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Case Report

Postpartum Postural Orthostatic Tachycardia Syndrome in a Patient with the Joint Hypermobility Syndrome

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Postural orthostatic tachycardia syndrome (POTS) commonly affects women of childbearing age. We report on a 37-year-old woman who developed symptoms of recurrent syncope in the postpartum period. Her head up tilt test and clinical presentation was consistent with POTS.

1. Introduction

Recurrent unexpected syncope may have severe consequences and can result in serious injury, especially in a postpartum period when the maternal syncope can have the disastrous effect on the newborn infant as well as the mother. Postpartum syncope has been reported to result in death due to dropping of the infants [1]. We report on a 37-year-old woman who developed recurrent episodes of syncope in the postpartum period.

2. Case

A 37-year-old woman with a past medical history of migraine headache and reflux esophagitis was seen in our autonomic clinic for evaluation of recurrent syncope. In the last nine years, she had experienced episodes of debilitating recurrent syncope. Her first episode occurred six months after she gave birth to her daughter. At that time, she described an episode that occurred while standing at work during which she became "fuzzy", lightheaded, and subsequently suffered from an episode of syncope with a brief loss of consciousness. She had no convulsive activity during this episode. She continued to experience episodes of lightheadedness without frank syncope. Six years after her first episode the symptoms and the frequency of episodes progressed to the point where she experienced approximately eight episodes of lightheadedness and palpitations over a period of six months, occasionally resulting in syncope. In the interim, multiple neurologists evaluated her. Ultimately, a cardiologist sent her for head up tilt test (HUTT). Upon the assumption of upright posture during the tilt test, her heart rate increased from 86 beats per minute (bpm) (baseline) to 126 bpm within 5 minutes, and her blood pressure dropped from 126 mm Hg (baseline) to 90 mm Hg, associated with symptoms of lightheadedness, palpitations and loss of consciousness. She was initially treated with fludrocortisone, which failed to relieve her symptoms. Midodrine (an alpha agonist) and methylphenidate (noncatecholamine sympathomimetic) were also tried but ineffective. She suffered multiple injuries (including head injuries) during these episodes of syncope, and her quality of life had markedly decreased. During one traumatic syncopal episode, she fell while attending physical therapy. In addition, she also suffered from loss of memory and balance problems.

In our clinic, she presented with a blood pressure of 100/80 sitting and 90/64 standing. Her supine heart rate was 70 beats per minute and immediately upon standing rose to 111 beats per minute. The rest of the physical examination was normal except for the presence of joint hypermobility in the bilateral wrists, thumbs, fingers, elbows, and ankles. After review of her history, physical exam, and the extensive evaluation, the diagnostic impression was autonomic dysfunction and orthostatic intolerance most consistent with new onset postpartum postural orthostatic tachycardia syndrome. Her overall clinical picture of orthostatic intolerance and joint findings were most consistent with joint hypermobility.

The initial core management choices here were reasonable; indeed the prior management was essentially exactly as our center would recommend.

She was commenced on Duloxetine, a serotonin/norepinephrine reuptake inhibitor. During her next clinic visit, she reported marked improvement in symptoms, except for headache and mild cognitive impairment. She was started on Cerefolin to help the memory loss [2].

3. Discussion

Multiple cardiovascular adaptations occur during pregnancy, which are essential for successful completion of pregnancy. These include an increase in cardiac output, sodium, and water retention with increase in expansion of blood volume and a reduction in peripheral vascular resistance and diastolic blood pressure [3]. These cardiovascular adaptations continue in the postpartum period and allow for return to a nonpregnant state. These changes in the postpartum period have not been well reported or studied [4]. Our patient developed recurrent episodes of syncope in the postpartum period. Postpartum syncope with significant maternal morbidity and one infant mortality has been reported previously [1]. There have been reports that patients with POTS can have a favorable outcome during pregnancy and in postpartum period [5, 6]. The joint hypermobility syndrome might have predisposed our patient to symptoms of orthostatic intolerance and made her vulnerable especially as she returned to the prepregnant state with gradual loss of estrogen/progesterone, induced fluid retention in the postpartum period.

In patients with POTS, the main mechanism is the consistent failure of the peripheral vascular system to increase resistance during upright posture. Patients with joint hypermobility syndrome even have more difficulty owing to loss of supporting connective tissues in the vessels. Orthostatic intolerance develops in these patients due to the presence of abnormally elastic connective tissue in the vasculature. This results in an increase in vessel distensibility in response to the augmented hydrostatic pressure that occurs during orthostatic stress. Consequently, there is excessive peripheral venous pooling with a resultant compensatory tachycardia. About 70% of patients with hypermobility syndrome may suffer from some form of orthostatic intolerance due to sympathetic dys-regulation [7]. Patients with POTS can present with syncope without a substantial fall in blood pressure. Increase in cerebrovascular resistance occurring during orthostatic stress can explain loss of consciousness in these patients [8].

These patients are usually treated with fludrocortisone [9] midodrine [10], methylphenidate [11], and selective serotonin reuptake inhibitors [12, 13]. Combined selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors such as duloxetine are most effective. Duloxetine is postulated to alter serotonin receptor density in brainstem area and thus alter autonomic tone.

In our experience, we have found that use of combined selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors has been more effective in POTS than in neurocardiogenic syncope [14].

4. Conclusion

POTS in the postpartum period can have serious consequences; indeed the risks associated with syncope can be life threatening not only to mother but also to the child as well. Early recognition and proper management of these patients are essential to prevent serious morbidity and mortality associated with this clinical entity. Long-term outcomes in patients with postpartum POTS are unknown.

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Letters to the Editor

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Non-musculoskeletal symptoms in joint hypermobility syndrome. Indirect evidence for autonomic dysfunction?

SIR, Joint hypermobility syndrome (JHS) is a chronically disabling disorder manifested as widespread pain, fatigue, multiple soft tissue lesions and fragility of skin and supportive connective tissues [1]. It is a condition that is often overlooked by clinicians [2]. Moreover, clinical experience suggests that previously unrecognized non-musculoskeletal symptoms, including presyncope, palpitations and bowel disturbance, are also common in JHS. Recent evidence demonstrates dysfunction of the autonomic nervous system as an explanation for these symptoms [3]. Recognition of these symptoms by clinicians is an important part of patient assessment and education, even if the pathophysiology remains unclear.

We have examined the prevalence of non-musculoskeletal complaints and explored their associations to determine whether they reflect a tendency to report multiple, non-specific concerns.

One hundred and seventy women aged between 18 and 65 yr were seen in a teaching hospital hypermobility clinic over a 2-yr period. Each was diagnosed with JHS using the 1998 Brighton criteria [4]. Individuals completed a self-reported questionnaire enquiring about symptoms experienced on a 'regular basis'. The questionnaire was structured so that patients were unaware of any hypothesis. Fifty female hospital staff acted as controls, having been identified as non-hypermobile by the use of a five-part self-report questionnaire [5]. The symptoms explored clustered into five domains: (i) (pre)syncope (feel faint, actually faint, dizziness and light-headedness); (ii) cardiorespiratory (CR) (palpitations, chest pain and shortness of breath); (iii) gastrointestinal (GI) (nausea, stomach ache, diarrhoea and constipation); (iv) common JHS concerns (fatigue, joint pain, anxiety and depression); and (v) non-specific (migraine, allergy, rash, nocturia, dysuria, flushing, night sweats, fever, lymph gland pain and poor sleep).

Similar symptoms were combined for analysis. For example, dizziness and light-headedness were considered synonymous with presyncope and were not treated as mutually exclusive. They were combined, so that a person giving both in their response was only counted once within the domain.

We found that 41, 26 and 37% of individuals with JHS reported at least one symptom suggestive of a (pre)syncopal, CR or GI complaint respectively. This compared with 15, 12 and 16% of controls, despite controls being older by a mean of 13 yr [32 yr (range 18–65) *vs* 45 yr (range 23–64)].

Pain, fatigue, anxiety and depression were, as one would expect, more common in JHS patients (91, 71, 32 and 38% respectively) than controls (30, 30, 12 and 8% respectively). Migraine, rashes and poor sleep were also over-represented amongst JHS patients. Other non-specific complaints (allergy, nocturia, dysuria, flushing, night sweats, fever and lymph gland pain) were equally distributed in cases and controls (Fig. 1).

Analysis was extended to look just at JHS patients, comparing those reporting (pre)syncopal, CR or GI concerns (or any combination of the three domains) against those who did not. Sixty per cent of patients recorded at least one type of concern relating to (pre)syncopal, CR or GI symptoms. Of this 60%, 28% reported concerns in one domain, 20% concerns within two domains, and 12% in all three. Those JHS patients classified as having symptoms in two or more of the three domains were found to account for 90% of all JHS patients reporting flushing or night sweats. Moreover, this group were three times more likely to complain of fatigue and anxiety [odds ratio 2.8 (95% confidence interval 1.3–6.3), $P = 0.01$] than their peers, fatigue and anxiety also being found to be independently associated with migraine and poor sleep (odds ratio 2.6 and 3.5 respectively). Age was not a confounder. No association was found with the other non-specific complaints (Fig. 2).

We conclude that non-musculoskeletal symptoms are common in patients with JHS and that individuals with these symptoms may express more fatigue, anxiety, migraine, flushing, night sweats

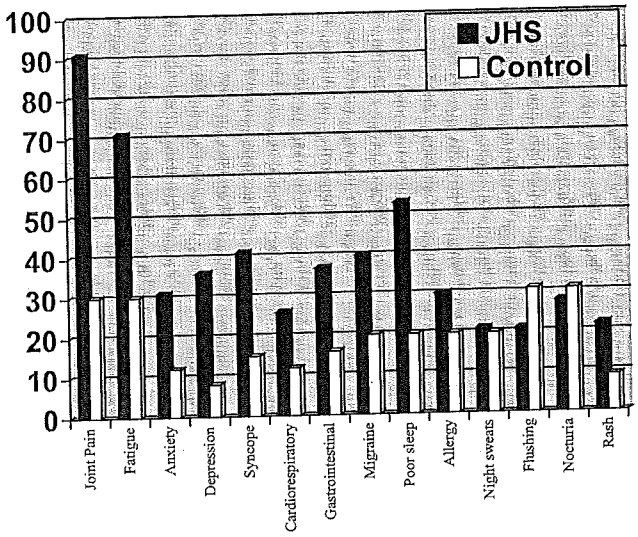

FIG. 1. Bar chart showing the percentage proportions of patients and controls reporting symptoms.

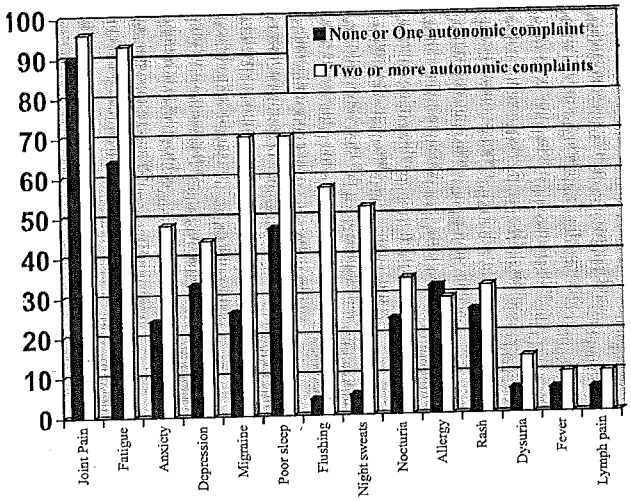

FIG. 2. Bar chart showing percentage proportions of symptom reporting in JHS patients only, classified by the presence or absence of at least two autonomic symptom domains.

and poor sleep than their peers. The pathophysiological basis for these symptoms needs to be explored further but may be a complication of autonomic dysfunction. Alternative explanations might include the side-effect of medications, particularly analgesics and antidepressants, or the presence of comorbidity. In our experience, however, the majority of patients seeing us for the first time are no longer taking such medications as they have often been of little benefit. We note also that very few patients have specific cardiovascular, respiratory or bowel disease.

Potential manifestations of autonomic pathology include cardiac dysrhythmias, postural orthostatic tachycardia syndrome, orthostatic hypotension and orthostatic intolerance. Mechanisms leading to such phenomena in JHS patients may include weakened vascular tissue elasticity and impaired peripheral vasoregulation as a consequence of adrenoceptor or neuronal abnormalities. Similar symptoms are found in chronic fatigue syndrome [6]. Consequently, these disturbances might also be secondary and reflect a degree of physical deconditioning rather than a primary autonomic or connective tissue pathology. Further studies are required. In the meantime, clinical assessment should include an enquiry as to the presence of such symptoms, and health professionals should acknowledge that they are often encountered among patients with JHS.

Ethical approval for the use of a general questionnaire identifying features of JHS both in clinical and epidemiological studies was gained from Guy's Hospital, London. Verbal consent was deemed sufficient.

The authors have declared no conflicts of interest.

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The mobile phone as an imaging tool in SLE

SIR, I recently reviewed a patient with SLE at out-patients. Over many years she had described a recurring but always transient rash, which sometimes lasted for just a few hours but which had never been seen or properly documented by a physician.

On this occasion she brought with her a mobile phone, one of the newer models with an inbuilt digital camera. Stored on the database were several images of her rash, which had appeared on a shopping trip and lasted for about 3 h before vanishing. It appeared as a typical urticarial rash, as she had described, and not a photosensitive manifestation, as had sometimes been suspected on account of its distribution.

I believe this is the first report of a mobile telephone being used as diagnostic imaging technique in rheumatology.

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Pregnancy in a rheumatoid arthritis patient on infliximab and methotrexate

SIR, A lady was diagnosed with rheumatoid arthritis at the age of 29. She was initially treated with sulphasalazine (3 g/day) and then azathioprine (eventually 250 mg/day) was added. This failed to control her disease, so hydroxychloroquine (400 mg/day) was added. On this combination of drugs (with 5 mg prednisolone and diclofenac 150 mg/day) her disease appeared to be coming under control.

At this point the patient decided she would like to try for a baby. The hydroxychloroquine and sulphasalazine were stopped and the prednisolone was increased to 7.5 mg/day, and she continued on the azathioprine 250 mg/day (with diclofenac 150 mg/day). She tried to conceive for 9 months but was unsuccessful. The infertility clinic found she was not ovulating. Her antiphospholipid antibodies were negative. Her diclofenac (150 mg/day) was stopped and she was commenced on clomifene for infertility. After 2 months of treatment she became pregnant. The baby was stillborn at 36 weeks due to an acute hypoxic event. After several months she again became pregnant on clomifene but miscarried at 15 weeks. She very quickly became pregnant again on clomifene and this time her azathioprine was eventually stopped and her prednisolone was reduced during pregnancy. She gave birth to a healthy boy at 34 weeks. Six months later she became pregnant again on clomifene and gave birth to a girl at 35 weeks. She was restarted on the azathioprine (with prednisolone 7.5 mg/day and diclofenac 150 mg/day) after each pregnancy. The azathioprine (250 mg/day) failed to control the arthritis after her second pregnancy, so it was stopped and she was commenced on methotrexate (eventually at 20 mg/week with folic acid 5 mg/week) in addition to prednisolone 7.5 mg/day and diclofenac 150 mg/day for 12 months. This was ineffective, so infliximab (3 mg/kg) every 8 weeks (after the loading doses) was added to this regime.

Prior to commencing infliximab she was counselled again about avoiding pregnancy and using adequate contraception. Once on infliximab, her disease activity score improved from 6.43 initially to 4.24 at 6 months and her prednisolone was reduced to 5 mg/day. After 9 months on infliximab she became pregnant, which was unplanned. They had been using only

Original Article

Comparative Clinical Profile of Postural Orthostatic Tachycardia Patients With and Without Joint Hypermobility Syndrome

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Abstract

Background: Autonomic dysfunction is common in patients with the joint hypermobility syndrome (JHS). However, there is a paucity of reported data on clinical features of Postural orthostatic tachycardia syndrome (POTS) in patients suffering from JHS.

Methods: This retrospective study was approved by our local Institutional Review Board (IRB). Over a period of 10 years, 26 patients of POTS were identified for inclusion in this study. All these patients had features of Joint Hypermobility Syndrome (by Brighton criterion). A comparison group of 39 patients with other forms of POTS were also followed in the autonomic clinic during the same time. We present a descriptive report on the comparative clinical profile of the clinical features of Postural Orthostatic Tachycardia patients with and without Joint Hypermobility syndrome. The data is presented as a mean±SD and percentages wherever applicable.

Results: Out of 65 patients, 26 patients (all females, 20 Caucasians) had POTS and JHS. The mean age at presentation of POTS was 24±13 (range 10-53 years) vs 41±12 (range 19-65 years), P=0.0001, Migraine was a common co morbidity 73 vs 29% p=0,001. In two patients POTS was precipitated by pregnancy, and in three by surgery, urinary tract infection and a viral syndrome respectively. The common clinical features were fatigue (58%), orthostatic palpitations (54%), presyncope (58%), and syncope (62%).

Conclusion: Patients with POTS and JHS appear to become symptomatic at an earlier age compared to POTS patients without JHS. In addition patients with JHS had a greater incidence of migraine and syncope than their non JHS counterparts.

Keywords: postural orthostatic tachycardia; joint hypermobility syndrome; autonomic dysfunction

Introduction

Joint hypermobility syndrome (JHS) is one of the most common heritable collagen disorders [1,2]. In addition to articular manifestations these patients can present with multiple extraarticular manifestations such as cutaneous scaring, ocular lid laxity, genitourinary dysfunction, peripheral nervous disorders and chronic fatigue syndrome [1-6]. Autonomic dysfunction has been reported to occur in patients with JHS and include symptoms of syncope, presyncope, palpitations, chest discomfort, fatigue, and heat intolerance, orthostatic hypotension, postural orthostatic tachycardia syndrome, and uncategorized orthostatic intolerance [8,9]. Although, postural tachycardia syndrome (POTS) has been reported to occur in patients with JHS there is paucity of data on the clinical features and outcome of POTS in patients who suffer from JHS as opposed to those with POTS from other causes. We present a comparative clinical profile of postural orthostatic tachycardia patients with and without joint hypermobility syndrome.

Methods

The study was a retrospective descriptive analysis of the patients followed at the University of Toledo Medical Center. Our Institutional Review Board approved the study. We identified 26 patients of POTS with preexisting JHS. Patients were diagnosed as having JHS based on their clinical findings, Brighton criterion as well as Beighton score [10, 11] of $\geq$ 4/9. These patients were diagnosed as having POTS primarily based on their history, clinical features and findings from head upright tilt table testing (HUTS). They were diagnosed as suffering from POTS if they had symptoms (>6 months) of orthostatic intolerance associated with a heart rate increase of 30 bpm (or rate that exceeds 120 bpm) that occurs within the first 10 minutes of standing or upright tilt, not associated with other chronic debilitating conditions such as prolonged bed rest or the use of medications known to diminish vascular or autonomic tone. A group of POTS patients (n=39) without pre-existing JHS who were being followed at our center during the same time frame was selected to serve as a control group. Some of these patients were referred from various other centers to our clinic for second opinions regarding diagnosis and management. Thus the group was not a consecutive group of patients who had been diagnosed at our center only. All of these patients were primarily seen for symptoms of orthostatic intolerance. The patient charts and physician communications and letters were reviewed and the information about the demographics, clinical features, comorbid conditions, tilt table test results were collected.

The data is observational and is presented as mean ± SD and percentages. The t test for comparison of means and chi square test for comparison of percentages was used. The statistical significance was reached at $P< 0.05$.

Results

Table 1 summarizes the clinical features of patients with and without JHS. The POTS patients with JHS tended to be younger (30 ±13, range 10-53) when compared to patients without JHS (40±11, range 19-65) $P<0.05$.

Precipitating Event

The most common precipitating events for POTS in patients with JHS were pregnancy (12%), surgery and urinary tract infection (4%) each. In patients without JHS the common precipitating events were viral infection (15%), pregnancy (5%) and trauma (5%). All of these patients had persistent symptoms of orthostatic intolerance for more than 6 months duration from the onset of precipitating event.

Table 1: Baseline Clinical characteristics of patients of Postural Tachycardia Syndrome with and without Joint Hypermobility Syndrome.

	POTS with JHS (N=26)	POTS without JHS (N=39)	*P*
Age(years)	30 ±13	40±11	**0.01**
Sex(Female)	26(100%)	35(90%)	**0.09**
Race (Caucasian %)	20(77%)	35(90%)	0.2
Comorbidity			
Migraine	19(73%)	11(28%)	**0.001**
Precipitating Event			
Trauma	0(0%)	2(5%)	0.5
Surgery	1(4%)	0(0%)	0.4
Pregnancy	3(12%)	2(5%)	0.4
Viral Infection	0(0%)	6(15%)	**0.07**
UTI	1(4%)	0(0%)	0.4
Symptoms			
Fatigue	15(58%)	23(59%)	1
Orthostatic palpitation	14(54%)	19(49%)	0.8
Dizziness/ presyncope	15(58%)	29(74%)	0.2
Syncope	16(62%)	13(30%)	**0.04**

Comorbidity

Migraine was the most common co morbidity seen in patients of POTS with JHS (73%) in comparison to 28% in patients of POTS without JHS $P< 0.05$. All of these patients had a screening transthoracic echocardiogram performed. None of the patients with migraine had any evidence of persistent foramen ovale (PFO) as assessed by a transthoracic echocardiography. No further evaluations to determine the presence or absence of a PFO (such as transesophageal echocardiography) or agitated saline tests were performed.

Symptoms of POTS

Fatigue, orthostatic palpitations, dizziness and presyncope were similar in patients with and

without JHS. However, syncope was significantly higher in patients of POTS with JHS (62%) in comparison to POTS patients without JHS (30%) ($P< 0.05$).

Discussion

Postural orthostatic tachycardia syndrome (POTS) is defined as the presence of symptoms of orthostatic intolerance associated with a heart rate increase of 30 bpm (or rate that exceeds 120 bpm) that occurs within the first 10 minutes of standing or upright tilt, not associated with other chronic debilitating conditions such as prolonged bed rest or the use of medications known to diminish vascular or autonomic tone [12]. The early descriptions of the disorder focused on a group of patients who had been previously healthy until a sudden febrile illness (presumably viral) brought on an abrupt onset of symptoms. Later investigations revealed that POTS is a physiological state most commonly due to inability of the peripheral vasculature to maintain adequate resistance in the face of orthostatic stress, allowing for excessive pooling of blood in the more dependent areas of the body [8,9,13]. The resultant functional decline in circulatory volume elicited a compensatory increase in heart rate and myocardial contractility. While compensatory in mild cases, this mechanism is unable to fully compensate in more severe cases, resulting in a reduction in effective circulation and varying degrees of cerebral hypoperfusion. Later investigations revealed that POTS is not a single condition, but rather a heterogeneous group of disorders resulting in similar physiological state. In 1999 Rowe and colleagues [8] first reported a potential link between what is now referred to the Joint Hypermobility syndrome and POTS. Joint Hypermobility Syndrome is an inherited connective tissue disorder characterized by joint hypermobility, connective tissue fragility, soft 'velvety' skin and variable amounts of tissue hyperextensibility. The condition is assosiated with high incidence of premature varicose veins, easy bruising, diffuse muscle and joint pain as well as pronounced orthostatic acrocyanosis [14]. Subsequently in 2002 Barron et al [7] reported a similar association in a large group of young people suffering from POTS and severe fatigue. In 2003 Gazit et al [9] published a study wherein a group of 48 patients with hypermobility syndrome were compared to a group of 30 healthy control subjects. Each patient underwent a comprehensive series of autonomic tests including tilt table testing, catecholamine level measurement and adrenoreceptor responsiveness. In the hypermobility group 78% tested abnormal as opposed to 10% of control subjects, suggesting that the presence of the condition predisposes the individual to autonomic dysregulation. The authors suggested that the association could have several possible explanations, such as peripheral neuropathy, blood pooling in the lower limbs or impaired central sympathetic control. Other studies have reported that various types of peripheral neuropathies occur more frequently in the joint hypermobility syndrome [15]. It is currently thought that the connective tissue laxity seen in hypermobility patients allows for a greater than normal degree of vascular distensibility leading to an exaggerated amount of blood pooling in the lower extremity during upright posture. As was alluded to previously this then leads to a compensatory tachycardia and increase in cardiac inotropy [9,16]. This could potentially contribute to higher incidence of syncope reported in patients of POTS with preexisting JHS. POTS with preexisting JHS seem to develop symptoms more than a decade earlier than those POTS patients without JHS. While the reasons for this earlier onset are unclear, it is possible that the aforementioned inherent vulnerability of the JHS patients make them more susceptible to environmental stressors than their non JHS peers. [7,9]. Migraines were most common comorbidity observed in POTS patients with JHS. This has been seen in other studies as well [17]. Again, the reasons for this are unclear but may potentially relate to abnormal vascular reactivity within the cerebral vasculature. No patient in our study was found to have any evidence of a PFO on 2-D echocardiographic and Doppler evaluation. Syncope was reported in significantly greater number of patients with JHS (62%) as opposed to patients without JHS (30% $p<0.05$). Some patients with POTS experience syncope in the absence of significant decline in blood pressure. Sudden increase in cerebrovascular resistance resulting in

decline in cerebral oxygenation that occurs in the presence of orthostatic stress has been reported in these patients [18-21].

Limitations

This was a retrospective analysis of a relatively small patient population. The group of patients reported here included those referred from multiple other centers for a second opinion regarding diagnosis and management. Thus these patients were not true consecutive patients and hence a true incidence of POTS in JHS could not be estimated from this study population. None of the patients with migraine had any evidence of persistent foramen ovale (PFO) as assessed by a transthoracic echocardiography. No further evaluations to determine the presence or absence of a PFO (such as transesophageal echocardiography) or agitated saline tests were performed.

Conclusion

Patients with POTS and JHS appear to become symptomatic at an earlier age compared to POTS patients without JHS. In addition patients with JHS had a greater incidence of migraine and syncope than their non JHS counterparts.

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