13 ± 28.4
3-hydroxymethylglutarate	8.41 ± 8.37	13.72 ± 16.2
Pyroglutamate	17.04 ± 9.93	31.5 ± 122.6

Discussion

Measurement of many metabolic markers in OAT revealed reduced metabolism of glucose (elevated lactic acid and pyruvic acid), fatty acids (elevated adipic acid and suberic acid), and proteins (elevated glycolic acid, glyceric and oxalic acid) as well as reduced metabolism of citric acid in individuals with CFS. In this regard, elevation of these Organic acids reflects energy loss into urine. The metabolism of each of the above is linked to mild functional vitamin B2 deficiency, and is supported by the elevated glutaric acid marker – representative of functional B2 deficiency. In addition, levels of citric acid were raised, which is characteristic of a block in the iron-sulphur enzyme aconitase. We have shown previously that such a block is due to uncoupling of the enzyme aconitase when levels of ferritin in serum drop below 60 ug/L [16-18].

Functional vitamin B2 deficiency inevitably results in functional

vitamin B12 deficiency, which can be misdiagnosed, or missed, as vitamin B12 levels in serum can be normal or even elevated – a condition called "Paradoxical B12 deficiency" results [19]. Measurement of many markers in OAT indicated moderate to severe vitamin B12 deficiency in all individuals with a diagnosis of CFS, as analysed in the current study.

Thus, levels of MMA, the "traditional" marker of Adenosyl B12 deficiency, were increased to as much as twenty-four 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 (Figures 2-3, Table 2). In addition, the CoQ10 precursor molecule, 3-hydroxymethylglutarate, was elevated as too pyroglutamate, a standard marker of intracellular methyl B12 deficiency, and subsequent reduction in intracellular methylation. 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.

Production of CoQ10, requires three methylation steps, whilst the production of the ATP shuttle vector, creatine, also requires methylation via Guanidinoacetate-N-methyl Transferase (GNMT). Creatine biosynthesis consumes around 40% of methyl groups produced as S-adenosylmethionine, hence any reduction in methylation capacity will have a dramatic effect on the production of creatine [20]. The sequelae for these findings would be that there was reduced production of CoQ10, the essential electron transport molecule in the Electron Transport Chain, and also reduced production of creatine, and hence lower amounts of ATP transfer inside the cell with resultant fatigue [21].

Lack of activity of GNMT has previously been shown to result in reduced muscle strength, and fatigue, and reduced activity in the brain is associated with difficulty in finding words, poor mental processing, and slurred speech, conditions similar to the "Brain fog" often described by those with CFS [22-26]. In conditions of reduced creatine production, the body "attempts" to over-come the creatine deficiency by over-production of the enzyme creatine kinase, which is common in conditions such as CFS [27].

The reduced production of CoQ10 in CFS is supported by earlier findings (Clark et al, 1984; Sobreira et al, 1997), and was found to be accompanied by lower respiratory activity [28, 29].

Thus, the reduced energy production from fats, sugars and proteins, plus low levels of the methylation products CoQ10 and creatine, appear to logically account for the chronic fatigue seen in CFS individuals.

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): Norepinephrine + SAM (PNMT) => Epinephrine and the production of Melatonin by the methylation of N-Acetylserotonin by the enzyme Hydroxy-Indole-O-methyl transferase (HIOMT).

Overproduction of serotonin in CFS would occur due to lower production of SAM, and thereby reduced synthesis of melatonin. This would potentially result in three major effects. First, the excess serotonin would eventually lead to serotonin receptor suppression and thereby lead to symptoms of depression, and anxiety – both of which are common in CFS (Wright et al, 2020; Loades et al, 2021; Groven et al, 2021; Daniels et al, 2017; Stoll et al, 2017) [30-34]. Second, the reduced production of gut melatonin would affect the maturation of the gut wall and when combined with over-production of serotonin, lead to indigestion, diarrhoea, and symptoms such as irritable bowel syndrome, also common in CFS. Third, lack of production of melatonin by the pituitary glands would result in difficulty sleeping, another common symptom in CFS [35-40].

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 as has been found in several studies of CFS [41]. Functional B2 deficiency is common in those with improperly treated hypothyroidism, something that was common in those with CFS in the current study (37%). It can also occur due to prolonged infection, due to the need for FMN/FAD to fight infection, and is common in those who over-train and do not supplement. Low functional B2, both through the reduced ability to make active B6 (PLP), also reduces the activity of the enzyme serine-hydroxymethyltransferase (SHMT) and then greatly reduces the production of 5,10-methylene-THF, which in turn results in reduced activity of the methylation cycle.

The current study demonstrates that the functional deficiency in vitamin B2, observed in the test cohort, leads to an expected deficiency in functional vitamin B12 of note is the potential that any of the deficiencies would ultimately lead to reduced methylation and cerebral creatine deficiency, with the accompanying symptoms.

The current studies fill a critical gap in the understanding of the mechanism behind the factors involved in the energy loss and fatigue behind the condition and therefore provide a potential mechanism for the treatment of CFS.

Methods

Study Sample

This study is a retrospective audit of data obtained from 316 participants from a cohort of 316 adults who had been diagnosed with CFS from countries including USA, Canada, United Kingdom,

Ireland, Germany, Spain, France, Italy, Bulgaria, India, Sweden, Bulgaria, Serbia, Dubai, Croatia and Australia. No selection was made in the acceptance of data, with no data being rejected, not made privy to either the methods of assessment nor of the severity of the Chronic Fatigue Syndrome. No information was obtained on either the methods of assessment nor of the severity of the Chronic Fatigue Syndrome. 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.

This data, (that from those with CFS) 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 as Scattergrams (see Figures 1 to 3).

Conclusions

Urinary Organic Acid Tests, which were carried out on 326 persons with chronic fatigue syndrome, identified two main areas of metabolic insufficiency, functional vitamin B2 deficiency and functional vitamin B12 deficiency. Initiation of CFS appears to occur under conditions of prolonged functional B2 deficiency, which eventually results in functional vitamin B12 deficiency. The functional B2 deficiency results in reduced efficacy of metabolism of fats, sugars and proteins, whilst the functional B12 deficiency reduces the production of CoQ10 and creatine. The combination event reduces not only the efficiency of energy production from fats, sugar and proteins, but also the efficiency of energy conversion due to reduced production of CoQ10 and creatine. The functional B12 deficiency can often be missed, as paradoxically, serum B12 may be normal or higher than normal and as such is often over-looked by the clinician. Resolution of the condition involves establishment of functional vitamin B2 sufficiency as well as high dose administration of vitamin B12, either through injection or via TransdermOil™ application.

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