



Dysautonomia in chronic fatigue syndrome: facts, hypotheses, implications

Jochanan E. Naschitz^{a,*}, Daniel Yeshurun^a, Itzhak Rosner^b

^a Department of Internal Medicine A, Bnai Zion Medical Center and Bruce Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, P.O. Box 4940, Haifa 31048, Israel

^b Department of Rheumatology, Bnai Zion Medical Center and Bruce Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, P.O. Box 4940, Haifa 31048, Israel

Received 14 February 2003; accepted 20 October 2003

Summary The diagnosis of chronic fatigue syndrome (CFS) is based on patient history and treatment on cognitive behavior therapy and graded exercise. There is increasing evidence that dysautonomia occurs in CFS manifest primarily as disordered regulation of cardiovascular responses to stress. We impart our experience relating to diagnosis, monitoring, and treatment of CFS based on identification and management of dysautonomia. Recently proposed methods for assessment of the cardiovascular reactivity, the 'hemodynamic instability score' (HIS) and the 'Fractal and Recurrence Analysis-based Score' (FRAS), served for this purpose. On HUTT, a particular dysautonomia is revealed in CFS patients that differ from dysautonomia in several other disorders. This distinct abnormality in CFS can be identified by $HIS > -0.98$ (sensitivity 84.5% and specificity 85.1%) and $FRAS > +0.22$ (sensitivity 70% and specificity 88%). Therefore, the HIS and FRAS may be used, in the appropriate clinical context, to support the diagnosis of CFS, which until now, could only be subjectively inferred. A pilot study suggested that midodrine treatment, directed at the autonomic nervous system in CFS, results first in correction of dysautonomia followed by improvement of fatigue. This finding implies that dysautonomia is pivotal in the pathophysiology CFS, at least in a large part of the patients, and that manipulating the autonomic nervous system may be effective in the treatment of CFS.

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Introduction

Clinically evaluated, medically unexplained fatigue of at least six months duration, that is of new onset, is not a result of ongoing exertion, not substantially alleviated by rest, and substantially reducing previous levels of activity is called chronic fatigue syndrome (CFS) [1]. Though CFS has received considerable attention, it remains a controversial disorder. Heterogeneity within patient groups labeled as having CFS makes it likely that there are multiple factors contributing to this disorder [2].

The etiology and pathogenesis of CFS are poorly understood. A close connection between impairment of autonomic functions, i.e., dysautonomia and CFS has been demonstrated [3–5].

Clinical practice guidelines for diagnosis and treatment of CFS have been recently published by independent working groups [2,6–8]. Accordingly, the diagnosis of CFS is based on patient history and exclusion of other diagnosable medical or psychiatric illness. Many therapies have been suggested in CFS. Systematic review of 350 studies on treatment of CFS showed that only two interventions have potential, namely cognitive behavior therapy and graded exercise [7]. However, both of these modalities are palliative at best.

* Corresponding author.

E-mail address: naschitz@tx.technion.ac.il (J.E. Naschitz).

In this paper, we impart our experience, and certain non-conventional views, relating to diagnosis, monitoring, and treatment of CFS.

Diagnosis

Two recent findings may advance the 'objective' diagnosis of CFS. The first is a recent study showing that 72% of subjects in a group of patients with CFS had increased plasma levels of an abnormal 37 kDa protein [9]. The possible application of this finding for diagnostic purposes has not been assessed. The second development is the increasing evidence of dysautonomia as a possible marker of CFS.

The use of the head-up tilt test (HUTT) to assess autonomic function in CFS has been intensively investigated. The fast response of blood pressure (BP) and heart rate (HR) to acute stimuli is under autonomic nervous control and thus BP and HR measurements during orthostatic challenge can be used as one measure of cardiovascular autonomic activity, providing there is no evidence of organic heart disease, venous insufficiency or hypovolemia [10]. Recognized pathological reactions to the HUTT are the vasodepressor and cardioinhibitory reactions, orthostatic hypotension, and the postural tachycardia syndrome. In studies utilizing these outcome measures, evidence for abnormal cardiovascular reactivity was found in one half of CFS patients [3,4,11]. These responses to tilt are non-specific, however, also occurring in a variety of disorders unrelated to CFS. Heart rate variability during the HUTT is another measure of abnormal cardiovascular reactivity in CFS. As with the classical outcome measures of the HUTT, abnormalities of HR variability in CFS are not specific for this disorder and thus have no practical application in the diagnosis of CFS [12]. A difficulty in assessing cardiovascular reactivity by the above-described classical methods arises from the high degree of non-linearity between external stimuli and cardiovascular response that characterizes autonomic cardiovascular modulation. A proposed approach for addressing this difficulty has been offered by the simultaneous quantification of BP and HR fluctuations, in addition to the utilization of non-Euclidian mathematical analysis [13]. This approach was utilized in two methods recently proposed for the assessment of cardiovascular reactivity, the 'hemodynamic instability score' (HIS) and the 'Fractal and Recurrence Analysis-based Score' (FRAS).

The HIS involves computing BP- and HR-changes during the course of a HUTT, followed by processing the data curves generated by utilizing image analysis techniques [14]. An equation was deduced to

compute the HIS (Fig. 1). Patients with CFS usually exhibited HIS values greater than -0.98 . Reproducibility of the HIS with reference to the -0.98 threshold, on repeated HUTTs at 2–4 week intervals, was 100%. In an initial study, the HIS threshold of -0.98 differentiated CFS patients from healthy subjects with 97% sensitivity (in patients who completed the full duration of the HUTT) and 96.6% specificity [14]. In a second study, the specificity of the proposed HIS threshold of -0.98 for CFS was evaluated comparing patients with CFS and other patients with disorders of clinical similarity to CFS, as well as disorders in which dysautonomia is known to be present [15]. In this second study, the HIS threshold -0.98 differentiated between CFS patients (HIS = $+2.02$ (SD 4.07)) and healthy subjects (HIS = -2.48 (SD 4.07)) as well as those suffering from fibromyalgia, neurally mediated syncope, and non-CFS fatigue. The overall specificity of the HIS for the diagnosis of CFS was 85.1% [15,16].

The finding that the HIS calculated for CFS separated out these patients from others with dys-

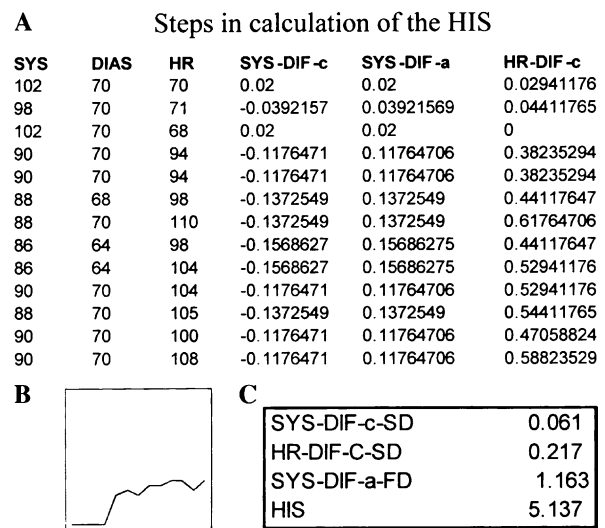


Figure 1 Processing the HIS. Systolic, diastolic BP, and HR values of a CFS patient, taken throughout the HUTT are represented A. From the measured values, the relative changes of BP and HR were calculated, according to the equation: BP difference = $BP_{(n_1, \dots, n_{13})} - BP_{n_3} / BP_{n_3}$. Absolute values were then obtained by converting all results to positive numbers. Shown in the table are systolic BP differences as current (c) and absolute (a) values, as well as HR differences in current values (c). The BP and HR changes were utilized to calculate the SYS-DIF-c-SD and HR-DIF-c-SD (C), which are independent predictors of the HIS. The third independent predictor of HIS is the SYS-DIF-a-FD, and it was processed from the time-curve of the systolic BP differences (B) by a fractal analysis program. Finally, the three independent predictors were applied to compute the HIS (C). In this specific case, HIS $+5.137$ is typical for a CFS patient.

autonomia suggests that there are unique features to the CFS dysautonomia phenotype. To further support the prospect of defining a characteristic dysautonomia in CFS patients, an additional technique was proposed to assess the cardiovascular reactivity during the HUTT. Beat-to-beat measurements of the heart rate (HR) and the pulse transit time (PTT) were rendered. Ten minute recording with the patient supine was followed by recording 600 cardiac cycles on tilt, i.e., 5–10 min. Data were processed by recurrence plot and fractal analysis. On multivariate analysis, the best predictors of CFS were determined, and, based on these predictors, the FRAS was calculated [17]. The best cut-off differentiating CFS from the control population was $FRAS = +0.22$. $FRAS > +0.22$ was associated with CFS (sensitivity 70% and specificity 88%). This study attested that CFS is associated with a distinctive dysautonomia. The possibility of distinguishing the cardiovascular reactivity of CFS, with the aid of the HIS and FRAS, from reactivity in other functional somatic syndromes, such as fibromyalgia [17] and neurally mediated syncope as described above tends to support that a CFS-characteristic dysautonomia may be operative. The three cross-sectional studies [15–17] converge to support the existence of a distinctive dysautonomia in CFS patients. The presence of phenotypic dysautonomia in CFS may provide objective criteria to the diagnosis of CFS, which until now, could only be subjectively inferred. The difference between diagnosing CFS by CDC criteria alone or based on combined, CDC and HIS or FRAS criteria is unclear, as no presently available test definitely establishes the diagnosis of CFS and can serve as a gold standard.

Monitoring the course of fatigue

Severity of fatigue is the main parameter used to monitor the course of CFS. Patients' feeling of fatigue can be assessed with self-administered fatigue questionnaires [18,19]. There is shortage of an objective measure to monitor the course of CFS. In particular, recognition of subtle changes, which may predict a clinical remission, would be important. The HIS may be useful as such. A prospective study (Naschitz et al, personal communication) was conducted in CFS patients to correlate changes in dysautonomia and the severity of fatigue with the HIS and fatigue questionnaires administered sequentially. Two questionnaires were employed, the unidimensional Chalder's fatigue severity scale (11 items) [18] and the multidimensional 'fatigue impact scale' (40 items) [19]. CFS patients were evaluated at regular intervals along a median 6 months period, at each point filling out both fatigue ques-

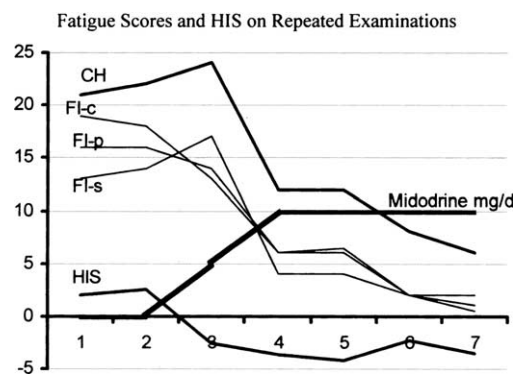


Figure 2 Longitudinal study of fatigue scores and HIS in a patient with CFS. Questionnaires and tilt tests were taken at 2–4 week intervals, before and along the treatment with midodrine. Normalization of the HIS occurred first, followed 2 weeks later by moderate improvement in fatigue. Considerable improvement in fatigue occurred 4–6 weeks following normalization of the HIS.

tionnaires and performing the HUTT. Analysis of the data showed that the simple Chalder's scale gave results comparable to the more complex and demanding fatigue impact scale. In general, the HIS and fatigue severity correlated consistently in patients with CFS, but normalization of the HIS preceded remission of fatigue by an interval of 3–6 weeks (Fig. 2). Thus, it would appear that the HIS might serve as an objective means to monitor the course of CFS. Further, the HIS may provide early information concerning the evolution of fatigue.

Treatment

Many therapies have been suggested in CFS but none has proven successful [2,6–8]. Since dysautonomic cardiovascular reactivity is frequently present in CFS patients, it may be that therapies directed at the autonomic nervous system may also improve fatigue symptoms. We hypothesized that midodrine treatment could benefit patients with the CFS. Midodrine HCl, a potent α -1-adrenergic agonist, is efficient in the treatment of hemodynamic disturbances such as symptomatic orthostatic hypotension, vasovagal syncope and postural tachycardia syndrome [20]. Ten patients with CFS and five control patients with non-CFS fatigue were studied. The patients were off medications for at least 2 weeks before entering the study. A dysautonomic reaction on HUTT (i.e., $HIS > -0.98$) was present in all CFS but not in the non-CFS control patients. Six patients showed subjective and objective improvement, which was maintained during 12 months of treatment. On last HUTT the average HIS was -1.51 (range -0.87 to -1.98). Non-CFS fatigue patients, with normal HIS at

baseline, had no improvement in HIS and fatigue scores while taking midodrine (Naschitz et al., personal communication). Results of this pilot study may spur larger prospective studies on the principle of manipulating the autonomic nervous system to improve both dysautonomic phenomena and fatigue in CFS.

CFS – facts, hypotheses, hopes

The importance of HIS and FRAS as measures of dysautonomia in supporting the diagnosis of CFS is apparent; however, the difference between diagnosing CFS by use of CDC criteria alone versus combined CDC and HIS criteria remains to be demonstrated. A pilot study suggested that midodrine treatment, directed at the autonomic nervous system in CFS, results first in correction of dysautonomia followed by improvement of fatigue. This finding implies that dysautonomia is pivotal in the pathophysiology CFS, at least in a large part of the patients, and that manipulating the autonomic nervous system may be effective in the treatment of CFS occurrence of dysautonomia has been demonstrated.

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