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Lack of Initial Orthostatic Hypotension in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Following Infectious Mononucleosis

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Abstract

Background/Objective: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic disease characterized by substantial fatigue, post-exertional malaise, unrefreshing sleep, and cognitive impairment, among other symptoms. We examined whether initial orthostatic hypotension (IOH) is more common in those who develop ME/CFS following infectious mononucleosis (IM) than in recovered controls.

Methods: This study was part of a prospective cohort study in which we studied college students for the development of IM and then followed them for the development of ME/CFS six months later. Participants included 50 students who met criteria for ME/CFS six months following IM and 62 recovered controls who had available objective heart rate and blood pressure results recorded.

Results: There was no significant relationship between the presence of IOH in patients with ME/CFS following IM versus controls.

Conclusions: IOH is not seen in college students with ME/CFS following IM more commonly than in recovered controls.

Keywords: *Myalgic encephalomyelitis, Chronic fatigue syndrome, Initial orthostatic hypotension, Infectious mononucleosis*

Introduction

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic illness that affects daily functioning across physical, mental, and psychosocial domains [1], characterized by substantial fatigue, post-exertional malaise, unrefreshing sleep, and other symptoms. At least 9-12% of individuals meet criteria for ME/CFS six months following infectious mononucleosis (IM) [2-5], and some studies have shown a high frequency of Orthostatic Intolerance (OI) in adolescents with CFS [6-9].

Orthostatic Intolerance (OI) is defined as an inability to tolerate an upright position that is relieved by recumbence. There are at least three common types of OI. One is simple fainting, or vasovagal syncope which is associated with vagally induced bradycardia [10]. Two other, common types of OI are Postural Orthostatic Tachycardia Syndrome (POTS) and Orthostatic Hypotension (OH). POTS is defined as a sustained increase in Heart Rate (HR) of at least 30 beats per minute (40 beats per minute if 12-19 years of age) in the first 10 minutes when going from a supine to an upright position in the absence of OH [11]. OH is defined as a decrease of at least 20 mmHg in systolic Blood Pressure (BP) or a decrease of at least 10 mmHg in diastolic BP upon changing positions [12].

Excessive postural tachycardia is defined as a sustained increase in HR of at least 30 beats per minute when going from a supine to upright position in those 20-22 years of age and an increase in HR of at least 40 beats per minute in those 18-19 years of age on a 10-minute head-up tilt test [10-13]. Initial Orthostatic Hypotension (IOH) is defined as a decrease of at least 40 mm Hg in systolic BP or a decrease of at least 20 mm Hg in diastolic BP upon standing up for one minute [14,15].

Excessive postural tachycardia has been shown to be unrelated to OI in youth [13] and generally not associated with POTS [12]. IOH has been shown to be common in adolescents; it may lead to transient reflex tachycardia in the POTS range [14,16-18], and in older adults can be associated with fainting [19].

We did not see a difference in orthostatic tolerance testing between participants who developed ME/CFS six months following IM vs recovered controls using a 10 minute standing test in a previous study [20]. We therefore decided to study IOH in a prospective cohort of college students who either recovered from IM or met criteria for ME/CFS 6 months later.

Methods

We studied IOH in a population of patients who did and did not develop ME/CFS following IM. Any student with compatible

symptoms was diagnosed with IM if they had a positive monospot or specific Epstein-Barr virus serologies. Students were defined as having ME/CFS if they met the Fukuda [21], Canadian 1 or Institute of Medicine [22] criteria. Participants who met > 1 set of criteria for ME/CFS were termed as having severe ME/CFS (S-ME/CFS) [23].

Our sample was derived from a group of 4501 college students studied prospectively. Two hundred thirty-eight developed IM. Five months after the diagnosis of IM, participants deemed not recovered and a number of matched, recovered controls were invited back for a comprehensive medical and psychiatric examination [24]. Fifty-five of the 238 students with IM met the criteria for ME/CFS 6 months later; 67 recovered students were chosen as matched controls [24]; for more details, see Jason et al [24].

Participants in the cohort for the present study included the 50 students who met criteria for ME/CFS six months following IM and 63 recovered controls, who at the 6 month post IM medical examination, had HR and BP recorded after being recumbent for 5 minutes and then after 1 minute of standing. One control and one participant with ME/CFS were missing systolic blood pressure data; one patient with ME/CFS was missing HR data. Seventeen of the 50 patients with ME/CFS six months following IM met criteria for S-ME/CFS. The patient's chart was reviewed to verify the diagnosis (ME/CFS, S-ME/CFS or recovered based on the medical examination and confirming self-report information), for basic demographic information (age, sex), and to record the heart rate and blood pressure readings that were obtained during the routine physical examination, first after being recumbent for 5 minutes resting in the dark and then after 1 minute of standing. For the purposes of this study, postural tachycardia, (PT), as a component of IOH, was defined as a sustained increase in HR of at least 30 beats per minute when going from a supine to upright position in those 20-22 years of age and an increase in HR of at least 40 beats per minute in those 18-19 years of age [10-13]. IOH was defined as a decrease of at least 40 mm Hg in systolic BP or a decrease of at least 20 mm Hg in diastolic BP upon standing up for one minute [14,15]; however, a preliminary examination of our data did not reveal any BP changes of this magnitude, so we also examined a decrease of at least 20 mmHg in systolic BP or a decrease of at least 10 mmHg in diastolic BP upon standing up for one minute, as per OH criteria [10].

Chi square statistics were used to determine if there was a relationship between the presence of PT, IOH and the diagnosis of ME/CFS following IM where the N was > 5 in all groups; where the N was < 5 in some groups, Fisher's exact test was used.

The study was approved by the Institutional Review Boards of all involved institutions.

Results

Tables 1-3 show the results of our analyses. As mentioned in the Methods section, a preliminary examination of our data did not reveal any changes in systolic BP of > 40 mm Hg (maximum was 32 mm Hg in a single participant) nor any changes in diastolic BP > 20 mm Hg (maximum was 18 mm Hg and 13 mm Hg in 2 different participants, neither of whom had the systolic BP change of 32 mm Hg). Therefore, all data in Tables 2 and 3 reflect OH BP criteria [10].

Table 1: Comparison of participants with ME/CFS, S-ME/CFS and Recovered Controls: ME/CFS and Postural Tachycardia (PT).

	Recovered Control	ME/CFS	S-ME/CFS
PT	6% (N=4)	15% (N=5)	18% (N=3)
No PT	94% (N=59)	85% (N=27)	82% (N=14)
Missing Data		3% (N=1)	
Total	100% (N=63)	100% (N=33)	100% (N=17)

P values: Control vs ME/CFS – 0.16.
Control vs S-ME/CFS – 0.16.

Table 2: Comparison of participants with ME/CFS, S-ME/CFS and Recovered Controls: ME/CFS and IOH (using OH BP cutoffs [10]).

	Recovered Control	ME/CFS	S-ME/CFS
IOH	14% (N=9)	21% (N=7)	18% (N=3)
No IOH	86% (N=54)	79% (N=26)	82% (N=14)
Total	100% (N=63)	100% (N=33)	100% (N=17)

P values: Control vs ME/CFS – 0.39
Control vs S-ME/CFS – 0.71

Table 3: Comparison of participants with ME/CFS, S-ME/CFS and Recovered Controls: ME/CFS and PT or IOH (using OH BP cutoffs [10]).

	Recovered Control	ME/CFS	S-ME/CFS
PT and/or IOH	21% (N=13)	36% (N=12)	35% (N=6)
No PT or IOH	79% (N=50)	64% (N=21)	65% (N=11)
Total	100% (N=63)	100% (N=33)	100% (N=17)

P values: Control vs ME/CFS – 0.10
Control vs S-ME/CFS – 0.21

Participants with ME/CFS, S-ME/CFS, and recovered controls were compared. Students ranged in age from 18-23 years (median 20 years); there were 73 females and 40 males. There were no significant mean age differences between conditions: 18.8 (0.5) years for students with S-ME/CFS, 18.9 (0.9) years for students with ME/CFS and 18.7 (2.6) years for the recovered controls [24]. None of our patients had a positive Romberg test, which in some studies has been linked to OI [25].

Table 1 shows the relationship between participants with ME/CFS, S-ME/CFS and recovered controls with respect to PT. There was no relationship between participants with ME/CFS and PT compared with recovered controls (Fisher's exact test: S-ME/CFS vs Control: p = 0.11; ME/CFS vs Control: p=0.42, ME/CFS and S-ME/CFS vs Control: p = 0.18; overall p = 0.17).

Table 2 shows the relationship between participants with ME/CFS, S-ME/CFS and Recovered Controls with respect to IOH (using OH BP criteria10). Again, there was no relationship between participants with ME/CFS having more IOH (using OH BP criteria10) than recovered controls (S-ME/CFS vs Control: x2 = 1.53, p = 0.22, ME/CFS vs Control: x2 = 0.38, p=054, ME/CFS and S-ME/CFS vs Control: x2 = 1.09, p = 0.3; overall x2 = 1.56, p = 0.46).

Table 3 shows the relationship between participants with ME/CFS, S-ME/CFS and Recovered Controls with respect to either PT and/or IOH (using OH BP criteria10). Again, there was no relationship between participants with ME/CFS having either PT or IOH (using OH BP criteria10) when compared with recovered controls (S-ME/

CFS vs Control: x2 = 1.50, p = 0.22 ME/CFS vs Control: x2 = 1.02, p=31, S-ME/CFS and ME/CFS vs Control: x2 = 1.76, p = 0.19; overall x2 = 1.9, p = 0.39).

Discussion

In a well-studied population of college students six months following IM, we found no significant relationship between PT or IOH (even using the less stringent OH BP criteria 10) and ME/CFS following IM. If a patient had both ME/CFS and IOH, therapeutic maneuvers (e.g., static handgrip or lower body tensing) might be helpful in alleviating some symptoms [26,27].

Autonomic dysfunction is thought to play a role in the pathophysiology of OH and POTS [28,29], although autonomic complaints may not correlate with the presence of autonomic dysfunction on physical examination [30]. The relationship between ME/CFS and autonomic dysfunction has been seen in many [6-9,28,29,31,32] but not all [20,33] previous studies. There are studies that suggest that OI may characterize only a subgroup of those with ME/CFS [34,35], and the data presented here and previously [20] do not exclude that possibility. If present, the diagnosis of OI in patients with ME/CFS may provide some direction for management of the often debilitating symptoms of ME/CFS, such as increasing salt and fluid intake and the use of compression stockings and certain medications [28,29,36].

Strengths of our study include its prospective nature and the gathering of data before the final diagnosis (ME/CFS vs recovered control) was known, leading to unbiased data collection. The main limitation of our study is the lack of performing a 10 minute standing test of orthostatic intolerance, although we did this in a previous study in a similar population of patients with ME/CFS following IM [20] and found no relationship between the diagnosis of ME/CFS following IM and OI. Other limitations include the lack of tilt table testing and not examining patients on bad days, when OI may be more prominent [25].

Conclusions

In conclusion, we found no significant relationship between IOH and the diagnosis of ME/CFS in a well-studied prospective cohort of college students who developed ME/CFS six months following IM, as we found no relationship between abnormalities in orthostatic tolerance testing between a similar sample of participants with ME/CFSD following IM and recovered controls [20].

List of Abbreviations

BP: Blood Pressure; HR: Heart Rate; Ig: Immunoglobulin; IM: Infectious Mononucleosis; IOH: Initial Orthostatic Hypotension; ME/CFS: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; OH: Orthostatic Hypotension; OI: Orthostatic Intolerance; POTS: Postural Orthostatic Tachycardia Syndrome; PT: Postural Tachycardia; S-ME/CFS: Severe ME/CFS; VCA: Viral Capsid Antigen

Declarations

Ethics approval and consent to participate: The study was approved by the Institutional Review Boards of DePaul University (Protocol # LJ09031PSY-R36) and the Ann & Robert H Lurie Children's Hospital of Chicago (IRB 2020-34867 in accordance with the Declaration of Helsinki. Written consent was obtained from all participants.

Consent for Publication

N/A

Availability of Data/Materials

Materials described in this manuscript, including all relevant (de-identified) raw data will be freely available to any researcher wishing to use them for non-commercial purposes, without breeching participant confidentiality. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors report that there are no competing interests to declare.

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Authors' Contributions

SS, ES, ML and JF made substantial contributions to the acquisition, analysis, and interpretation of data, have made substantial revisions to the work, have approved the submitted version and have agreed both to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which they were not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

LAJ and BZK made substantial contributions to the conception and design of the work and helped in the acquisition, analysis and interpretation of the data. BZK drafted the first version of the work. LAJ and BZK have made substantial revisions to the work, have approved the submitted version, and agree to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which they were not personally involved are appropriately investigated, resolved and the resolution documented in the literature.

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