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A Novel Nutriceutical Treatment of Myalgic Encephalitis/Chronic Fatigue Syndrome (ME/CFS): "What it is and what it is not"

Frank Comhaire*

Emeritus Professor at Department of Endocrinology and Metabolic Diseases, Ghent University Hospital, Belgium

***Corresponding author:** Frank Comhaire, Brakelmeersstraat 18, Sint Martens-Latem, Belgium, Tel: 0032475618555; E-mail: Frank@comhaire.com
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Abstract

Ten patients suffering from pathology considered to be refractory ME/CFS have been prospectively offered treatment with a novel nutriceutical that increases the activity of pyruvate dehydrogenase and enhances mitochondrial energy production by the aerobic metabolism of the Kreb's cycle. Whereas half of the patients presented highly significant improvement of their health and condition, the other half did not experience any benefit. The latter patients were found to suffer from different pathology that should be classified as "ME/CFS-nondisease".

Keywords: Chronic fatigue syndrome; Myalgic encephalitis; Nutriceutical; Treatment; Nondisease

Introduction

The diagnosis of the Chronic Fatigue Syndrome (CFS), also referred to as Myalgic Encephalitis (ME) [1] when associated with fibromyalgia, is usually based on diagnostic criteria from history taking. The Fukuda criteria [2] have been updated and refined by several other systems [3,4], but the validity of these tools is hard to certify since there is no "gold standard" to compare with. When patients present the signs and symptoms suggesting a particular diagnosis, but the disease is not found, they should be categorized as suffering from a "nondisease" [5]. The latter requires a different therapeutic strategy.

Definite diagnostic and biological markers of ME/CFS are either lacking or are difficult to apply for screening purposes. Probably the study of the metabolome most closely approaches the required accuracy for detecting the biological disturbances alleged to be associated with ME/CFS [6]. There is good evidence that CFS is due to a systemic immune disorder [7] whereby oxidative, immunological and epigenetic mechanisms may increase the activity of the pyruvate dehydrogenase kinase (PDHK) and inhibit the pyruvate dehydrogenase activity. This will result in reduced aerobic pyruvate metabolism in the Krebs cycle [8,9]. The anaerobic escape route which uses lactate dehydrogenase (LDH) to generate lactate and lactic acid is engaged, including the Cori cycle of gluconeogenesis [10], in order to temporarily compensate for the paucity of aerobic energetic ATP production (Figure 1).

This pathogenic hypothesis reconciles all clinical, biological and theoretical observations, and may explain the increased lactate concentration in blood after oral glucose intake observed in some patients (Figure 2). Based on this concept the author has developed a composite nutriceutical containing the sodium salt of one of the halogenated organic acids present in a particular genus of algae, vitamin B1, alfa lipoic acid, acetyl-l-carnitine, and the oxidoreductase ubiquinone Q10 (patent pending).

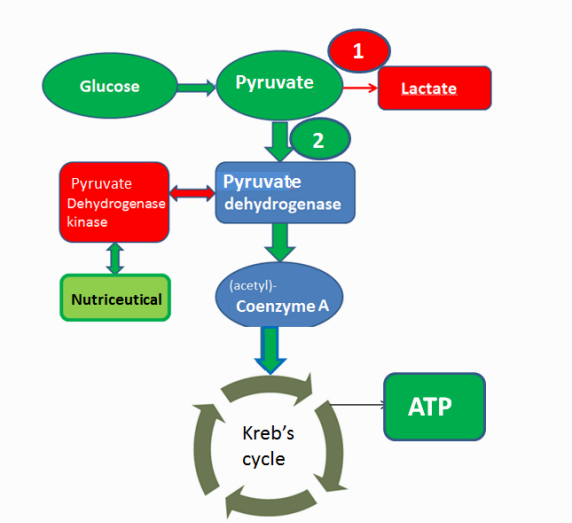

Figure 1: The glucose metabolism is represented in a simplified flowchart. Glucose is metabolized by glycolysis to pyruvate. In an anaerobic environment (1, in red) the enzyme lactate dehydrogenase in the cellular cytoplasm metabolizes pyruvate into lactate that is converted into lactic acid. The normal aerobic metabolism takes place in the mitochondria where pyruvate is metabolized into coenzyme A by the enzyme pyruvate dehydrogenase (2, in green). An acetyl group attaches to the coenzyme A to form acetyl-coenzyme A to which fatty acids are bound. Together with citric acid these enter the Krebs cycle where ATP is generated. In patients suffering from CFS the activity of the pyruvate dehydrogenase is reduced by phosphorylation because of the excessive activity of the pyruvate dehydrogenase kinase (in red). The novel nutriceutical increases the pyruvate dehydrogenase activity by antagonising the pyruvate dehydrogenase kinase.

This nutriceutical is expected to enhance the activity of PDH, to improve the insulin sensitivity, and to increase the aerobic metabolism

of the mitochondria (Figure 1). The present paper reports the results of the initial, open-label prospective cohort trial, and the findings in a few exemplary patients with "ME/CFS-nondisease".

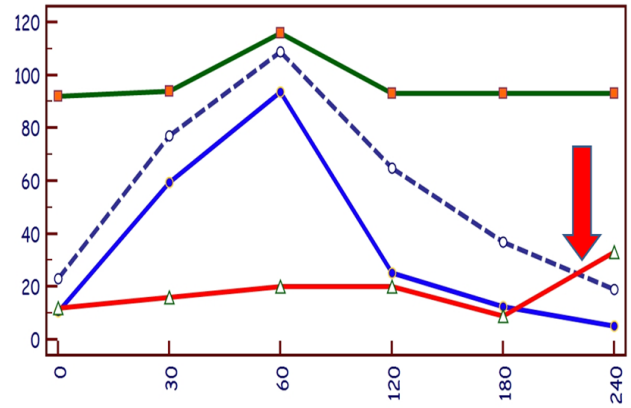

Figure 2: Prolonged oral glucose tolerance test. Values on the vertical axis for: Blood glucose concentration (green line; in mg/dL), insulin concentration (full blue line; in µU/mL); C-peptide concentration (broken blue line; µg/dL); lactate concentration (red line; in µg/mL). Measurements were performed on blood taken before ingestion of 75 g of glucose (time 0 on the horizontal axis), and after 30, 60, 90, 120, 180 and 240 minutes.

Materials and methods

A cohort of 10 patients, 6 women and 4 man, mean age 42.3 years (SD: 10.7 years), were selected because the diagnosis of ME/CFS was certified by an official CFS reference centre of the Belgian universities, and the duration of complaints exceeded 5 years (mean: 8.1 years; SD: 2.2 years)(Table 1). All patients were refractory to treatment by cognitive behaviour therapy (CBT) with graded exercise training (GET) [11-14].

Initials	Gender	Age	Duration-disease	Before	After	Change	Group
VLN	F	27	10	90	76	-18	1
SM	F	53	10	69	12	-90	1
DN	F	49	9	51	29	-41	1
BP	M	47	12	78	39	-50	1
PK	F	47	8	84	44	-47	1
NC	F	52	8	58	54	-3	2
PT	F	34	6	52	48	-7	2
FB	M	31	6	85	85	0	2
PP	M	29	5	86	85	-1	2
LH	M	54	7	87	88	1	2

Table 1: Gender: F=Female; M=Male; age in years, duration of disease in years, Before=Fatigue severity score before treatment (%); After=Fatigue severity score after 1 month of intake of the novel nutriceutical (%); Change=Difference between fatigue score before treatment minus fatigue score after treatment divided by fatigue score before treatment (%); Group 1=Responders; Group 2=Non-responders.

Several patients also had long-term antibiotic treatment for alleged chronic Lyme disease [15], or hormone treatment with hydrocortisone, thyroid hormone, growth hormone or melatonin. At intake into the trial all patients received pain killers, and/or antidepressant medication, and/or hypnotics. In spite of these treatments their symptoms persisted. Patients were given the innovative nutriceutical as part of an open-label prospective cohort trial.

After routine clinical and biological investigation, the patients were requested to complete a questionnaire deduced and translated from FSS RAND-36 questionnaire [16] or the Fatigue Severity Scale (FSS) [17]. The results of these questionnaires were calculated as sum of scores given per item divided by the maximum score and expressed (%), and also as average score per 9 items given in the FSS. When applying the latter calculation, the average score of healthy subjects is 3.0 [18].They were given the innovative nutriceutical, and returned after 1 and 3 months to report the effect of treatment and to complete the questionnaire once again.

Patients who did not experience any positive effect of treatment (non-responders) were assessed further using advanced diagnostic methods including: nuclear magnetic resonance imaging, positron emission tomography, electroencephalography (EEG), electromyography (EMG), extended 4-hour oral glucose tolerance test with measurement of insulin, C-peptide and lactate (Figure 2), cluster differentiation of lymphocytes, in depth immunological and hormone testing, genetic analyses, dual-energy X-ray absorptiometry (DEXA) of bone mineral density, as required.

Results

None of the patients reported adverse events or side effects. In 5 patients (responders; group 1, Table 1) health situation was significantly improved with respect to their physical performance capacity, brain function, and the reduction of muscular pain and exhaustion. The scores on the questionnaires decreased significantly (students' paired sample t-test: P=0.01) from an average of 74.4% (SD: 15.2%) (FSS score 5.21) before treatment to 40% (SD: 23,5%)(FSS score 2.80) after 1 month of intake of the nutriceutical, corresponding to a mean reduction of 49.2% (SD: 26%). During follow-up the improvement was maintained or enhanced further.

However, the other half of the patients (non-responders; group 2, Table 1) experienced no significant beneficial effect (P=0.20) with mean fatigue score of 73.6% (SD: 16.6%) (FSS score 5.15) before treatment and 72.0% (SD: 19.3%) (FSS score 5.04) after treatment. These non-responders were submitted to advanced investigations.

In one patient (NC), who was diagnosed to suffer from ME with predominant fibromyalgia, hyperparathyroidism with severe osteoporosis was detected (Figure 3). A parathyroid adenoma was removed surgically, after which the patient received 2 injections of Denosumab. Bone density increased and the pain regressed. Several months after interruption of the Denosumab injections bone density decreased rapidly, and pain resumed. In fact, the original diagnosis of fibromyalgia was incorrect and the pain resulted from osteoporosis [19]. Therefore, the patient should be classified as suffering from "ME/CFS-nondisease".

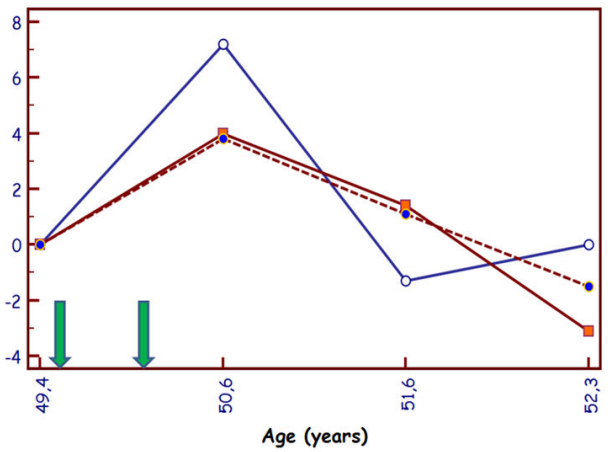

Figure 3: Bone mineral density scan of patient CN. The change of bone density compared to the initial value was plotted (on the vertical axes, in %) in relation to the patient's age at time of registration (on the horizontal axis). Blue full line: lumbar spine L1-L4 (initial T-score=-2.8); brown full line: left side femoral neck (initial T-score=-1.6); brown broke line: right side femoral neck (initial T-score=-1.8). The green arrows indicate the moment of injection of Denosumab.

Another patient (PT) who did not respond to nutriceutical treatment was found to present elevated white blood cell counts (13000 to 15000/μL) with excess (80%) neutrophilic granulocytes, moderately elevated sedimentation rate and alfa-2 globulin concentration. No evident cause for these abnormalities were found upon urine analysis and chest radiograph. A fluorodeoxyglucose positron emission tomography (PET scan) was performed in order to detect and localize a possible focus of infection. This revealed maxillary sinusitis together with tonsillitis, which was confirmed as pan-sinusitis upon CT-scan. The patient was treated surgically. The diagnosis at reference was incorrect since the cause of her problem was occult focal bacterial infection, and this patient should be classified as "ME/CFS-nondisease".

The third case (FB) was a patient with long lasting disease, recurrent periods of moderate fever, non-specific gastro-intestinal complaints, fatigue, and memory problems. Together with elevated hepatic enzymes (Gamma glutamyl transpeptidase and Alanine aminotransferase) he was found to present active infection with Cytomegalovirus, as evidenced by highly positive titres of both IgM and IgG, elevated number of monocytes, and high C-reactive protein concentration. Long-term treatment with Valaciclovir [20] was initiated which resulted in improvement of his health condition within 3 months.

Patient PP suffered disabling problems of impaired memory, extreme fatigue and exhaustion. His complaints were related to a genetic enzymatic deficiency which was presumed to explain the permanent increase of the concentration of creatine phosphokinase (CPK) in blood. However, testing for known enzymes in muscular biopsy tissue did not reveal any abnormalities. Since the patient did not experience any improvement when taking the novel nutriceutical, hormone analysis were performed which revealed low concentrations of total and free testosterone (172 ng/dl and 3.6 ng/dl respectively). The patient was prescribed androgen substitution therapy by transdermal application of testosterone gel.

The fifth patient (LH) had similar symptoms with deficient memory, and intellectual exhaustion. He too was found to present a low testosterone concentration due to the "late onset hypogonadism" (LOH) syndrome [21,22]. Substitution treatment with injections of testosterone undecanoate restored his androgen status, but failed to improve his brain function. Thorough psychometric testing and nuclear magnetic resonance examinations of the brain did not reveal any abnormalities. A treatment attempt with the novel nutriceutical was ineffective. The patient, who was a private investment banker, scored high in the Maslach Burnout Inventory [23]. In this patient the diagnosis should be "burn-out syndrome" rather than ME/CFS, implying a different therapeutic approach.

Discussion

The observations reported in the present paper are exemplary of the problematic aspects of the diagnose of the ME/CFS disease, and its implications for treatment. So far, there is no generally accessible objective method to ascertain this diagnosis, which is usually based on history taking and complementary examinations, including psychological assessment, registration of the sleep pattern, exercise tolerance test, etc. Patients are treated by different regimens, but many of them fail to improve [11-13]. These patients are considered refractory, and they commonly continue suffering from a disabling condition with incapacity to work, or even to perform their daily activities.

The metabolic hypothesis seems to be the most acceptable for explaining the clinical aspects of the disease, with impaired enzymatic activity of the pyruvate dehydrogenase (PDH) being of pivotal importance. This is sustained by the fact that approximately half of the patients reacted positively to the innovative nutriceutical treatment that increases the activity of PDH, either directly or indirectly via the inhibition of the pyruvate dehydrogenase kinase activity. In the responders the FSS score was reduced to values similar to those reported in healthy subjects [18]. However, as many patients did not experience any beneficial effect. In the cases presented here there were no differences between the responders and the non-responders regarding age (responders mean 44 yrs., SD: 10.1; non-responders mean 40.0 yrs., SD: 12.0), duration of disease (responders mean 9.8 yrs., SD: 1.5; non-responders mean 8.0 yrs., SD: 1.1) and severity of fatigue before treatment (responders mean score: 74.4%, SD: 15.2; non-responders mean score: 73.6%, SD: 17.1).

Thorough complementary investigations revealed a different pathology causing the ME/CFS-like syndrome in the non-responders. The examples described herein included hidden focal (bacterial) infection, active viral disease [24], hormone deregulation with severe osteoporosis or with hypoandrogenism, and the burn-out syndrome. These patients should be classified as suffering from "ME/CFS-nondisease", and they require a different therapeutic approach.

A possible diagnostic method for detecting deficient enzymatic activity of the PDH and selecting patients for nutriceutical treatment would be by measuring the concentrations of pyruvate and of acetyl coenzyme A in the patient's monocytes. This method is presently being explored, but it requires advanced laboratory technology. Whether the extended glucose tolerance test with measurement of lactate concentration may offer a diagnostic alternative needs further exploration.

Another strategy may be to apply a test treatment with the innovative nutriceutical to patients suffering from ME/CFS symptoms. In case a favorable response to this treatment does not occur within one month, complementary technical examinations are required.

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