TREATMENT OF CHRONIC FATIGUE SYNDROME WITH SPECIFIC AMINO ACID SUPPLEMENTATION

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ABSTRACT: Chronic fatigue syndrome (CFS), is rapid onset of debilitating fatigue with no clearly defined origin or effective therapy . In an open trial, fasting plasma amino acid levels were measured in 25 CFS subjects. Amino acid mixtures were formulated based upon individual test results. Twenty subjects completed the study by taking 15 grams of the formulation daily for three months. Near complete symptom resolution was seen in 75% of subjects, 15% had moderate and 10% had little or no relief. Follow-up testing showed improved amino acid levels. Specific amino acids may affect metabolic processes increasing energy production in CFS patients.

Key Words: Chronic fatigue syndrome, amino acids, cellular energy, ATP, treatment

INTRODUCTION

Chronic fatigue syndrome (CFS) has received much attention recently, yet it is not known whether this syndrome represents one disease process or several which can cause similar sets of symptoms (1). No known effective therapy is available. The common symptom of debilitating fatigue may represent an impairment of production of mitochondrial adenosine triphosphate (ATP) chemical energy, the fundamental cellular energy source. Mental/emotional symptoms of poor attention, memory loss, lack of concentration and depression may also be reflective of insufficient central nervous system ATP availability and/or impaired neurotransmitter production. Several essential amino acids supply precursors to the tricarboxylic acid (TCA) cycle for ATP production as well as precursors for neurotransmitters. Oral administration of specific amino acids can significantly affect these processes (2). Several studies have shown that potassium and magnesium aspartate salts can significantly improve fatigue symptoms in patients presumably by precursor stimulation of the TCA cycle (3, 4). Blood lactate levels are elevated in CFS patients (5), indicating suboptimal aerobic ATP production. If CFS symptoms are caused by a metabolic deficit depleting ATP, inhibiting optimal ATP generation and/or neurotransmitter production, then oral administration of amino acids that influence these functions may improve symptomology. The following represents an open trial of the efficacy of amino acid supplementation which may stimulate further interest in the use of amino acids as therapeutic agents in CFS.

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MATERIALS AND METHODS

Subjects were admitted to an open trial of this hypothesis if they met an established definition of CFS (1). Forty one fasting plasma amino acids were measured in 25 CFS patients (16 females and 9 males, ages 23 to 56) using a Beckman 6300 amino acid analyzer. This apparatus consisted of a dedicated HPLC system for temperature controlled ion exchanged chro-

matography using three buffer changes and a post column ninhydrin derivatization.

Subjects were administered a free form amino acid mixture formulated according to measured plasma levels. This consisted of a base formulation (**Table 1**) containing 8 essential and 2 semi-essential pharmaceutical grade free form amino acids with pyridoxal-5-phosphate and alpha-ketoglutaric acid as metabolic synergists (Courtesy of Metabolic Maintenance, Inc. Sisters, OR). Additional amounts of specific amino acids (including taurine) were added to this base formulation if the amino acid level was below an optimized reference range (6). The additional amount of an amino acid added varied proportionally with the degree of deviation from the low normal range. The total weight of amino acids in the mixture was brought to 300 grams by adding sufficient amounts of base formula to the total computed amount of low amino acids. All subjects completed symptom questionnaires (**Figure 1**) at the beginning of the trial, then received 15 grams of their individualized mixture daily for three months and were interviewed at the end of the trial. Using the post-trial interview, changes in 25 symptoms were graded on a 1 to 5 scale, 1 representing no improvement or worsening, 5 indicating 100% improvement. A second fasting plasma amino acid level was taken on those subjects who indicated moderate to high improvements in symptoms.

RESULTS

Five subjects dropped out of the trial. Of these, two noticed no effect, two developed gastrointestinal distress (diarrhea and cramping) within one month of starting the amino acids, and one had a complete relapse of symptoms after 2 months of modest improvement. Of the 20 subjects who completed the trial period, the post-trial interview regarding questionnaire symptoms showed 75% (n = 15) experienced 50-100% improvement, 15% (n = 3) had a 25-50% improvement, and 10% (n = 2) had no improvement in symptoms. No other changes in treatment or lifestyle during the three-month period were offered by subjects which they felt may account for this improvement. Of the subjects exhibiting the greatest positive response, energy levels were reported to increase substantially within 2 weeks. Some cases improved dramatically within several days, including two subjects with a 15 year history of this disease process. The most commonly reported improvement was in mental function with greatly enhanced ability to concentrate and elimination of mental fatigue or "brain fog". After

Table 1. Base Amino Acid Formulation

Amino Acid	Percentage per weight
L-Valine	11.00
L-Leucine	12.70
L-Isoleucine	9.40
L-Phenylalanine	12.70
L-Tryptophan	2.00
L-Methionine	7.60
L-Threonine	6.80
L-Lysine	9.30
L-Histidine	10.50
L-Arginine	9.30
Pyridoxal-5-Phosphate	0.30
Alpha-ketoglutaric acid	8.40

Table 2. Percentage frequency of amino acids below reference range in 25 CFS subjects

Amino Acid	Percentage
L-Histidine	0.
L-Valine	4.
L-Threonine	4.
L-Lysine	8.
L-Methionine	20.
L-Arginine	24.
L-Leucine	52.
L-Isoleucine	60.
Taurine	64.
L-Phenylalanine	72.
L-Tryptophan	80.

the trial, 90% of these subjects have continued to take the amino acid mixture (often at a reduced dosage) as they report a decrease in energy level and recurrence of other symptoms when the formulation is discontinued.

All subjects exhibited multiple amino acids levels out of reference range (**Table 2**). Retesting of subjects after three months showed improvement in these levels. There was no discernible difference in initial amino acid level patterns between those experiencing improvement and those who did not or dropped out. All subjects experiencing 50-100% symptom improvement showed marked improvement of amino acid levels, although no consistent pattern of individual amino acids was noted. In this group an average of 3.67 amino acids returned to normal reference range after treatment. In the 25-50% symptom improvement group, an average of 2.5 amino acids returned to normal reference range after treatment.

DISCUSSION

The difficulty in defining and diagnosing this illness suggests a potential multifactorial etiology (7). Regardless of the cause, a common etiology in this disease may be one or more metabolic blocks that prevent optimal ATP production in cells. CFS patients exhibit elevated blood lactate levels which could reflect such a deficit (5). Recent organic acid profiles on CFS patients in a post-exercise condition reveal significant abnormalities in levels of the citric acid cycle intermediates indicating derangements in this critical ATP production cycle (8). Red blood cell magnesium was also found to be deficient and intravenous administration of magnesium improved symptoms in CFS patients (9). Magnesium is an essential element in ATP utilization. The considerable energy requirements of the brain would make this organ particularly susceptible to a deficit in ATP production and utilization. Amino acids directly impact the TCA cycle and could enhance ATP production.

Adenosine monophosphate (AMP) has been used successfully to treat other viral infections perhaps by stimulating increased ATP production (10). If CFS has a viral origin, an increase in ATP production may be a factor in recovery.

The two most commonly deficient amino acids seen in CFS subjects are phenylalanine and tryptophan. These serve as precursors to catecholamines and serotonin, neurotransmitters that are intimately involved in depressive disorders. Depression is a common symptom in CFS patients. Significant improvement was seen in fibromyalgia patients (a disease similar to CFS) with administration of 5-hydroxytryptophan (11). Yet electrophysiological evidence can apparently differentiate CFS type patients from patients with clinical depression, suggesting an additional metabolic impairment in CFS patients (12).

Determination of deficient metabolic factors, such as amino acids, that can be reintroduced into the system to correct potential metabolic blocks by mass action may represent a new, effective approach to treatment of CFS patients in whom a final common defect is an inability to generate optimal amounts of cellular energy or other critical metabolites. Additional double-blind/placebo controlled clinical trials are needed to confirm the efficacy of amino acid therapy for CFS as well as research into underlying mechanisms regarding the metabolic fate of these substances and their mode of action.

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