

Research Paper

## Autonomic Dysfunction Presenting as Postural Orthostatic Tachycardia Syndrome in Patients with Multiple Sclerosis

Khalil Kanjwal, Beverly Karabin, Yousuf Kanjwal, Blair P Grubb 

Department of Medicine, Division of Cardiology Section of Electrophysiology, The University of Toledo, Toledo, OH 43614, USA.

 Corresponding author: Blair P Grubb, MD, Director Electrophysiology Services, Division of Cardiology, Department of Medicine, Health Sciences Campus, University of Toledo Medical Center, Mail Stop 1118, 3000 Arlington Ave., Toledo OH 43614, USA. Phone 419-3833778; Fax: 419-383-3041.

Received: 2010.03.01; Accepted: 2010.03.10; Published: 2010.03.11

### Abstract

**Background:** Autonomic dysfunction is common in patients suffering from multiple sclerosis (MS) and orthostatic dizziness occurs in almost 50% of these patients. However, there have been no reports on postural orthostatic tachycardia syndrome (POTS) in patients suffering from MS.

**Methods:** The patients were included for analysis in this study if they had POTS with either a prior history of MS or having developed MS while being followed for POTS. Postural orthostatic tachycardia (POTS) is defined as symptoms of orthostatic intolerance (>6 months) accompanied by a heart rate increase of at least 30 beats/min (or a rate that exceeds 120 beats/min) that occurs in the first 10 minutes of upright posture or head up tilt test (HUTT) occurring in the absence of other chronic debilitating disorders. We identified nine patients with POTS who were suffering from MS as well. Each of these patients had been referred from various other centers for second opinions.

**Results:** The mean age at the time of diagnosis of POTS was  $49 \pm 9$  years and eight of the 9 patients were women. Five patients (55%) had hyperlipidemia, 3 (33%) migraine and 2 (22%) patients had coronary artery disease and diabetes each. Fatigue and palpitations (on assuming upright posture) were the most common finding in our patients (9/9). All patients also had orthostatic dizziness. Syncope was seen in 5/9 (55%) of patients. Four patients (44%), who did not have clear syncope, were having episodes of near syncope. The presence of POTS in our study population resulted in substantial limitation of daily activities. Following recognition and treatment of POTS, 6/9 (66%), patients were able to resume daily activities of living. Their symptoms (especially fatigue and orthostatic intolerance) improved. The frequency and severity of syncope also improved. Three (33%) patients failed to show a good response to treatment.

**Conclusion:** Patients suffering from MS may manifest autonomic dysfunction by developing POTS. Early recognition and proper management may help improve the symptoms of POTS.

Key words: Multiple sclerosis, Postural tachycardia syndrome, syncope, dizziness, fatigue.

### Introduction

Multiple sclerosis (MS) is a chronic demyelinating inflammatory disorder, presumed to be of autoimmune etiology. Autonomic dysfunction (AD) is

commonly seen in patients with MS. The most common manifestations of the AD in patients with MS include bladder dysfunction, sleep disturbances,

sweating, gastrointestinal and cardiovascular disturbances. Another common symptom seen in patients of MS is fatigue. Orthostatic dizziness (OD) has been reported to occur in up to 50% of MS patients (1-4). Autonomic dysfunction has an important impact on the disability that patients with MS experience and can substantially restrict the activities of daily living in these individuals.

Autonomic dysfunction in patients with MS is felt to occur because of involvement of several critical pathways of autonomic nervous system, including the brain stem, spinal cord, hypothalamus and cerebral cortex. Demyelinating plaques may disrupt reflex pathways in the insular, cingulate and ventromedial prefrontal cortices, central nucleus of the amygdala, paraventricular hypothalamus and the medulla. In addition there can be interference with the descending autonomic nervous system pathways during their course in the brainstem or spinal cord (6). Although orthostatic dizziness has been commonly seen in patients of MS, to date there have been no studies or reports on the occurrence of postural orthostatic tachycardia syndrome (POTS) in patients with MS. We report on a series of nine MS patients with POTS.

## Methods

The study was a retrospective descriptive analysis of the patients followed up at the University of Toledo Autonomic Disorder Center. The study was approved by our Institutional Review Board. The data of these patients had been collected from 1998-2008. Nine patients were identified that were included in the analysis. These patients were initially seen elsewhere and were seen in our clinic for second opinions. All but two patients were diagnosed with multiple sclerosis. The diagnosis of MS was based on clinical history, neurological examination and supported by cerebrospinal fluid analysis and Magnetic Resonance Imaging of the brain in each case. Two patients with POTS, who were followed at our clinic, developed multiple sclerosis after being diagnosed with POTS.

Criterion for diagnosis of POTS: The diagnosis of POTS was based on clinical history, clinical examination and a positive (POTS pattern) head up tilt test (HUTT). The HUTT criterion for diagnosing POTS was an absolute heart rate >120 bpm or an increase by >30bpm within the first ten minutes of an upright tilt. We did not routinely evaluate catecholamine levels in any of these patients.

A neurologist followed each of these patients and close contacts were maintained between our center and the patients' neurologist. The patients' neurological and autonomic center data (charts and/or

physician letters) were then carefully reviewed for demographic characteristics, comorbid conditions, symptoms of MS, symptoms of POTS, medications and response to medication. The data obtained are presented as mean  $\pm$  standard deviation or as percentages where applicable.

### Response to therapy

Response to therapy was subjectively assessed in each patient. None of the patients underwent a repeat HUTT test for objective assessment of symptom response to therapy. The therapy was considered successful if it provided symptom relief.

## Results

Nine patients with POTS who either had a prior history of MS or developed MS were identified for inclusion in the study. The mean age at the time of diagnosis was  $49 \pm 9$  years and 8 of the 9 patients were women. All the patients were Caucasians. All patients were being followed by a neurologist who specialized in MS. The results are summarized in Table 1.

### Comorbidity

Five patients (55%) had hyperlipidemia, 3 (33%) migraine and 2 (22%) patients had coronary artery disease and diabetes each.

### Symptoms of POTS

Fatigue and palpitations (on assuming upright posture) were the most common finding in our patients (9/9). All patients also had orthostatic dizziness. Syncope was seen in 5/9 (55%) of patients. Four patients (44%), who did not have frank syncope, were having episodes of near syncope. Each patient had experienced symptoms for greater than six months.

Head up Tilt Test (HUTT): All nine patients underwent HUTT. All patients demonstrated either an absolute heart rate of >120bpm or an increase of >30bpm within the first ten minutes of an upright tilt. All patients demonstrated symptoms of orthostatic intolerance similar to that reported during their spontaneous episodes. None of the patients had a resting heart rate >100 bpm. We did not evaluate catecholamine levels in any of these patients.

### Symptoms of Multiple Sclerosis

Visual disturbances in the form of episodic blurring of vision were seen in 4/9 (44%) patients. Sensory disturbances including numbness, tingling, pins and needles sensation in extremities were seen in 4/9 (44%) patients. Gait problems (leg and/or arm weakness) were also seen in 4/9 (44%) patients. Seizures were seen in two (22%) patients. Two (22%)

patients had recurrent bladder symptoms in form of incontinence and retention. Another two (22%) had been having excessive sweating.

**Table 1:** Clinical characteristics of the patients of Multiple Sclerosis and orthostatic intolerance.

Characteristics	Values
Age(years)	49±9
Race (Caucasians %)	100
Sex (Females)	8/9 (89%)
<b>Comorbid Condition</b>	
Hyperlipidemia	5/9 (55%)
Migraine	3/9 (33%)
Coronary artery disease	2/9 (22%)
Diabetes	2/9 (22%)
<b>Symptoms of POTS</b>	
Fatigue	9/9 (77%)
Dizziness/Near Syncope	9/9(100%)
Palpitation	9/9(55%)
Syncope	5/9(55%)
<b>Symptoms of Multiple Sclerosis</b>	
Visual Disturbances(optic neuritis)	4/9(44%)
Gait Problem/ Weakness	4/9 (44%)
Sensory disturbances	4/9 (44%)
Urinary Symptoms	2/9(22%)
Seizures	2/9 (22%)
<b>Medications</b>	
SSRI	7/9(77%)
Pyridostigmine	6/9(66%)
Midodrine	4/9 (45%)
Betablockers	3/9(33%)
Fludrocortisone	2/7(22%)
Modafinil	1/9(11%)
Combination	5/9(55%)
<b>Onset of POTS in relation to Multiple Sclerosis(MS)</b>	
Followed MS	7/9(77%)
Preceded MS	2/9(22%)
<b>Response of POTS symptoms to medical therapy</b>	
Successful	6/9(66%)
Failure	3/9(33%)
Number of patients requiring Pacemaker	2/9(22%)

#### Onset of POTS in relation to MS

Two patients developed POTS prior to diagnosis of MS. One of these patient developed POTS three years, and another, one and a half years before the onset of MS. Seven (77%) patients' developed POTS over a mean period of (22 months) from the diagnosis of the multiple sclerosis.

#### Daily activities and lifestyle in our study patients

Each of the patients reported a constant fear of experiencing syncope. This fear had greatly limited

their daily activities to a point that they were scared of assuming an upright posture and had become home bound. One patient had a recurrent feeling of a sense of impending doom.

#### Medications

Treatment aimed at minimizing symptoms was initiated in each patient following the diagnosis of POTS. The majority of these patients were on selective serotonin reuptake inhibitors (venlafaxine and duloxetine) (7/9, 77%). Six (66%) patients were on pyridostigmine, 4(44%) on midodrine, 3(33%) on beta-blockers (propranolol), 2 (22%) on fludrocortisone and one (11%) on modafinil. Five (55%) patients were receiving a combination of one of these medications.

#### Response to Medical therapy

The therapeutic management approach for these patients was based on our previous experience with the management of patients with POTS. Initial therapy consisted of an increase in salt and fluid intake as well as aerobic reconditioning with resistance training to increase lower extremity strength. Pharmacotherapy was used alone or in combination in the following order: fludrocortisone 0.1mg po bid, midodrine 5-10 mg po tid, propranolol 10 mg po tid, pyridostigmine 60 mg po bid, serotonin reuptake inhibitor or modafinil 100 mg po qam. Not every patient received every medication. Following recognition and treatment of POTS, 6/9(66%) patients were able to engage in daily activities of living. Fatigue and orthostatic intolerance were the symptoms which improved most. The frequency and severity of syncope also improved significantly. Three (33%) patients failed to demonstrate a good response to medical therapy and continued to experience recurrent syncope. Two out of these three patients had convulsive activity without prodrome during syncope. These two patients were further investigated by placement of an implantable loop recorder and were found to have periods of prolonged asystole during their episodes of syncope felt to be neurocardiogenic in nature. Thus these two patients had MS with POTS as well as episodes of neurocardiogenic syncope. Both of them received a dual chamber pacemaker. Following pacing one patient experienced complete elimination of syncope while the other experienced a significant reduction in frequency and severity of her events. Another patient did not show a good response to therapy and continues to have episodes of orthostatic dizziness and syncope.

## Discussion

POTS is defined as an excessive increase in heart rate associated with symptoms of more than 6 months' duration (in the absence of other conditions that could mimic this such as dehydration and deconditioning). In POTS, the heart rate increases 30 beats per minute (or exceeds 120 beats per minute) within the first 10 minutes of standing or HUTT. More complete descriptions of the diagnosis and management of POTS are given elsewhere (7-11). Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating disease of the central nervous system (CNS) that is a leading cause of disability in young adults.

Autonomic dysfunction is commonly seen in patients with MS (1-5). In patients of MS, autonomic dysfunction (AD) has been thought to be related to involvement of reflex pathways in the brainstem (12).

Both decreased heart rate variability and decreased blood pressure response in tilt table testing occur as a result of AD in patients with MS (12-16). On cardiovascular reflex testing it has been shown that both sympathetic as well as parasympathetic dysfunction can occur in patients with MS (12-16). Reduced heart rate variability and vasomotor dysfunction in MS appears to correlate with the degree of plaque burden seen on MRI in the midbrain areas, also with the presence of hemispherical lesions (17). Autonomic regulatory abnormalities are thought to occur due to involvement of central autonomic interconnections (18). In a study of carotid baroreflex in MS patients the baroreflex dysfunction involved both cardiovagal limb of the baroreflex as well the sympathetic modulation of blood vessels (19). In addition, impaired sympathetic nervous system mediated vasomotor control may result in orthostatic intolerance and dizziness that is seen in almost 50% of MS patients (20). Autonomic cardiovascular dysfunction may progress over time as was shown in a report by Nasser et al. (21, 22). Sympathetic vasomotor dysfunction may also contribute to fatigue in patients with MS (23). As has been noticed previously the majority of our patients were females. Both POTS and MS occur more commonly in women of childbearing age. All of our patients were of Caucasian descent.

### *Symptoms of POTS and MS*

The most common symptom in our study population was fatigue. Fatigue is a characteristic finding in MS, usually described as physical exhaustion that is unrelated to the amount of activity performed. Many patients complain of feeling exhausted on waking, even if they have slept soundly. Fatigue can also occur during the day but may be only par-

tially relieved by rest. In addition, there appears to be a correlation between fatigue and disrupted sleep in MS patients. In our patients, we were not able to obtain any information about their sleep habits. Despite being a common symptom of MS there has been no correlation between fatigue and the overall severity of disease (24-26). All of our patients had orthostatic intolerance. Fifty percent patients of POTS have been reported to have orthostatic dizziness in various studies. Syncope which is uncommon in MS patients occurred in almost 5/9(55%) of patients in this study. Increase in cerebrovascular resistance occurring during orthostatic stress can explain loss of consciousness in these patients (27). In two patients the episodes of syncope were associated with prolonged periods of asystole felt to be neurocardiogenic in origin. Postural orthostatic tachycardia with asystole has been reported during HUTT testing (28). In addition to fatigue our patients also presented with episodic visual disturbances (blurring of vision, optic neuritis), extremity weakness and sensory abnormalities like numbness and tingling. Seizures which occur usually in 2-3% (29) of MS patients were seen in 2/9 (22%) of patient in this selected cohort. This high incidence of seizure, syncope and asystole in this series might be due to the selection bias in this small group of patients.

### *Management of POTS in patients with MS*

The pharmacological management of POTS in patients of MS was similar to that in patients without a history of MS. In our small group of patients, six patients showed a good response to a combination of medications (Table 1). Two patients who had recurrent episodes of abrupt onset syncope with convulsive activity were found to have periods of prolonged asystole on implantable loop recorder (ILR) monitoring and subsequently received a pacemaker. In one of these patients, her episodes of syncope were eliminated whereas in another, the episodes now have a prodrome and have decreased in severity and frequency. Patients who have abrupt onset syncope with convulsive activity might have prolonged episodes of bradycardia or an asystole as a cause for their syncope (30, 31).

Another patient continues to experience palpitations and episodes of syncope and has failed multiple medications when used either alone or in combination. Interestingly two (22%) patients in our series had an onset of POTS prior to the diagnosis of MS while seven (77%) developed POTS over months to years following diagnosis of MS. It is difficult at this time to predict which POTS patients could develop MS, or which MS patients could develop POTS during the

progression of their disease.

### *Daily activities and lifestyle in our study patients*

MS is a debilitating disease and the concurrent diagnosis of POTS in our study population has resulted in substantial limitation of daily activities. POTS can have tremendous effect on the quality of life often resulting in severe limitation of daily activities; in addition, an often neglected but nonetheless important aspect of this disorder is the tremendous social, economical and emotional toll it takes on the patients but also on their families.

POTS, when it occurs in patients of MS can add to the morbidity and disability these patients are already suffering from. As seen in our patient population recognition and management of POTS in patients of MS may result in improved quality of life.

### *Limitations*

Our study was a single center, retrospective and nonrandomized descriptive analysis of a small number of patients, which predisposed it to an inherent selection bias. One of the major limitations of this study was the manner in which the patients were included in this small study. These patients had accumulated over years and had been referred from multiple centers for second opinion. Thus it was difficult to determine the incidence of POTS in MS patients based on the analysis of this small population. There was no age matched control group of MS patients without POTS. This study reviewed the subjective reports on the symptoms of POTS in MS patient. The nature of the severity of symptom improvement and/or worsening with medication was again subjective and not assessed by a response to HUTT. These limitations do not influence our conclusion that POTS can occur in patients with MS.

### *Conclusion*

Autonomic dysfunction in the form of POTS can occur in MS patients.

### **Conflict of Interest**

The authors have declared that no conflict of interest exists.

### **References**

- Anema JR, Heijnenbroek MW, Faes TJ, Heimans JJ, Lanting P, Polman CH. Cardiovascular autonomic function in multiple sclerosis. *J Neurol Sci* 1991;104:129-134.
- Frontoni M, Fiorini M, Strano S, Cerutti S, Giubilei F, Urani C, Bastianello S, Pozzilli C. Power spectrum analysis contribution to the detection of cardiovascular dysautonomia in multiple sclerosis. *Acta Neurol Scand* 1996;93:241-245.
- Linden D, Diehl RR, Berlit P. Subclinical autonomic disturbances in multiple sclerosis. *J Neurol* 1995;242:374-378.
- Vita G, Fazio MC, Milone S, Blandino A, Salvi L, Messina C. Cardiovascular autonomic dysfunction in multiple sclerosis is likely related to brainstem lesions. *J Neurol Sci* 1993;120:82-86.
- Acevedo AR, Nava C, Arriada N, Violante A, Corona T. Cardiovascular dysfunction in multiple sclerosis. *Acta Neurol Scand* 2000;101:85-88.
- Vita G, Fazio MC, Milone S, Blandino A, Salvi L, Messina C. Cardiovascular autonomic dysfunction in multiple sclerosis is likely related to brainstem lesions. *J Neurol Sci* 1993;120:82-86.
- Sandroni P, Opfer-Gehrking TL, McPhee BR, Low PA. Postural tachycardia syndrome: Clinical features and follow-up study. *Mayo Clin Proc* 1999; 74:1106-1110
- Grubb BP, Kanjwal Y, Kosinski DJ. The postural orthostatic tachycardia syndrome: Current concepts in pathophysiology, diagnosis, and management. *J Interv Card Electrophysiol* 2001; 5:9-16.
- Grubb BP, Kosinski DJ. Syncope resulting from autonomic insufficiency syndromes associated with orthostatic intolerance. *Med Clin North Am* 2001; 85:457-472.
- Kanjwal Y, Kosinski D, Grubb BP. The postural orthostatic tachycardia syndrome: Definitions, diagnosis, and management. *Pacing Clin Electrophysiol* 2003; 26:1747-1757.
- Grubb BP, Kanjwal Y, Kosinski DJ. The postural tachycardia syndrome: A concise guide to diagnosis and management. *J Interv Card Electrophysiol* 2006; 17:108-112.
- Acevedo AR, Nava C, Arriada N, Violante A, Corona T. Cardiovascular dysfunction in multiple sclerosis. *Acta Neurol Scand* 2000;101:85-88
- Linden D, Diehl RR, Berlit P. Subclinical autonomic disturbances in multiple sclerosis. *J Neurol* 1995;242:374-378
- Nordenbo AM, Boesen F, Andersen EB. Cardiovascular autonomic function in multiple sclerosis. *J Auton Nerv Syst* 1989;26:77-84
- Pentland B, Ewing DJ. Cardiovascular reflexes in multiple sclerosis. *Eur Neurol* 1987;26:46-50.
- Pomeranz B, Macaulay RJ, Caudill MA, Kutz I, Adam D, Gordon D, Kilborn KM, Barger AC, Shannon DC, Cohen RJ, et al. Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol* 1985;248:H151-153.
- Saari A, Tolonen U, Paakko E, Suominen K, Pyhtinen J, So-taniemi K, Myllyla V. Cardiovascular autonomic dysfunction correlates with brain MRI lesion load in MS. *Clin Neurophysiol* 2004;115:1473-1478.
- Thomaides TN, Zoukos Y, Chaudhuri KR, Mathias CJ. Physiological assessment of aspects of autonomic function in patients with secondary progressive multiple sclerosis. *J Neurol* 1993;240:139-143.
- Sanya EO, Tutaj M, Brown CM, Goel N, Neundorfer B, Hilz MJ. Abnormal heart rate and blood pressure responses to baroreflex stimulation in multiple sclerosis patients. *Clin Auton Res* 2005;15:213-218.
- Vita G, Fazio MC, Milone S, Blandino A, Salvi L, Messina C. Cardiovascular autonomic dysfunction in multiple sclerosis is likely related to brainstem lesions. *J Neurol Sci* 1993;120:82-86.
- Nasseri K, TenVoorde BJ, Ader HJ, Uitdehaag BM, Polman CH. Longitudinal follow-up of cardiovascular reflex tests in multiple sclerosis. *J Neurol Sci* 1998;155:50-54
- Nasseri K, Uitdehaag BM, van Walderveen MA, Ader HJ, Polman CH. Cardiovascular autonomic function in patients with relapsing remitting multiple sclerosis: a new surrogate marker of disease evolution? *Eur J Neurol* 1999;6:29-33.
- Flachenecker P, Rufer A, Bihler I, Hippel C, Reiners K, Toyka KV, Kesselring J. Fatigue in MS is related to sympathetic vasomotor dysfunction. *Neurology* 2003;61:851-853.
- Attarian HP, Brown KM, Duntley SP, et al. The relationship of sleep disturbances and fatigue in multiple sclerosis. *Arch Neurol* 2004; 61:525.

25. Bakshi, R, Miletich, RS, Henschel, K, et al. Fatigue in multiple sclerosis: Cross-sectional correlation with brain MRI findings in 71 patients. *Neurology* 1999; 53:1151.
26. Tartaglia, MC, Narayanan, S, Francis, SJ, et al. The relationship between diffuse axonal damage and fatigue in multiple sclerosis. *Arch Neurol* 2004; 61:201.
27. Jordan J, Shannon JR, Black BK, et al. Raised cerebrovascular resistance in idiopathic orthostatic intolerance: evidence for sympathetic vasoconstriction. *Hypertension*. 1998; 32:699 -704.
28. Alshekhlee A, Guerch M, Ridha F, Mcneeley K, Chelimsky TC. Postural tachycardia syndrome with asystole on head-up tilt. *Clin Auton Res*. 2008 Feb; 18(1):36-9.
29. Koch, M, Uyttenboogaart, M, Polman, S, De Keyser, J. Seizures in multiple sclerosis. *Epilepsia* 2008; 49:948.
30. Khalil Kanjwal, Yousuf Kanjwal, Beverly Karabin, Blair P Grubb. Clinical Symptoms associated with asystolic or brady-cardic responses on Implantable Loop recorder monitoring in patients with recurrent syncope. *Int J Med Sci* 2009; 6:106-110.
31. Khalil Kanjwal, Beverly Karabin, Yousuf Kanjwal, Blair P Grubb. Differentiation of convulsive syncope from epilepsy with an implantable loop recorder. *Int J Med Sci*. 2009; 6(6):296-300.