## CLINICAL STUDY

# Comparison of Oral Nicotinamide Adenine Dinucleotide (NADH) versus Conventional Therapy for Chronic Fatigue Syndrome

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*Objective.* **To compare effectiveness of oral therapy with reduced nicotinamide adenine dinucleotide (NADH) to conventional modalities of treatment in patients with chronic fatigue syndrome (CFS).**

*Background.* **CFS is a potentially disabling condition of unknown etiology. Although its clinical presentation is associated to a myriad of symptoms, fatigue is a universal and essential finding for its diagnosis. No therapeutic regimen has proven effective for this condition.**

*Methods.* **A total of 31 patients fulfilling the Centers for Disease Control criteria for CFS, were randomly assigned to either NADH or nutritional supplements and psychological therapy for 24 months. A thorough medical history, physical examination and completion of a questionnaire on the severity of fatigue and other symptoms were performed each trimester of therapy. In addition, all of them underwent evaluation in terms of immunological parameters and viral antibody titers. Statistical analysis was applied to the demographic data, as well as to symptoms scores at baseline and at each trimester of therapy.**

*Results.* **The twelve patients who received NADH had a dramatic and statistically significant reduction of the mean symptom score in the first trimester ($p < 0.001$). However, symptom scores in the subsequent trimesters of therapy were similar in both treatment groups. Elevated IgG and Ig E antibody levels were found in a significant number of patients.**

*Conclusions.* **Observed effectiveness of NADH over conventional treatment in the first trimester of the trial and the trend of improvement of that modality in the subsequent trimesters should be further assessed in a larger patient sample.**

*Key words : Chronic fatigue syndrome, NADH, Viral syndrome.*

Chronic fatigue syndrome (CFS) is a clinical disorder characterized by prolonged, debilitating and occasionally incapacitating fatigue frequently accompanied by multiple other non-specific symptoms (1). The condition is usually diagnosed in the presence of fatigue, which has been active for at least six months and fulfillment of criteria established by the Centers for Disease Control (2). The diagnosis of CFS is difficult, as it shares symptoms present in many other conditions. Based on this, some authors have suggested four subclasses of CFS: that primarily manifested by nervous system dysfunction (impaired memory or concentration disorders and headaches), chronic fatigue primarily manifested by endocrine system disorders (unrefreshing sleep and post exertional malaise), that primarily manifested by musculoskeletal system dysfunction (muscle pain and joint pain) and chronic fatigue primarily presenting immune system alterations and or infectious disorders (sore throat, tender lymph nodes) (3).

The reported prevalence rate of CFS in the United States is 4 to 10 cases per 100,000 in adults 18 years or older. Various recent studies and presentations have informed a several-fold higher prevalence rate. The condition is diagnosed with a four times higher frequency in women between the ages of 30 to 50 years.

CFS may have an abrupt clinical presentation, but its onset can also be gradual. An acute infectious process, such as a respiratory or viral gastrointestinal illness or mononucleosis can be traced to the beginning of symptoms in around 33% of the cases. It has been also related to exposition to emotional or physical trauma. In more than 50% of cases a co-existing psychiatric diagnosis such as depression or anxiety has been reported. At present there are no specific laboratory or radiological markers for this disorder.

Several theories have been proposed as explanations for CSF (4). Exposition to infectious agents such as Epstein Barr virus (EBV), Borrelia burgdorferi, Herpes virus 1 and

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2 (HSV1, HSV2) and Cytomegalovirus (CMV) among others, have been postulated by some authors as triggers for the condition, either directly or by the secondary induction of an immunological disturbance. A second theory postulates that disturbances at the hypothalamic-pituitary–adrenal axis with deficiency of cortisol may account for the symptomatology. A third theory proposes that CFS constitutes predominantly an immunological disorder. Under this theory it is felt that the illness involves a continuous antigenic challenge to the immune system with a consequent constant immunologic response to that exposure. According to this concept, the immune system responds to that antigenic challenge with production of excess levels of inflammatory mediators and cytokines that trigger the flu- like symptoms exhibited by these patients. However, consistent evidence of abnormal cytokine levels has not been found in all cases (5).

No specific treatment has proven effective for CSF including administration of various therapeutic agents such as steroids, IV gamma globulin, monoamine oxidase inhibitors and 5-HT3 receptor antagonists (6-9). Some authors have reported utility in the control of symptoms with the oral administration of reduced nicotinamide adenine dinucleotide (NADH) (10-11). It is known that NADH triggers ATP production and various studies have demonstrated an increase of dopamine metabolites and reduction of serotonin metabolites in the urine of treated patients. This has provided indirect evidence that NADH may lead to endogenous production of L-DOPA, dopamine, norepinephrine and other catecholamines and replenishment of the cellular stores of ATP. Those metabolic effects of the drug have been associated with amelioration of the cognitive dysfunction and the fatigue in some patients (12).

The aim of this report is to present the results of a study conducted by us to compare the effectiveness of the administration of a stabilized oral absorbable form of NADH versus nutritional supplements and psychological counseling in the reduction of symptoms of patients with CFS referred to our Clinical Immunology Clinic. Particular attention was given to amelioration of baseline symptomatology through the analysis of symptom scores and the improvement in functional capacity of those patients.

## Methods

A total of 31 patients were randomly assigned to either NADH therapy or nutritional supplements and psychological therapy for 24 months. Only those who stayed in the assigned therapy without interruption for at least twelve months were included in the analysis. Thus, eleven patients who did not comply with that requisite were excluded. In that manner a total of twenty patients were used in the analysis for a compliance rate of 64.5%. The percent of improvement from baseline was calculated each trimester. The trimester percentage of improvement from baseline for each subject was calculated according to the following formula:

$$\text{Trimester percentage of improvement} = \frac{\text{Baseline score - trimester score}}{\text{Baseline score}} \times 100$$

A standardized format for gathering personal data, the presenting symptoms and the findings at physical examination was utilized for data collection. Written consent was obtained from each participant. The study group consisted of men and women 18 years old and older. For inclusion the patients had to have experienced fatigue for at least six months and to fulfill either two major or at least four minor CDC criteria for the disease (Table 1).

**Table 1.** Diagnostic Criteria for Chronic Fatigue Syndrome *

**Major Criteria**

1. Persistent or relapsing, debilitating fatigue or easy fatigability for at least 6 months
2. Exclusion of other causes of chronic fatigue by examination and appropriate investigations

**Minor Criteria**

**Symptoms**

1. Oral temperature between 37.5° C and 38.6° C
2. Sore throat
3. Painful cervical or axillary lymph nodes
4. Unexplained general muscle weakness
5. Myalgia
6. Prolonged postexercise fatigue
7. Generalized headaches
8. Migratory arthralgia without findings
9. Neuropsychologic complaints (eg, forgetfulness, irritability, depression, photophobia)
10. Sleep disturbance
11. Abrupt onset of symptoms

**Signs**

1. Oral temperature between 37.6° C and 38.6° C
2. Nonexudative pharyngitis
3. Palpable or tender, small (< 2 cm) cervical or axillary) lymph nodes

* Adapted from Holmes GP, Kaplan JE, Gantz NM, et al. Chronic fatigue syndrome: a working definition. Ann Intern Med 1988; 108 (3):387-9

Patients were excluded if they had any condition known to cause an immunodeficency state or that could be accountable for symptoms such as malaise or fatigue.

All patients were randomly assigned to receive either NADH or nutritional and psychological therapy for 24 months. A thorough medical history, physical examination and completion of a questionnaire on the severity of fatigue and other symptoms were performed each trimester of therapy. All patients underwent an initial laboratory

evaluation that included quantitative determination of immunoglobulin levels, rheumatoid factor, ANA, T lymphocyte profile, viral antibody titers for CMV, HSV, EBV and a hepatitis profile; T3, T4, TSH and liver function tests were also determined.

The questionnaire contained a scale with values from 1 to 4 for gradation of the severity of symptoms. In that scale 1 and 4 represented minimum and maximum severity of symptoms, respectively.

The patients in the NADH arm of the study were started on 5 mg of that medication and the dose was increased up to 10 mg, only if symptoms did not improve with the starting dose. The percent of improvement from baseline was calculated each trimester.

**Statistical analysis**. Continuous variables that were normally distributed were expressed as mean ± standard deviations (SD). Student t test or Wilcoxon two sample test were used, when appropriate to determine differences between patients who received NADH and those who did not. Fisher's exact test was employed to assess categorical variables. The repeated measures analysis of variance was applied to express the differences in improvement between the two treatment groups. Wilcoxon signed rank test was used to compare mean scores of trimesters by pairs.

## Results

The socio-demographic univariate analysis showed that the patients' age ranged from 22 to 54 years, with a mean of 31±9 years; ninety percent of which were women. Only seven out of twenty patients were employed during the two-year period of evaluation. Two patients reported ingesting ethanol socially and/or smoking more than 10 cigarettes per day. The majority of patients (80%) presented with co-events related to the onset of illness described as stress or a viral prodrome (Table 2).

**Table 2.** Clinical and socio-demographic characteristics (n = 20)

| | |
|---|---|
| Age (years) | 22 – 54 (mean 31± 9 yrs.) |
| Females | 18 (90%) |
| Employed | 7 (35%) |
| Unemployed | 13 (65%) |
| Toxic habits (Ethanol, smoking) | 2 (10%) |
| Stress, viral illness as co-events | 16 (80%) |
| Other medical conditions (Allergies, diabetes, migraine, depression, anxiety, bronchiectasis) | 15 (75%) |

As shown in Table 3, the four most frequent clinical symptoms at presentation were fatigue (100%), sleep disturbance (100%), myalgias (55%) and lymphadenopathy (50%). Less frequent symptoms were post-exertional malaise (5%), sore throat (15%), muscle weakness (20%) and arthralgias (30%). Twelve subjects (60%) received NADH and 8 (40%) were in the other therapies group. The majority of patients (60%) in the NADH group received a low dose (5mg) of that medication; most of the study participants (55%) were not receiving any concurrent therapy. Those that were taking other medications were receiving treatment for diabetes, anti-depressives, anxiolytic agents or antihistamines. No adverse events were reported with the use of NADH.

**Table 3.** Presenting symptoms*

| Symptom | Frequency | Percentage |
|---|---|---|
| Fatigue | 20 | 100 |
| Sleep disturbance | 12 | 60 |
| Myalgias | 11 | 55 |
| Lymphadenopathy | 10 | 50 |
| Neurocognitive difficulty | 8 | 40 |
| Fever | 8 | 40 |
| Headache | 6 | 30 |
| Arthralgias | 6 | 30 |
| Muscle weakness | 4 | 20 |
| Sore throat | 3 | 15 |
| Post-exertional malaise | 1 | 5 |

*Duration of symptoms prior to CFS diagnosis fluctuated from 6.0 to 36 months

As demonstrated in Table 4, the baseline mean symptom scores were very high (3.7 ± 0.5) for both groups of patients at entry into the study. Although, the baseline mean symptom scores were slightly higher in the NADH group (3.8 ± 0.4) than in the other therapies group (3.4 ± 0.5), the difference was not statistically significant (p> 0.05).

Assessment of clinical well-being and the severity of symptoms after the first trimester of therapy with NADH showed a dramatic reduction in the mean symptom score that ranged from 3.8 to 2.2 with a p value < 0.001. (Table 4 and Figure1). Symptom scoring in the subsequent trimesters showed no statistical difference in both treatment groups (p>0.05) (Figure 2).

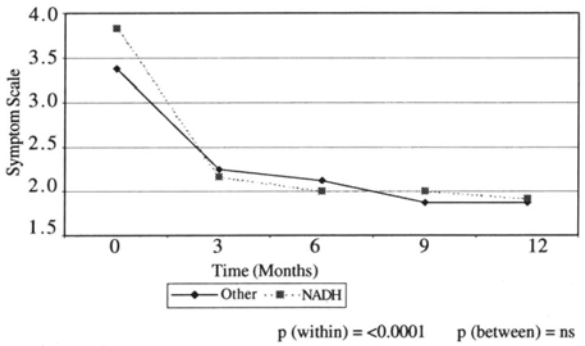


**Figure 1.** Symptoms scores by Trimester

**Table 4.** Symptoms Score for NADH Treatment by Trimester

| Comparisons | Trimester X Mean score | Trimester Y Mean score | Difference | p-value* |
|---|---|---|---|---|
| Baseline vs. Trimester 1 | 3.8 | 2.2 | 1.6 | < 0.001 |
| Trimester 1 vs. Trimester 2 | 2.2 | 2.0 | 0.2 | ns |
| Trimester 2 vs. Trimester 3 | 2.0 | 2.0 | 0.0 | ns |
| Trimester 3 vs. Trimester 4 | 2.0 | 1.9 | 0.1 | ns |

* Wilcoxon signed-rank test

Baseline immunological parameters and viral antibody titers were also performed. Eighteen (90%) of patients exhibited elevation of serum Ig G levels and 5 out of 20 patients had elevated serum Ig E. All patients studied had normal T cell populations. Only one patient had anti CMV and HSV1 antibodies, both Ig G type; another patient had elevated EBV (Ig G type) antibody titers.

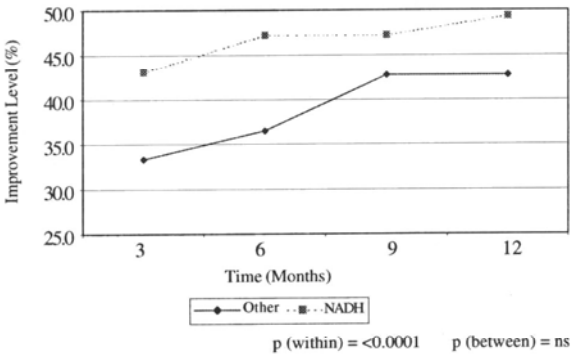


**Figure 2.** Porcentage Improvement from Baseline by Trimester

## Discussion

Great deal of speculation and misinformation still surrounds CFS. At present it remains a disease of unknown cause and of an unpredictable clinical course. What is well known is that this chronic debilitating condition has great impact on the quality of life and sense of well - being of patients and represents an economic burden to society. Similarly to the study by Forsyth et al., this study although performed in a referral population, showed a higher occurrence of the condition in women and had comparable symptoms at its clinical presentation. The mean duration of fatigue in that study was 7.2 months versus 10 months in ours (11).

The results of our study showed a beneficial effect of NADH with amelioration of the symptom scores during the first three months of treatment, when compared to the other modalities of therapy. Use of NADH was also characterized by slightly higher effectiveness in reduction of symptoms over the conventional therapies in subsequent trimesters, although the difference did not reach statistical significance. Nevertheless, the dramatic effect of NADH in the first trimester and its slightly higher effectiveness in long-term treatment could be clinically relevant when subjected to examination in a larger sample of patients. Forsyth et al. have reported that four times as many patients responded to NADH in contrast to placebo in their study.

Various studies focused on determination of altered immunological parameters in this condition, have identified increased number of activated cytotoxic T cells, low natural killer cell cytotoxicity, poor lymphocyte response to mitogens, low $IgG_1$ and $IgG_3$ production and increased levels of TH2 - type cytokines, among others. However, no consistent pattern of immunological abnormalities has been found (13-14). In our studied population there was a high incidence of elevated Ig G levels, suggesting the presence of immune complexes, in the absence of an active infection as evidenced by negative Ig M antibody titers. Another finding of interest in this study is that five out of twenty patients tested had elevated Ig E levels. This suggests a relation of CFS to allergic disorders that warrants further investigation. In contrast to other reports none of our patients showed alterations in T-cell populations. We acknowledge that our study represents a small sample of patients afflicted with CFS and as such its findings are not conclusive. Expansion of the present study in the future should also include psychological assessment of patients and their response to cognitive-behavioral therapies since physiological and psychological factors work together to precipitate and perpetuate the condition (15-16). Learning how to effectively control a potentially incapacitating symptom such as fatigue will certainly improve the level of performance and quality of life of patients with CFS.

## Resumen

El síndrome de fatiga crónica, de etiología desconocida, ha sido tratado sin éxito con varias modalidades terapeúticas. El presente estudio tuvo como propósito el comparar la efectividad de la terapia oral con dinucleótido de adenina reducido (NADH) con medidas convencionales en el manejo de pacientes con el síndrome de fatiga crónica. El estudio demostró una superioridad estadísticamente significativa para NADH sobre las otras modalidades terapeúticas durante el primer trimestre de terapia p<0.001). Por otro lado en los trimestres sub siguientes el control de la sintomatología fue similar en ambos grupos de

tratamiento. Este hallazgo debe ser estudiado en una muestra de pacientes más significativa.

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