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Orthostatic Tolerance Testing in a Prospective Cohort of Adolescents With Chronic Fatigue Syndrome and Recovered Controls Following Infectious Mononucleosis

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Abstract

Chronic fatigue syndrome (CFS) is a complex condition responsible for marked functional impairment. The authors recently reported that 6 months following acute infectious mononucleosis (IM), 13%, of adolescents met criteria for CFS. The authors' objective was to assess standing orthostatic tolerance (SOT) in adolescents with CFS and in controls 6 months following IM. In all, 36 of 39 adolescents diagnosed with CFS 6 months following IM and 43 of 50 recovered controls had SOT testing (SOTT) performed. χ^2 Analysis was performed to study the relationships between SOTT and the diagnosis of CFS. Adolescents diagnosed with CFS and recovered controls did not differ significantly in age, weight, or body mass index. The authors found that 9 of 36 adolescents with CFS (25%) versus 9 of 43 recovered controls (21%) had an abnormal SOTT, which was not a statistically significant difference. Adolescents who meet criteria for CFS 6 months following IM do not have, as a group, more standing orthostatic intolerance than recovered controls.

Keywords

adolescent health, chronic fatigue, mononucleosis, orthostatic tolerance

Introduction

Chronic fatigue syndrome (CFS) is a complex condition involving severe fatigue and disabling musculoskeletal and cognitive symptoms.[1] Chronic fatigue accounts for marked functional impairment and educational disruption among adolescents.[2-5]

Orthostatic intolerance (OI), defined by symptoms (eg, lightheadedness) or signs (eg, diaphoresis) when upright that are relieved by recumbence, is often reported among those with CFS, particularly young patients.[6,7] We recently reported the results of a 2-year prospective study of CFS following monospot-positive acute infectious mononucleosis (IM) in adolescents. It was found that 6 months following IM, 13% of adolescents met criteria for CFS.[8] As part of their 6-month evaluation, 36 of 39 adolescents diagnosed with CFS and 43 of 50 controls who had completely recovered from their IM participated in an orthostatic tolerance test. Here, we report the results of that testing.

Methods

Participants

We enrolled adolescents in the greater Chicago area with monospot-positive acute IM, identified via school nurses and pediatric practices, including the Pediatric Practice Research Group[9] and the Virology Laboratory of Children's Memorial Hospital. Then, 6 months following their IM diagnosis, a telephone screening interview identified IM patients who had not fully recovered and

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50 who had fully recovered who were willing to come for a clinical evaluation. The fully recovered patients comprised our controls. All aspects of the study were approved by the institutional review boards of Children's Memorial Research Center and the College of Applied Sciences of the University of Illinois at Chicago.

Definitions

We used the Jason et al[10] revision of the Fukuda[1] criteria to diagnose CFS. When a well-recognized underlying condition, such as primary depression, could explain the patient's symptoms, we classified him or her as having "CFS-explained." OI was defined by symptoms (eg, lightheadedness, nausea, headache, and heat) or signs (eg, hypotension, excessive tachycardia, bradycardia, pallor, and diaphoresis) that were relieved by recumbence.[6,7]

Evaluation

The 6-month clinical evaluation consisted of a complete history, physical examination, and laboratory screening to rule out medical causes of CFS (eg, cardiac, thyroid, or toxicologic). We did not ask about caffeine intake.

Using the data from the clinical evaluation, a diagnosis of CFS, CFS-explained, or recovered was made on each participant after review by an expert panel, as previously described.[8] All CFS case patients and controls underwent orthostatic tolerance testing 6 months following the diagnosis of IM.

Standing Orthostatic Tolerance Testing (SOTT)

SOTT was performed by Clinical Research Center study nurses blinded to patient category (recovered vs nonrecovered). Participants were standing freely and attached to an oscillometric blood pressure (BP) monitor (Hewlett Packard Omnicare 24C Model # M 1204A, Palo Alto, CA), which was set for recording every minute. The heart rate (HR) was obtained by auscultation. Participants were instructed to remain calm and to refrain from moving or speaking except when reporting symptoms of OI. Distractions were removed, and the lights were dimmed. A baseline BP and HR recording was obtained after a 20-minute supine resting period, after which participants were asked to rapidly stand up. Then, 10 subsequent HR and BP readings were recorded (once per minute) in the standing positions. Interpretation of SOTT data was performed by an expert (JMS) blinded to the participant's diagnosis.

Significant hypotension was defined as a >30 mm Hg decrease in systolic BP or a 15 mm Hg decrease in diastolic BP or both. Borderline hypotension was defined as >15 mm Hg decrease in systolic BP or a 10 mm Hg decrease in diastolic BP or both. Significant relative bradycardia was defined as a HR < 75% of the resting HR. Borderline relative bradycardia was defined as any decrease in standing HR to a value less than that recorded during supine rest. Significant tachycardia required an increase in HR by 40 or more beats/min (bpm) to a HR that was >90 bpm. The symptoms and signs of OI have already been defined. Both signs and symptoms needed to occur together in order to diagnose OI. Thus, for example, transient (usually <30 s) initial orthostatic hypotension,[11] a normal response to rapid standing, which provokes short-lived symptoms of OI but no detectable signs by current methods, was excluded. Postural tachycardia syndrome (POTS) is synonymous with chronic OI.[12] When upright, patients experience symptoms of OI, including lightheadedness, loss of vision, nausea, headache, fatigue, mental cloudiness, and hyperpnea. Symptoms are associated with an excessive postural tachycardia, which occurs within 10 minutes of becoming upright. In adults, this is defined by an increase in HR of 30 bpm or a HR that exceeds 120 bpm; an increase of 40 bpm is an appropriate increase in HR for adolescents. The original definition of POTS precluded hypotension.[13]

Syncope (fainting) is defined by a sudden, rapid, and transient loss of consciousness and postural tone as a result of cerebral hypoperfusion.[14] Syncope is usually associated with decreased BP and a prodrome that may include lightheadedness, nausea, cognitive loss, heat, hyperpnea, and diaphoresis. Presyncope or near syncope is defined by signs and symptoms of impending syncope (ie, the prodrome) without loss of consciousness. Simple postural faint is identified with vasovagal syncope, in which vasodilation causing hypotension and hypervagotonia causing bradycardia are relieved by recumbency.[15]

Analysis

χ^2 Tests were used to evaluate the correlation between SOTT and the diagnosis of CFS 6 months following IM.

Results

There were 301 adolescents with monospot-positive IM enrolled in the study. At 6 months following their IM diagnosis, 286 (95%) completed a telephone screening interview. Based on the screening interview, 70 of these adolescents (24%) were assessed as not fully recovered. A 6-month clinical evaluation was completed on 53

(76%) of these 70 not fully recovered adolescents, following which 39 of the 53 were classified as having CFS (13% of the original sample of 301 adolescents). Of the 39 participants with CFS at 6 months, 35 (90%) were female, and all were at least Tanner stage 4.

Also, 50 adolescents who had fully recovered from IM and who were willing to enter a clinical trial underwent the same 6-month evaluation and comprised the control population. There was no difference in age, race, and socioeconomic status between recovered adolescents who were and were not used as controls for this study.

Participant Characteristics

In all, 36 of the 39 adolescents diagnosed with CFS at 6 months (92%) and 42 of the 50 fully recovered controls (86%) participated in the orthostatic tolerance test. There was no difference between the cases and controls who did and did not undergo orthostatic testing in several parameters examined (age, socioeconomic status, body mass index, and modifiable activity questionnaire responses). Of the 43 recovered controls tested, 13 were male (30%), as were 4 of the 36 tested with CFS (11%; $P < .05$).

No patient was on bed rest or had significant thyroid or cardiac disease. Two case patients had mitral valve prolapse, and 1 had an episode of vasovagal syncope 2 to 3 years before entering our study. Of the control patients, 1 had 2 prior elevated BP measurements, and 1 had mitral valve prolapse. Commonly used medications included birth control pills (8 case patients, 2 control patients), asthma/allergy medications (8 case patients, 5 control patients), anti-inflammatory/antipyretic medications (5 case patients, 2 control patients), anti-migraine/anti-anxiety/ADHD/anti-seizure medications (3 case patients, 6 control patients), and acne medications (2 case patients, 4 control patients). Also, 1 case patient, but no control patient, admitted to smoking >5 cigarettes/d. Four case patients and 3 control patients drank more than occasionally. No case or control patients were active users of street drugs at the time of the study, and no case or control patient had an unexplained positive urine toxicology screen to any drug other than tetrahydrocannabinol (THC) that they were not prescribed.

Orthostatic Tolerance Testing

There was no correlation between the standing ratings on orthostatic tolerance testing and the diagnosis of CFS at 6 months by χ^2 analysis. Of 36 patients with CFS, 27 had normal SOTT (75%) compared with 34 of 43 recovered controls (79%). Two patients with CFS versus 4 recovered controls had either syncope or presyncope during the SOTT; 7 patients with CFS were characterized as having POTS compared with 5 recovered controls (see Table 1).

Table 1. Orthostatic Tolerance Testing at 6 Months Among Patients With CFS and Controls

	CFS (n = 36)	Controls (n = 43)
Supine		
Male	4	13
Normal	35	43
Abnormal	1	0
Standing[a]		
Normal	27	34
Abnormal	9	9
POTS	7	5
Presyncope/Syncope	2	4

Abbreviations: CFS, chronic fatigue syndrome; POTS, postural tachycardia syndrome.
[a]χ^2 for standing ratings × diagnoses (normal vs abnormal) = 0.18 ($P > .5$), POTS versus no POTS = 0.93 ($P > .1$); syncope/presyncope versus no syncope/presyncope = 0.39 ($P > .5$); male versus female = 4.2 ($P < .05$).

Peak HR differences were similar between cases (37 bpm) compared with the recovered controls (35 bpm), as were the number of cases and recovered controls with HR > 115 bpm (11 of 36 cases vs 9 of 43 controls). There was also no correlation between those with abnormal exercise testing as reported previously[16] and those with either syncope/presyncope or POTS (data not shown).

Discussion

Orthostatic tolerance can be quantified with standardized testing. Previous studies in adolescents with CFS have identified a higher prevalence of OI[17-23]; this has been true of some studies in adults with CFS as well.[24-27] Our data do not confirm these previous studies, which showed that OI occurred with increased prevalence in CFS compared with other, related conditions and compared with controls who did or did not have a history of syncope.[18-20,23-25,27]

One reason why our data differ from those previously reported could be our modest sample size (β error); there is a slight trend toward more abnormal SOTT in our CFS population when compared with recovered controls (25% vs 21%), although for this trend to be statistically significant would require a sample population many times larger than we could muster in the present study. Other differences between our study and previous studies include the lack of a healthy control group who were not recovering from IM, lack of data concerning caffeine consumption, the homogeneity of our population

(all cases and controls following an episode of mono-spot-positive acute IM) and possibly the relatively mild degree of orthostatic stress to which we subjected our participants (eg, only 10 minutes of standing and no upright tilt). Finally, OI by itself is not a reported complication following IM, and thus, one would not expect to find a higher incidence of OI in our controls than those reported in previous studies. The fact that more of our patients with CFS versus the recovered controls were female is expected and would have biased the study toward finding SOTT abnormalities in patients with CFS because OI is also more common in women.[17-20,22,23]

One strength of our study was that there was no systematic bias in terms of which case and which control patients were referred for orthostatic testing[18,19]; nearly all recovered control and case patients were tested. Another strength was that because none of our case patients were on bed rest, deconditioning was not a confounder.[28] In conclusion, we have shown that in adolescents with CFS following IM, standing OI is not a major component of the syndrome.

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