



Outcomes of Adolescent-Onset Postural Orthostatic Tachycardia Syndrome

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Objectives To determine the clinical course of adolescent-onset postural orthostatic tachycardia syndrome (POTS) and to assess health-related quality of life, 2-10 years after diagnosis.

Study design Pediatric patients, 13-18 years of age, diagnosed with POTS at Mayo Clinic, Rochester, from 2003 to 2010 were mailed a questionnaire if they were at least 18 years of age at the time of the mailing. The primary outcome measures were norm-based, age- and sex-adjusted, 36-Item Short Form Health Survey physical composite score and mental composite score.

Results The survey was mailed to 502 patients with a response rate of 34% (n = 172). The mean duration from diagnosis to survey completion was 5.4 (SD, 1.9) years; the mean age of the respondents at the time of the survey was 21.8 (2.2) years. The responders were predominantly females (84% vs 68% of nonresponders; $P < .001$). Only 33 (19%) respondents reported complete resolution of symptoms, and an additional 51% reported persistent but improved symptoms, and 28 (16%) had only intermittent symptoms. The majority (71%) consider their health at least "good." The mean physical composite score was significantly lower than the population norm (mean [SD], 36.6 [15.8] vs 50; $P < .001$), however, the corresponding mean mental composite score was normal (50.1 [11.2]).

Conclusions Overall, 86% of adolescents with POTS report resolved, improved, or just intermittent symptoms, when assessed via questionnaire at an average of 5 years after initial treatment. Patients with persistent symptoms have more physical than mental health concerns. (*J Pediatr* 2016;173:149-53).

Postural orthostatic tachycardia syndrome (POTS, sometimes also called postural tachycardia syndrome) is a potentially debilitating condition characterized by orthostatic intolerance, chronic fatigue, and, often, a variety of other symptoms.^{1,2} It occurs in up to 1% of the adolescent population and affects females more than males. Symptoms often begin after an illness such as infectious mononucleosis or an injury such as a concussion.^{1,3} Comorbidities can occur, including pain, gastrointestinal disorders, sleep disturbances, and psychosocial challenges.^{4,5} POTS is diagnosed when an adolescent patient: (1) has chronic symptoms such as dizziness, nausea, and/or vision change that are linked to assuming or maintaining an upright position; (2) also has an excessive increase in heart rate within 10 minutes of assuming an upright position (at least a 40 beats per minute change during standardized passive tilt testing); and (3) does not have an alternate explanation for the symptoms.¹ Treatment includes: (1) enhancement of vascular volume by increased oral fluid and salt intake (though the details of a "best practice" of salt intake have not been defined); (2) regular aerobic exercise; (3) biobehavioral strategies; and (4) medications (such as fludrocortisone, beta blockers, midodrine, and selective serotonin reuptake inhibitors).¹

POTS can be associated with severely impaired tolerance of academic and athletic activities.¹ Anecdotally, however, most affected adolescents eventually recover and do well. Unfortunately, there are limited data regarding actual outcomes in adolescents with POTS. In a follow-up survey 9-50 (mean 20) months after initiation of treatment, some general improvement was noted in 76% of adolescent respondents.⁶ In a 12-month follow-up study combining adolescents and adults with POTS, orthostatic symptoms improved in 70%, and 37% no longer met diagnostic criteria for POTS; data were not analyzed separately for the adolescent subgroup in this study.⁷ A study of Chinese children with a variety of types of orthostatic intolerance suggested that the degree of improvement relates to the initial extent of symptoms.⁸ An adult study showed a usually benign outcome with good return to daily activities 1-12 years after initial evaluation.⁹ The current study was designed to document improvement in symptoms and health-related quality of life in a cohort of adolescents with POTS.

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MCS	Mental component scale
PCS	Physical component scale
POTS	Postural orthostatic tachycardia syndrome
SF-36	36-Item Short Form Health Survey

Methods

Potential study subjects included patients, 13-18 years of age, diagnosed with POTS at the Mayo Clinic, Rochester, Minnesota during 2003-2010 who were at least 18 years of age at the time of the questionnaire mailing in 2013. A diagnosis of POTS was defined by orthostatic intolerance with a postural tachycardic increase of at least 40 beats per minute on 10-minute 70-degree head-up tilt table testing.

Patients with severe anemia, inflammatory rheumatologic disorders, adrenal insufficiency, diabetes, and other serious systemic illnesses were excluded from the study. In addition, patients who denied access to their medical records for research purposes or who were deceased at the time of the mailing were not included.

The study was approved by the Mayo Clinic Institutional Review Board. A questionnaire was mailed to all patients who met the above inclusion criteria. Nonresponders were re-mailed the questionnaire 1 month later. The questionnaire included the 36-Item Short Form Health Survey (SF-36), which is a validated self-reported tool composed of questions regarding health status, feelings, and ability to do usual activities.¹⁰ The SF-36 score is broken down into 2 summary scales derived from 8 subscales. The physical component scale (PCS) is composed of physical functioning, physical role functioning, bodily pain, and general health subscales. The mental component scale (MCS) is composed of vitality, social functioning, emotional role functioning, and mental health subscales. The questionnaire also included additional items about current symptoms, change in symptoms since the initial diagnosis, medication use, amount of exercise, amount of employment or school days missed as a result of health, and current salt and fluid intake.

Statistical Analyses

Statistical analysis was performed using the SAS v 9.2 software package (SAS Institute, Cary, North Carolina). Data were summarized using standard descriptive statistics: frequency and percentage for categorical variables and mean and SD or median and IQR for continuous variables. Sex distribution and age at diagnosis were compared between survey responders and nonresponders using the χ^2 test and 2-sample *t* test, respectively. Age- and sex-adjusted standardized z-scores were derived for each of the 8 SF-36 subscales using responses from 18- to 24- and 25- to 34-year-olds in the general US population to the 1998 National Survey of Functional Health Status that included the SF-36.¹¹ The PCS and MCS scores were derived using the established scoring algorithm and transformed to norm-based (mean = 50, SD = 10) scores.¹² The norm-based PCS and MCS scores were each compared against a fixed population mean of 50 using a 1-sample *t* test. Additional comparisons between groups (recovered vs not recovered, with vs without symptoms) of continuous measures were evaluated using the 2-sample *t* test. All calculated *P* values were 2-sided and *P* values less than .05 were considered statistically significant.

Results

Surveys were sent to 502 patients who met the inclusion criteria; responses were received from 172 (34%) patients. Respondents were more likely to be female ($P < .001$) and slightly older ($P = .013$). Among the 172 respondents, 144 (84%) were female and the mean age at diagnosis was 16.5 (SD, 1.3) years, compared with 226 (68%) and 16.1 (1.4) years for the 330 nonresponders. The mean duration from diagnosis to survey completion was 5.4 (1.9) years (range, 2.2-9.8 years). The mean age of respondents at the time of survey completion was 21.8 (2.2) years, ranging from 18.1-27.4 years. Of the 159 respondents between the ages of 18 and 24 years at the time of the survey, 129 (81%) had some college or technical training (nationally, 41% of all US 18- to 24-year-olds have some college training according to the National Center for Educational Statistics). Of the 53 respondents who were over 23 years of age at the time of the survey, 26 (49%) had graduated from college.

One hundred twenty-four (72%) respondents reported having used beta blockers sometime since their diagnosis, and 47 (27%) respondents reported current use of beta blockers at the time of the survey. Forty-eight (28%) respondents reported using a selective serotonin reuptake inhibitor; 20 (12%) respondents reported current use for their POTS management.

When asked their opinion on the treatment(s) that led to the greatest improvement in symptoms, 82 (48%) respondents affirmed the use of generous fluid intake, followed by conditioning (77, 45%), a high salt diet (77, 41%), beta blocker (50, 29%), midodrine (27, 16%), and selective serotonin reuptake inhibitor (13, 8%). Thirty-three (20%) respondents reported needing increased salt, water, and exercise to stay symptom free; 78 (45%) were still on a high-salt diet.

At the time of the survey, 122 (71%) respondents reported being in excellent, very good, or good health. Overall, 148 (86%) respondents reported on follow-up that their symptoms were resolved, improved, or just intermittent (**Figure 1**). Complete resolution of POTS-related symptoms (ie, "recovered") was reported by 33 (19%) respondents (36% of males and 16% of females, $P = .015$). Despite endorsing that their symptoms completely resolved, a small portion of the "recovered" patients still reported experiencing symptoms at the time of the survey compared with the not "recovered" patients (**Figure 2**). Time from diagnosis to survey was not different in those who reported recovery vs nonrecovery (mean [SD], 5.7 [1.9] vs 5.3 [1.9] years, $P = .23$). The frequencies of symptoms at the time of the survey are summarized in the **Table**.

The mean norm-based, sex- and age-adjusted PCS score was 36.6 (15.8); this is significantly lower than the population norm of 50 ($P < .001$). The mean PCS score was significantly higher for the 33 patients reporting complete resolution of symptoms compared with the remaining survey respondents

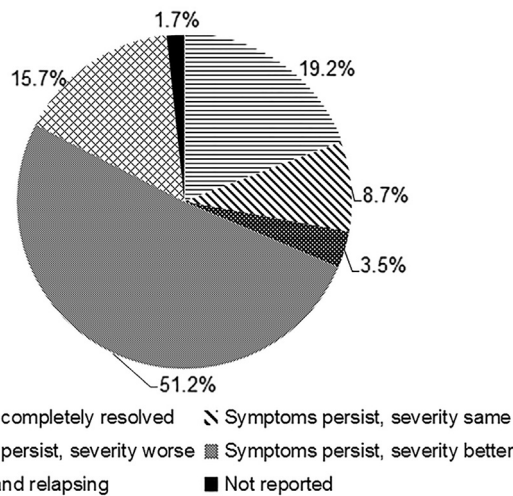


Figure 1. Symptom status as reported by all survey respondents (n = 172) at the time of survey compared with diagnosis.

(mean [SD], 51.5 [7.1] vs 33.0 [15.2], $P < .001$). The corresponding mean MCS score was 50.1 (11.2) and within the normal range. The mean MCS score was not significantly different between those reporting recovery and no recovery (52.9 [9.6] vs 49.4 [11.5], $P = .10$). As noted in the [Table](#), several specific ongoing symptoms were strongly associated with lower overall SF-36 scores.

When asked about overall progress, 76 (44%) respondents had seen some positive improvement in their health during the previous year, 73 (42%) reported little to no change in their health in the past year, and 23 (13%) reported a decline

in their health over the past year. One hundred twenty-six (73%) respondents reported some limitation in their physical ability to do vigorous activities such as running, lifting heavy objects, or participating in strenuous sports; 61 (36%) reported difficulty with moderate activities like using a vacuum cleaner, bowling, or playing golf. Ninety-eight (57%) reported limitation in climbing more than 1 flight of stairs, and 66 (28%) reported some degree of limitation in walking more than a mile. When asked about problems with work or regular daily activities as a result of their physical health, 65 (38%) reported a reduction in the amount of time spent on work or other activities. Overall, 85 (50%) reported that they still accomplished less than they would like to.

Regarding emotional health, 118 (69%) denied feeling downhearted or blue over the last month, 91 (53%) denied feeling significantly nervous, and 86 (50%) of respondents felt that they were calm and peaceful a significant portion of the time. Overall, 56 (33%) of the respondents reported that difficulty with their physical or emotional problems had interfered with their normal social activities with family and friends. In terms of health perception, 92 (53%) did not perceive themselves as being as healthy as other people.

Discussion

The finding of significant improvement in the majority of patients with adolescent-onset POTS is consistent with the 20-month follow-up data showing improvement in 76%⁶ and the combined adolescent-adult data showing improvement at 12 months in 70%.⁷ If anything, more affected patients (86%) show improvement by an average of 5 years after diagnosis. The fact that the majority of our

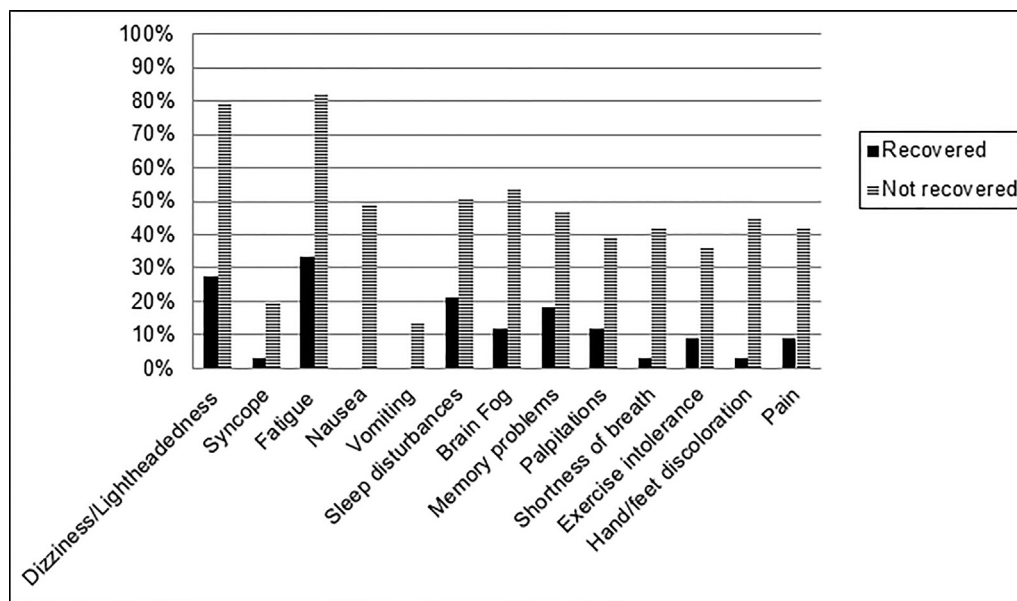


Figure 2. Symptom profile amongst self-identified “recovered” patients (n = 33) and not “recovered” patients (n = 139) at the time of survey.

Table. SF-36 norm-based, age- and sex-adjusted PCS scores based on presence/absence of specific symptoms at the time of survey completion*

Symptoms	With symptoms		Without symptoms		P value
	N	Mean (SD)	N	Mean (SD)	
Fatigue	123	34.2 (13.8)	46	48.8 (8.4)	<.001
Pain	60	26.5 (12.6)	109	44.7 (10.2)	<.001
Nausea	66	28.5 (12.3)	103	44.4 (11.4)	<.001
Sleep disturbance	77	31.9 (14.7)	92	43.5 (11.3)	<.001
Brain fog	78	29.8 (13.8)	91	45.4 (9.8)	<.001
Memory problems	70	30.8 (14.6)	99	43.4 (11.2)	<.001
Exercise intolerance	52	28.0 (14.7)	117	42.7 (11.2)	<.001
Purplish/bluish discoloration of hands and feet	62	32.7 (13.0)	107	41.4 (13.8)	<.001
Shortness of breath	58	29.1 (12.9)	111	42.9 (12.3)	<.001
Palpitations	56	31.6 (15.4)	113	41.5 (12.2)	<.001
Vomiting	18	21.1 (13.4)	151	40.2 (12.8)	<.001
Dizziness/light-headedness	117	34.1 (13.2)	52	47.3 (11.8)	<.001
Syncope	26	30.9 (16.4)	143	39.5 (13.3)	.004

*This Table is based on 169 patients who do not have missing age- and sex-adjusted PCS score; 3 patients are missing the score because of unanswered survey questions.

subjects were in college or had completed college at the time of the survey is also encouraging. However, it is not possible to determine from this study whether those who had not yet recovered would go on to recover or not. Furthermore, although pharmacologic interventions can be helpful, most of our patients reported that it was the nonpharmacologic interventions that were most helpful to them.

Anxiety and depression have been associated with POTS,¹³ and psychosocial factors are linked to the degree of functional disability in some subpopulations of patients with POTS.¹⁴ However, by the self-reporting in this study, it was only physical factors and not mental factors that related to the degree of perceived recovery from POTS. POTS is clearly a physical condition in which physical symptoms relate to the perceived degree of health impairment.

It is interesting that 27%-33% of patients who reported that they had fully recovered from POTS still had dizziness or fatigue, 2 of the cardinal symptoms of POTS. Similarly, a study of seemingly healthy adolescents in school found that 27% had postural dizziness when evaluated,¹⁵ and 31% of early adolescent girls in the US report fatigue more than once a week.¹⁶ It is also interesting to note that although 86% of respondents reported that their symptoms were resolved, improved, or just intermittent, only 71% of reported being in excellent, very good, or good health. It has been wisely stated that "satisfaction occurs when experience matches expectation." The lack of full recovery of symptoms might not actually represent pathology or persistent disease; rather, dizziness and fatigue are common in healthy teenagers. Patients with POTS should be counseled with the knowledge that improvement is possible but that the persistence of some symptoms can be part of a normal healthy life.

Similarly, approximately three-quarters of our patients recovering from POTS were not able to perform vigorous physical activity up to the level they desired. Some of this

could have been due to persisting autonomic dysfunction, but some of this could have also been due to either deconditioning (unrelated to ongoing POTS) or to excessively optimistic expectations of what their bodies should be able to accomplish. It is not clear how much these patients needed to modify their daily activities because of their symptoms.

Our study has limitations. We saw patients that were severely enough compromised to travel significant distances for definitive evaluation and care. Thus, they would likely be different from a collection of patients with POTS in a community practice. This retrospective uncontrolled cohort study included subjects treated at our center and did not include individuals without POTS or subjects with POTS who were not treated at our center. Besides the fact that the reported outcomes of this study depended on patients' perceptions of their own recovery, this study was also limited by the nature of surveys of large population groups. Even though the 34% response rate was reasonably good for patients who were sought years after their last clinical contact with the investigators' group, it is not known whether the nonresponders would have reported similar outcomes to the responders or not. In addition, although the SF-36 results are compared with reported "normals," we did not have pretreatment SF-36 data to compare progress in individual patients.

Further studies with objective measures of autonomic function should be able to help clarify detailed outcomes. In the meantime, clinicians should encourage their patients with adolescent-onset POTS that a good outcome is possible and that they will be functional and have improved overall symptoms even though they might continue to experience significant limitations in moderate to vigorous physical activities into adulthood. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Early versus Delayed Feeding of Low Birth Weight Infants: Effects on Physiologic Jaundice

Wennberg RP, Schwartz R, Sweet AY. *J Pediatr* 1966;68:860-6

This study was conducted during residency at Cleveland Metropolitan General Hospital at a time when low birth weight newborns were fasted for 24-48 hours. Studies had shown that premature newborns have an obligatory water/electrolyte loss following birth irrespective of fluid intake; the fear that early feeding might cause reflux and aspiration outweighed nutritional concerns. We found that early feeding of low birth weight infants, no matter what amount or content, decreased the serum bilirubin (SB) compared with fasting for 48 hours, whereas fasting or feeding only water resulted in lower blood glucose levels. This study, together with evidence that fasting promoted symptomatic hypoglycemia, soon ended the practice of withholding nutrition from small newborns.

During my fellowship, I was channeled into bilirubin research, resulting in the development of the peroxidase free bilirubin assay. Unfortunately, interest in free bilirubin waned when phototherapy and Rhogam revolutionized the management of neonatal jaundice. Kernicterus nearly vanished in affluent countries, but not in low/middle income countries (LMICs). This provided a recent opportunity to reexamine risk factors for acute bilirubin encephalopathy (ABE) in Egypt. ABE rarely occurred below a SB of 30 mg/dL in babies ≥ 35 weeks gestation unless severe hemolysis or sepsis was present.¹ Frequently, patient referrals were compromised by the inability to measure SB, stimulating our design of a low-cost point of care bilirubin assay for LMICs.² In Nigeria, $\sim 10\%$ of neonatal deaths after day 1 result from hyperbilirubinemia, and most babies with severe ABE arrive too late to benefit from treatment. Infrastructures assuring postnatal infant monitoring are nonexistent in many LMICs, complicated by high rates of home deliveries, so we have recently focused on empowering mothers to avoid harmful practices, to recognize when jaundice requires timely evaluation, and to decrease bilirubinemia by frequent nursing. Early feeding is still important 50 years later.

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