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Original article

Down-regulation of renin–aldosterone and antidiuretic hormone systems in patients with myalgic encephalomyelitis/chronic fatigue syndrome

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ABSTRACT

Background: Central nervous system dysfunction associated with myalgic encephalomyelitis (ME) has been postulated as the cause of chronic fatigue syndrome (CFS). A small heart or reduced left ventricular volume with reduced cardiac output has been reported to be common in patients with ME. The main circulatory blood volume regulators may be down-regulated.
Methods: Plasma levels of the neurohumoral factors that regulate circulatory blood volume were determined in 18 patients with ME and 15 healthy subjects (Controls).
Results: The echocardiographic examination revealed that the mean values for the left ventricular end-diastolic diameters, stroke volume index, and cardiac index as well as the mean blood pressure were all significantly smaller in the ME group than in the Controls. The mean plasma renin activity (1.6 ± 1.0 ng/ml/h vs. 2.5 ± 1.5 ng/ml/h, $p = 0.06$) was considerably lower in the ME group than in the Controls. Both the mean plasma aldosterone (104 ± 37 pg/ml vs. 157 ± 67 pg/ml, $p = 0.004$) and antidiuretic hormone (ADH) (2.2 ± 1.0 pg/ml vs. 3.3 ± 1.5 pg/ml, $p = 0.02$) concentrations were significantly lower in the ME group than in the Controls. Desmopressin (120 μg), a synthetic version of arginine vasopressin, was orally administered for five successive days to 10 patients with ME. In five patients (50%), the symptoms of orthostatic intolerance during a 10 min active standing test were ameliorated in association with a significant increase in urinary osmotic pressure and decrease in heart rate. Furthermore, in five patients (50%), the performance status scores for the activities of daily living were improved.
Conclusions: Both the renin–aldosterone and ADH systems were down-regulated despite the existence of reduction in cardiac preload and output in patients with ME. Desmopressin improved symptoms in half of the patients.

Introduction

Chronic fatigue syndrome (CFS) is characterized by severe disabling fatigue and post-exertional malaise, which are not resolved by rest, and causes a marked reduction in the activities of daily living, and impairs the quality of life [1–3]. Recently, dysfunction of the central nervous system associated with myalgic encephalomyelitis (ME) has been postulated as the main cause of CFS [4]. The International Consensus Criteria for ME differentiate patients with ME from those who are depressed and identify patients who are more physically debilitated and have greater physical and cognitive impairments [4].

It has been reported that, in many patients with ME/CFS, cardiac function was impaired in association with a low cardiac output due to a small left ventricle (LV) or a low cardiac volume, suggesting a hypovolemic condition [5,6]. Hemodynamic abnormalities, including a smaller LV chamber size and reduced cardiac stroke volume and performance during the exacerbation phase, improved during the remission phase, suggesting a direct relationship between the symptom severity and impaired cardiac function [6]. Indeed, patients with CFS have various possible cardiovascular complaints, including chest pain, palpitation, dyspnea, cold feet, dizziness, and fainting, although all of these symptoms are not necessarily attributable to cardiovascular dysfunction [7].

Most patients with ME/CFS have orthostatic intolerance (OI), which primarily restricts the daily functional capacity and in turn quality of life [8–13]. OI is characterized by the inability to remain upright without severe signs and symptoms, such as hypotension, tachycardia, light-headedness, pallor, fatigue, weakness, dizziness,

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diminished concentration, tremulousness, and nausea [10–12]. Most symptoms of OI appear to be related to reduced cerebral blood flow with or without impaired cerebral circulatory autoregulation, and the compensatory activation of the sympathetic nervous system. Both ME/CFS and OI affect many young individuals and have a strikingly high female preponderance. It has been reported that reduced cardiac performance with a small heart or LV and low cardiac output is pronounced in patients with both ME and OI [12].

In the present study, cardiac function was echocardiographically determined and blood levels of the neurohumoral factors including plasma renin enzymatic activity (PRA) and concentrations of aldosterone and antidiuretic hormone (ADH), the main regulatory factors for circulatory blood volume, were determined in patients with ME as compared with those in healthy controls. In addition, the therapeutic effects of orally administered desmopressin, a synthetic version of arginine vasopressin, a natural ADH, were investigated in patients with ME.

Methods

Study population

Patients who visited our clinic, were diagnosed with ME and gave informed consent to participate, were consecutively included in the present study. ME was diagnosed according to the International Consensus Criteria proposed in 2011 [4]. Briefly, symptoms related to neuroimmune exhaustion, such as marked, rapid physical and/or cognitive fatigability in response to exertion, prolonged recovery period, and low threshold of physical and mental fatigability, were compulsory for the diagnosis of ME. In addition, at least one symptom from 3 of the 4 symptom categories related to neurological impairments, including neurocognitive impairments, pain, sleep disturbance, and neurosensory, perceptual and motor disturbances, and at least one symptom from 3 of the 5 symptom categories related to immune, gastro-intestinal, and genitourinary impairments, including recurrent or chronic flu-like symptoms, susceptibility to viral infections, gastro-intestinal tract symptoms, genitourinary symptoms, and sensitivities to food, medications, odors, or chemicals, were required. Also, at least one symptom of the symptoms related to energy metabolism/ion transportation impairments, including cardiovascular symptoms such as orthostatic intolerance, respiratory symptoms, loss of thermostatic stability, and intolerance of extremes of temperature, was required.

The study population comprised 18 patients with ME (group ME), including 6 men and 12 women with a mean age of 32 ± 8 (range: 17–45) years, to compare with 15 age- and sex-matched sedentary healthy subjects (Controls), including 5 men and 10 women with a mean age of 30 ± 9 (range: 18–44) years. All patients with ME complained of OI. The study is in compliance with the standards in the 1964 Declaration of Helsinki and its later amendments and was approved by the ethical committee of our institute on October 28, 2013. All of the study patients gave informed consent, and the study began on November 1, 2013 and ended on February 28, 2015.

Blood assay of neurohumoral factors

Blood samples were taken from the study subjects in either the morning or the afternoon after they had spent 15 min in the recumbent position. The plasma was separated by refrigerated centrifugation at -4 °C and stored at -70 °C until the assay. PRA was assayed by the conversion of angiotensinogen to angiotensin I by a radioimmunoassay technique using a PRA kit (TFB, Tokyo, Japan). Plasma aldosterone concentrations (PACs) were measured by radioimmunoassay using a Spack S Aldosterone kit (TFB). Plasma ADH (arginine vasopressin) concentrations were determined by double antibody radioimmunoassay using an AVP RIA neo ⌜LSIM⌟ kit (Mitsubishi Chemical Medience, Tokyo, Japan).

Echocardiography

All of the study subjects underwent standard M-mode and 2-dimensional echocardiography. The LV dimensions were measured according to the recommendations of the American Society of Echocardiography [14]. The LV volume was calculated using the Teichholz formula [15], and the ejection fraction was also calculated.

Desmopressin trial

Desmopressin 120 μg, a synthetic version of arginine vasopressin, was orally administered after breakfast for five successive days to 10 ME patients with OI. Another informed consent was obtained from these patients prior to the treatment with oral desmopressin with the possible effects of circulatory volume expansion. The patients underwent the conventional 10 min active standing test following the echocardiographic examination in the morning before and on the 5th day of the administration. Also the performance status (PS) score of daily living [16] and the spotty urinary osmotic pressure were examined before and on the 5th day of the administration.

PS was graded according to symptom severity as reported previously [16] before and after the administration of desmopressin.

Active standing test

The conventional 10 min active standing test was performed following the echocardiography, as reported previously [16]. Postural orthostatic tachycardia (POT) was diagnosed as an increase in heart rate of $\geq$30 beats/min and/or heart rate of $\geq$120 beats/min during the 10 min standing test. Instantaneous or delayed orthostatic hypotension was diagnosed as a decrease in systolic blood pressure of $\geq$20 mmHg or diastolic pressure of $\geq$10 mm Hg and/or systolic pressure of $\leq$90 mmHg during the test. Neurally mediated hypotension was diagnosed as orthostatic hypotension with a decrease in heart rate of $\geq$20 beats/min during the test.

Statistical analysis

Continuous variables are presented as the mean $\pm$ standard deviation. Student's *t*-test was used to compare continuous variables. Comparisons of the echocardiographic parameters and urinary osmotic pressures before and after the administration of desmopressin were performed using Student's paired sample *t*-test. The value for significance was set at $p < 0.05$.

Results

The echocardiographic findings are summarized in Table 1. The mean heart rate was comparable between the ME group and the Controls. The mean blood pressure was significantly lower in the ME group than in the Controls while the mean value of the calculated total systemic resistance was not significantly different between the groups. The mean values for LV end-diastolic diameter (EDD), stroke volume index, and cardiac index were all significantly lower in the ME group than in the Controls.

The comparative plasma levels of the neurohumoral factors between the ME group and the Controls are summarized in Table 1 and Figs. 1–3. There was a strong trend ($p = 0.06$) toward lower PRA in the ME group compared with that in the Controls (Fig. 1). The

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