The Postural Orthostatic Tachycardia Syndrome: A Potentially Treatable Cause of Chronic Fatigue, Exercise Intolerance, and Cognitive Impairment in Adolescents

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KARAS, B., ET AL.: **The Postural Othostatic Tachycardia Syndrome: A Potentially Treatable Cause of Chronic Fatigue, Exercise Intolerance, and Cognitive Impairment in Adolescents.** *Head upright tilt table testing has become an accepted method to measure an individual's predisposition to autonomically mediated periods of hypotension and bradycardia severe enough to cause frank syncope. At the same time it has become increasingly apparent that less profound falls in blood pressure, while not sufficient to result in loss of consciousness, may cause symptoms such as near syncope, vertigo, and dizziness. We describe a subgroup of adolescents that have a mild form of autonomic dysfunction that exhibit disabling symptoms such as postural tachycardia and palpitations, extreme fatigue, lightheadedness, exercise intolerance, and cognitive impairment. During baseline tilt table testing at a 70° angle, these patients demonstrated a heart rate increase of ≥ 30 beats/min (or a maximum heart rate of ≥ 120 beats/min) within the first 10 minutes upright (not associated with profound hypotension), which reproduced their clinical symptom complex. Similar observations have been made in the adult population and has been termed the postural orthostatic tachycardia syndrome (POTS). We report that POTS may also occur in adolescents and represents a mild, potentially treatable form of autonomic dysfunction that can be readily identified during head upright tilt table testing. (PACE 2000; 23:344-351)*

autonomic dysfunction, adolescents, POTS

Introduction

Transient alterations in autonomic tone that produce neurocardiogenic hypotension and bradycardia has been recognized as a common cause of syncope in children and adolescents.[1] Tilt table testing has emerged not only as a valuable diagnostic tool for identifying individuals predisposed to these episodes, but has permitted more detailed investigations into the nature of these disorders than was previously possible.[2,3] During the course of these studies it became apparent that a sudden alteration in autonomic tone could cause varying degrees of hypotension that, while not severe enough to produce full loss of consciousness, were sufficiently profound to cause symptoms such as near syncope, lightheadedness, vertigo, and transient ischemic attacks.[4,5] In the midst of these investigations both we and other centers became aware of a subgroup of adult patients who demonstrated a mild form of orthostatic intolerance who complained of orthostatic palpitations and tachycardia, lightheadedness, disabling fatigue, exercise intolerance, and cognitive impairment.[6] This disorder has become known as the postural orthostatic tachycardia syndrome (or POTS).[7] We then realized that POTS was a potential problem among adolescents as well that could produce disabling symptoms that could cause significant functional impairment. The present study describes our initial observations on the clinical presentation of adolescents afflicted by this disorder, their responses to tilt table testing, and their outcomes on various pharmacotherapies.

Method

A total of 35 adolescent patients were identified for inclusion in the evaluation and principally were recruited from the adolescent medicine clinic. Patients were included in the analysis if they < 18 years of age and if they had a 5-month

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or greater history of orthostatic intolerance manifested by at least three of the following: orthostatic palpitations or tachycardia, lightheadedness, weakness, fatigue, exercise intolerance, and near syncope. Patients who had experienced recurrent true syncope (the transient loss of consciousness and postural tone with spontaneous recovery) were not included. Any patient receiving antihypertensives, diuretics, anorectics, antidepressants, anticholinergics, or hypoglycemic agents were excluded. In addition, any patients with diabetic neuropathy, multisystem disease of any etiology, or who had been immobilized for prolonged periods of time were excluded from analysis. Each patient had a thorough history and physical examination, as well as a detailed blood chemistry analysis (including complete blood count with differential, electrolytes, urea nitrogen, creatinine, and liver function studies), thyroid profile analysis, and 12-lead electrocardiogram. Echocardiography was performed in 30 patients. Twelve patients had undergone computed axial tomography (CT) or magnet resonance imaging (MRI) of the brain prior to referral. Ten patients had undergone electrophysiological studies prior to referral to our institution.

Each patient underwent head upright tilt table testing in the fasting, nonsedated state after informed written consent was obtained from the patient (or parent or guardian). The study protocol had been approved by the Institutional Review Board. Any potential cardioactive agent or inhaled beta-adrenergic bronchodilators were terminated > 5 half-lives prior to the morning of the test. Each patient had an intravenous line inserted for medication administration or volume infusion. Additionally, a standard electrocardiographic monitor for continuous evaluation of heart rate and rhythm and a standard sphygmomanometer were connected to each patient. After baseline determinations of heart rate and blood pressure, each patient was positioned at an angle of 70° from horizontal for up to 30 minutes. Blood pressure measurements were obtained every 2 minutes, and ECG monitoring was performed continuously. Respiratory rate was monitored by direct observation. The patient was continued upright for the entire 30-minute period. A positive test was defined as one that reproduced the patient's symptom complex, associated with an increase in heart rate of ≥ 30 beats/min (or a heart rate ≥ 120 beats/min) within the first 10 minutes of upright tilt. If the patient was asymptomatic during the course of the passive tilt, they were lowered to the supine position and an intravenous infusion of isoproterenol was started at 1 μg/min. The supine heart rate response was noted and the dose was titrated to produce a stable heart rate approximately 20% above the greater supine resting heart rate. Head upright tilt was then performed as before for a total of 10 minutes.

Therapeutic Trials

In each of the patients in whom tilt table testing reproduced their clinical symptoms (in conjunction with the aforementioned hemodynamic changes), therapy was initiated with one or more pharmacological agent in an attempt to lessen the severity of the symptoms. The particular agents used were selected based on our experience treating children and adolescents with other autonomic disorders (such as neurocardiogenic syncope) and in treating adult patients with POTS.[6,8] Each patient was first counseled on the importance of maintaining adequate hydration, increasing salt intake, and exercise. The following agents were then used if required: fludrocortisone 0.1–0.2 mg po bid, midodrine 5–10 mg po tid, serotonin reuptake inhibitors (fluoxetine HCl 10–20 mg po q day, sertraline hydrochloride 50–100 mg po q day, paroxetine 5–20 mg po q day), methylphenidate 5–10 mg po tid, and atenolol 25–50 mg po q day. Erythropoietin 4,000 IU sq twice weekly was used in select patients. Not every drug or drug combination was tested in every patient as trials were stopped once an efficacious therapy was found.

Results

Of the 35 patients, there were 25 young women and 10 young men. The mean age of the patients was 15 ± 6 years (range 12–18 years). All blood tests were within normal limits, as well as all the electrocardiograms. Echocardiography was normal in 25 patients and were read as mild mitral valve prolapse in 5 patients. CT or MRI scans were normal in the 12 patients who underwent them, and the 10 patients who underwent electrophysiological studies had normal findings. The mean duration of symptoms was 9 months (range 5 to 24 months).

The three principal symptoms reported by this group of patients are listed in Table I, while the total percentage of the group complaining of a particular complaint is listed in Table II. These included orthostatic tachycardia, extreme fatigue, lightheadedness/near syncope, dyspnea, exercise intolerance, and significant cognitive impairment. Many of these patients were unable to complete normal educational activities or occupational duties. In 14 patients the onset of symptoms was acute in nature and followed a severe "flu-like" illness (presumed to be viral) that was characterized by fever, cough, rhinitis, and malaise. The remainder reported a slow progressive awareness of symptoms. Five of these patients had gone

Table I.

Patient Characteristics

Pt.	Age (yrs)	Sex	Approximate Symptom Duration	Three Principal Complaints	Potential Precipitating Event
1	12	F	7 months	OT, fatigue, n. sync	—
2	16	M	1 year	EI, fatigue, n. sync	postviral
3	18	F	1.5 years	Fatigue, OT, n. sync	postviral
4	16	F	8 months	OT, fatigue, n. sync	—
5	13	F	1 year	OT, fatigue, n. sync	—
6	14	F	2.5 years	CI, fatigue, n. sync	—
7	17	M	13 months	CI, fatigue, n. sync	—
8	19	F	12 months	OT, EI, IV sync	—
9	16	F	9 months	CI, fatigue, n. sync	—
10	16	M	4.5 months	EI, fatigue, OT	postviral
11	16	F	16 months	CI, fatigue, n. sync	—
12	14	F	10 months	CI, fatigue, n. sync	—
13	14	M	6 months	EI, fatigue, CI	—
14	19	F	2 years	EI, fatigue, n. sync	postviral
15	18	F	2 years	OT, EI, fatigue	—
16	16	F	8 months	EI, fatigue, n. sync	—
17	17	M	9 months	OT, EI, fatigue	—
18	12	M	8 months	EI, fatigue, CI	postviral
19	14	F	6 months	Fatigue, OT, EI	postviral
20	18	F	2 years	OT, fatigue, EI	—
21	13	F	7 months	EI, fatigue, syncope	—
22	14	M	9 months	Fatigue, CI, OT	postviral
23	16	M	6 months	CI, fatigue, n. sync	—
24	18	F	9 months	Fatigue, CI, EI	—
25	13	F	1 year	EI, fatigue, n. sync	postviral
26	13	F	1 year	OT, fatigue, n. sync	postviral
27	17	F	1.5 years	OT, fatigue, CI	postviral
28	17	M	8 months	Fatigue, EI, CI	postviral
29	16	M	9 months	Fatigue, CI, n. sync	postviral
30	14	F	12 months	EI, near syncope, OT	—
31	14	F	8 months	Fatigue, OT, CI	postviral
32	15	F	6 months	OT, EI, n. sync	postviral
33	16	F	14 months	Fatigue, EI, CI	—
34	13	F	10 months	Fatigue, n. sync, CI	—
35	15	F	12 months	CI, EI, n. sync	—

CI = cognitive impair; EI = exercise intolerance; n. sync = near syncope; OT = orthostatic tachycardia/palpitation.

through a period of very rapid growth (up to 3–4 inches in height) in the year preceding onset of symptoms. Each of the patients reported that their symptoms were limiting and 18 felt that they were disabling. Three patients had severe migraines in addition to other symptoms, and one patient was felt to have clinically significant depression.

Responses to Tilt Table Testing

The responses seen during head upright tilt table testing are listed in Table II. On the assumption of upright posture during the baseline tilt phase, each patient demonstrated a sudden in-

Table II.

Total Percentage of Patient Group Complaining of a Particular Postural Symptom

Tachycardia/palpations	65%
Fatigue	75%
Near syncope/lightheadedness	60%
Exercise intolerance	64%
Cognitive impairment	54%
Visular blurring	30%
Chest wall pain	20%
Anxiety	25%

crease in heart rate of ≥ 30 beats/min or a maximum heart rate of ≥ 120 beats/min. Symptoms identical to those experienced clinically were elicited during tilt in each patient. While 12 patients became near syncopal during tilt, no patient had a complete loss of consciousness. Many of the patients displayed a marked response to isoproterenol, with a mean increase in supine heart rate of 36 beats/min (the usual upper limit of normal is reported at approximately 15 beats/min).[7] Interestingly, at the moment of maximum tachycardia and minimum blood pressure during baseline passive tilt, the lower limbs of 12 patients darkened to a deep mottled blue color suggesting the presence of significant venous pooling. Eleven patients were so distressed by the symptoms provoked during passive upright tilt that they refused to continue (and therefore isoproterenol was not given). Hyperventilation was not observed in any patient during passive tilt (although one patient began to hyperventilate with isoproterenol).

Responses to Therapy (Table III)

An increase in salt and fluid intake was effective in relieving symptoms in only two patients. Each patient was encouraged to begin a moderate exercise program (only after effective pharmacotherapy was established), slowly working toward a goal of 20 minutes of aerobic exercise 3 days a week. Nine patients improved with fludrocortisone alone; five with midodrine alone; eight with a combination of midodrine and fludrocortisone; two with fludrocortisone and sertraline; two with a combination of fludrocortisone, paroxetine, and methylphenidate or midodrine; one with fluoxetine and fludrocortisone; one with midodrine and atenolol; and one with sertraline alone. In one patient, valproic acid was added for migraine control, and in one patient bupropion was added to sertraline to help relieve her depression. Two patients were difficult to control with oral medicines but responded dramatically to injected erythropoietin therapy.

Six patients were intolerant of fludrocortisone due to headaches and nausea, four patients were intolerant of midodrine due to nausea (3 patients) and rash (1 patient).

All 27 patients reported improvement on therapy over a mean follow-up time of 16 ± 7 months. Seven reported a moderate (but significant) reduction in symptoms, 16 a marked reduction in symptoms, and 12 near elimination of symptoms. Improvements were noted prior to starting an exercise reconditioning program (indeed, most felt they could begin regular exercise only because of the improvement in exertional tolerance produced by pharmacotherapy). All had a significant increase in functional status and were, for the most part, able to resume educational and/or employment activities.

Discussion

Transient alterations in autonomic nervous system tone leading to hypotension and bradycardia (neurocardiogenic syncope) have become a well-recognized cause of recurrent syncope in young people. During the course of our investigations of neurocardiogenic syncope, both we and other groups became aware of a subgroup of patients who appear to have a somewhat milder form of autonomic imbalance.[9] While these patients may not exhibit full syncope (the complete and transient loss of consciousness with spontaneous recovery) they do suffer from a host of disturbing (and sometimes incapacitating) symptoms of orthostatic intolerance such as postural tachycardia and palpitations, lightheadedness, near syncope, dizziness, and visual blurring or tunneling. In addition, these symptoms are often accompanied by exercise intolerance, chronic fatigue, and cognitive impairment. These symptoms may be so severe that the lives of the patients and their families may be completely disrupted. Not uncommonly, complaints such as these are dismissed as being psychiatric in nature. While this may sometimes be the case, our observations and those of others have shown that there exists a subgroup of individuals with these complaints who display both an abnormal cardiovascular response to the orthostatic stress of passive head-up tilt and report a marked reduction in symptoms following therapy directed at correcting the individual's autonomic imbalance.[6,9]

During head upright tilt table testing these patients display an exaggerated heart rate response of ≥ 30 beats/min within 10 minutes of upright tilt (or a heart rate of ≥ 120 beats/min within the first 10 minutes of passive tilt). While this increase in heart rate was usually not associated with significant hypotension, it accurately reproduced the patient's symptom complex. Furthermore, a number of these patients demonstrated an excessive heart rate response to low dose isoproterenol. This response pattern has never been observed in our normal subjects during tilt table testing during the last 11 years of our investigations.[2,6,10]

The recognition of these disorders is not new. In 1944 by MacLean et al. reported on four patients with orthostatic tachycardia and virtually identical complaints were presented.[11] They felt that the patients' symptoms could be from a defect in venous blood return to the heart. Later, in 1966, Frohlich described two similar patients with orthostatic tachycardia (≥ 140 beats/min without hypotension) with identical symptoms who also had exaggerated responses to isoproterenol,[12] followed thereafter by a similar report from Rosen.[13] A larger

Table III.

Response to Head-up Tilt for Pediatric POTS Patients

Patient	HR Supine	Maximum HR in First 10 min.	BP Supine mmHg	BP at max HR mmHg	↑ in Supine HR to 1μg/min iso in Beats/min	Therapy
1	60	98	94/64	99/55	26	hydration + salt
2	123	160	125/71	112/78	—	midodrine
3	70	102	101/66	114/65	50	fludrocortisone & midodrine
4	63	101	104/59	106/65	27	fludrocortisone
5	95	145	91/52	105/67	—	fludrocortisone valproic acid fluoxetine
6	78	112	123/75	121/72	45	fludrocortisone sertraline
7	60	115	104/67	108/63	26	fludrocortisone
8	82	130	121/80	128/86	42	fludrocortisone sertraline
9	70	122	108/58	96/60	18	fludrocortisone midodrine paroxetine
10	94	168	142/66	105/54	—	midodrine atenolol
11	65	102	115/63	102/64	22	fludrocortisone
12	65	105	109/57	101/60	—	fludrocortisone
13	80	100	116/64	109/66	22	midodrine
14	62	98	110/72	110/65	40	fludrocortisone
15	70	101	105/65	100/59	35	fludrocortisone
16	78	120	101/60	103/64	34	midodrine
17	58	96	102/70	98/64	—	fludrocortisone
18	76	104	107/65	93/70	32	fludrocortisone + midodrine
19	82	117	117/63	101/64	43	fludrocortisone
20	90	142	120/75	112/58	52	midodrine
21	70	125	130/90	124/70	—	fludrocortisone paroxetine methylphenidate
22	86	133	116/65	109/64	50	midodrine
23	68	110	111/58	98/73	—	hydration + salt
24	66	103	130/86	116/64	48	fludrocortisone and midodrine
25	63	119	115/58	123/71	—	fludrocortisone
26	110	150	110/71	104/80	—	fludrocortisone and midodrine
27	70	111	109/71	106/60	43	buproprion sertraline
28	70	125	100/60	90/55	25	fludrocortisone midodrine
29	50	110	110/70	85/60	34	fludrocortisone midodrine
30	60	130	115/65	80/50	18	fludrocortisone midodrine
31	55	145	120/70	90/60	—	fludrocortisone midodrine erythropoietin
32	65	160	106/68	80/50	—	fludrocortisone midodrine atenolol erythropoietin
33	67	118	90/65	90/60	29	fludrocortisone midodrine
34	75	132	120/80	100/70	16	fludrocortisone midodrine
35	70	110	100/60	90/55	32	fludrocortisone midodrine sertraline

BP = blood pressure; HR = heart rate.

group of virtually identical patients was reported in 1986 by Fouad who again found orthostatic tachycardia associated with only mild hypotension.[14] Streeten reported on a group of 11 patients with nearly identical complaints associated with orthostatic tachycardia.[15] Following reinjection of red cells labeled with sodium pertechnetate Tc 99 and gamma camera scanning, there was excessive gravity-mediated venous pooling in the lower extremities, a finding later confirmed by Hoeldtke.[16] Streeten later demonstrated that orthostatic tachycardia appears to be the most sensitive and earliest index of early orthostatic intolerance.[17]

Schondorf and Low coined the term postural orthostatic tachycardia syndrome (POTS) to describe a group of 16 adult patients who complained of orthostatic tachycardia, severe fatigue, exercise intolerance, and near syncope, who had initially been diagnosed as having psychiatric disorders.[9,18] Their cardiovascular responses to head-up tilt were markedly abnormal, with heart rates that varied from 120–170 beats/min, often occurring within the first 2 minutes of tilt. While some of their patients became hypotensive, the majority remained normotensive. They felt that POTS might represent an attenuated form of pandysautonomia, as many of their patients reported having a viral infection prior to the onset of symptoms. Similar findings were reported by Khurana et al.[19] The largest series of patients published to date has been a study by Grubb et al. that described a total of 28 patients with POTS.[6] A recent study by Furlan et al. looked at mean sympathetic nerve activity using miconeurography, and heart rate variability indices in these patients and found that the patients exhibit an overall enhancement of noradrenergic tone at rest and a postganglionic sympathetic response to standing (with a compensatory cardiac sympathetic overactivity).[20]

Our present findings not only further confirm and expand upon these earlier observations, they also demonstrate that POTS can be a disorder of adolescent patients as well. This emerging body of evidence appears to suggest that this group of individuals may suffer from a mild form of autonomic disturbance where an inability to properly augment peripheral vascular resistance in response to orthostatic stress is associated with excessive compensatory postural tachycardia.[7,21] This and other data demonstrate that these patients can be identified from their cardiovascular responses seen during tilt table testing. We have tended to focus on heart rate because it seems to be the earliest, most consistent, and easiest measure of orthostatic intolerance. In regard to the age range of reported cases of POTS (12–60 years), the increase in heart rate parameters used to define the disorder exceeds the 99th percentile reported for normal control subjects 10 to 83 years.[7,22] The present study shows that POTS not only affects the pediatric population, but that therapies directed at restoring autonomic balance can reduce (or sometimes eliminate) many of the symptoms they perceive as the most disruptive. Indeed, virtually all of the patients have been able to return to school and/or gainful employment on therapy.

It is important that the physician recognize the possibility of POTS in an adolescent, as many of these patients can be misdiagnosed as having psychiatric or anxiety disorders.[23] It has been our experience that patients with POTS can be misdiagnosed as having chronic fatigue syndrome. At the same time, it has become increasingly evident that there may be a considerable overlap between POTS and chronic fatigue syndrome in adult and pediatric patients.[24–27] Interestingly, both syndromes may be preceded by a viral infection, raising the idea that in some patients an immune-mediated mechanism may be involved.[23] We have also noted that POTS patients (including adolescents) can be misdiagnosed as having "inappropriate" sinus tachycardia. After undergoing radiofrequency catheter modification (ablation) of the sinoatrial node, these patients have noted a resolution of their tachycardia only to be left with a profound degree of incapacitating orthostatic hypotension.[6]

Our election of therapeutic agents was based on our experience with other autonomic disorders and on our and others experiences with adult POTS patients.[21,28] Increasing fluid and salt intake alone was only helpful in two patients. While other groups have successfully used beta-blockers, we only found them useful in three patients. When effective, we postulate that it is probably due to the ability of pure beta-blockers to increase peripheral vascular resistance via unopposed alpha-receptor activity (as opposed to their bradycardic effects). We did find that fludrocortisone was particularly helpful in adolescent POTS patients. While the drug seems to increase blood volume somewhat, its major action seems to be its ability to sensitize peripheral alpha-receptors to the patients own catecholamines, thus promoting vasoconstriction.[29,30] Midodrine and methylphenidate increase peripheral vascular resistance via their direct alpha-receptor stimulant effect and were particularly useful.[31–34] The serotonin reuptake inhibitors increase central nervous system levels of serotonin in the autonomic centers of the medulla and appear to enhance autonomic tone and function.[35–37] Erythropoietin may be useful in some patients because of its direct peripheral vasoconstrictive actions (which appear to be independent of its ability to augment red cell mass).[38–41] Overall, we felt the combination of fludrocortisone and midodrine appeared most effective. Based on our observa-

tions in managing neurocardiogenic syncope in adolescents, we anticipate that the majority of these patients will be able to be slowly weaned off therapy as they mature.[1,8] The average adolescent patient with neurocardiogenic syncope requires only 1 to 2 years of therapy, while a small number need therapy for several years (and a minority may require treatment indefinitely).[1] Thus far, only three of our patients have been weaned off therapy. Although all of the adolescent patients in this study showed an improvement on therapy, our experience with adult POTS patients has demonstrated that there are occasional patients that are completely unresponsive to or intolerant of all current forms of treatment and can become disabled by the disorder.[7] A major limitation in evaluating any treatment modality used was that a placebo group was not employed. Caution is also advised in extrapolating this data to small children where the criteria for POTS may potentially be different from those used in adolescents and adults. Lastly, the use of sphygmomanometry for blood pressure measurement may have missed early changes in blood pressure during orthostatic challenge.

Based on these observations, we conclude that POTS is a recognizable and treatable disorder of adolescents. It is manifested by orthostatic tachycardia, palpitations, fatigue, exercise intolerance, lightheadedness, cognitive impairment, and near syncope. On upright tilt table testing these patients demonstrate an increase in heart rate of ≥ 30 beats/min in the first 10 minutes of passive tilt or a pulse of ≥ 120 beats/min within the first 10 minutes of passive tilt not associated with profound hypotension or syncope. In either case, the patient's symptoms should be reproduced. Patients may also exhibit an exaggerated response to low dose isoproterenol infusion. Treatments aimed at augmenting peripheral vascular tone and increasing autonomic tone can lessen the degree of patient symptoms. By appropriately recognizing this disorder, physicians may help this highly symptomatic group of patients return to normal and productive lives. Additional, more detailed randomized studies will be necessary to better understand the nature of this and related autonomic disorders and to elucidate effective therapeutic modalities.

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