

Evaluation of the relationship between mast cell activation and postural orthostatic tachycardia syndrome in children and adolescents

 Yunus Emre Bayrak,¹  Ozlem Kayabey,²  Evic Zeynep Basar,²  Isil Eser Simsek,³
 Metin Aydogan,³  Abdulkadir Babaoglu²

¹Department of Pediatrics, Kocaeli University Faculty of Medicine, Kocaeli, Turkiye

²Department of Pediatric Cardiology, Kocaeli University Faculty of Medicine, Kocaeli, Turkiye

³Department of Pediatric Immunology and Allergy, Kocaeli University Faculty of Medicine, Kocaeli, Turkiye

ABSTRACT

OBJECTIVE: Postural orthostatic tachycardia syndrome (POTS) is one of the orthostatic intolerance syndromes that are common in young adolescents and impair quality of life. POTS is a multi-systemic disease. Many mechanisms have been defined in POTS etiology, such as autonomic denervation, hypovolemia, hyperadrenergic stimulation, low condition, and hypervigilance. Recently, mast cell activation (MCA) has also been on the agenda in etiology. There are few studies in the literature on the relationship between MCA and POTS in adulthood. However, data on children and adolescents is limited. In light of this information, we aimed to evaluate the relationship between POTS and MCA by measuring serum tryptase levels, a specific marker for MCA.

METHODS: This prospective study included patients who were admitted to Kocaeli University Faculty of Medicine Hospital Pediatric Cardiology outpatient clinic for syncope-presyncope between November 2018 and August 2019. Patients who underwent the TILT-table test were enrolled in the study. Patients with structural heart disease or chronic heart disease were not included in this study. Serum tryptase levels were obtained from all patients before the TILT-table test, and serum tryptase levels were re-studied after the test was terminated in patients with positive TILT-table tests for POTS. Patients diagnosed with POTS were classified as Group 1, and other patients were classified as Group 2.

RESULTS: Twenty-eight of the 58 patients included in the study (mean: 14.4±2.0 years; 38 girls, 20 boys) were diagnosed with POTS. The remaining 30 patients were diagnosed with vasovagal syncope and included in Group 2. The increase in mean heart rate during the test was 38±6 beats/min and 47.05%±15.65% in patients with POTS. Basal serum tryptase levels were not different between groups (3.2±1.3 ng/ml and 3.84±1.78 ng/ml, respectively; $p=0.129$), while serum tryptase levels (both baseline and after 45–60 min of the TILT-table test) were higher in patients presenting with symptoms related to MCA compared to others.

CONCLUSION: In the literature, MCA was considered to be one of the mechanisms leading to POTS. Although other mechanisms, such as neuropathic and hypovolemic POTS, may be active in the patients, the symptoms of MCA in these patients should be routinely questioned.

Keywords: Head-up TILT-table test; mast cell activation; postural orthostatic tachycardia syndrome; serum tryptase level.

Cite this article as: Bayrak YE, Kayabey O, Basar EZ, Simsek IE, Aydogan M, Babaoglu A. Evaluation of the relationship between mast cell activation and postural orthostatic tachycardia syndrome in children and adolescents. *North Clin Istanbul* 2024;11(4):315–321.



Received: June 09, 2023

Revised: July 18, 2023

Accepted: August 30, 2023

Online: August 02, 2024

Correspondence: Yunus Emre BAYRAK, MD. Kocaeli Universitesi Tip Fakultesi, Cocuk Sagligi ve Hastaliklari Anabilim Dalı, Kocaeli, Turkiye.

Tel: +90 262 303 75 75 e-mail: yeb6141@gmail.com

Istanbul Provincial Directorate of Health - Available online at www.northclinist.com

Postural orthostatic tachycardia syndrome (POTS) is one of the orthostatic intolerance syndromes that are common in young adolescents and impair quality of life. It is a clinical condition characterized by dizziness, palpitations, tremors, weakness, blurred vision, exercise intolerance, fatigue, and orthostatic tachycardia that is especially acute when standing up [1]. Moreover, patients may experience functional gastrointestinal complaints (chronic abdominal pain, nausea, constipation, bloating, and diarrhea), migraine-type headaches, chronic fatigue, sleep disorders, and musculoskeletal system complaints [2, 3].

POTS is a multi-systemic disease, unlike other orthostatic intolerance syndromes. Many mechanisms have been defined in POTS etiology, such as autonomic denervation, hypovolemia, hyperadrenergic stimulation, low condition, and hypervigilance [4]. Recently, mast cell activation has also been on the agenda in etiology.

It was observed that the symptoms of patients decreased when a mast cell stabilizer or leukotriene antagonist was used in the treatment [5, 6]. As a result, patients with mast cell activation of POTS need to be diagnosed and treated promptly. Mast cell activation (MCA) syndrome was first described as an idiopathic disease in 2010 [7]. The diagnosis of MCAS is made according to the presence of episodic, objective signs and symptoms involving at least two organ systems consistent with MCA. The diagnosis of MCA syndrome may also be defined as the response of symptoms to antihistamines and leukotriene antagonists. Many mediators that are released from mast cells play a role in the occurrence of clinical symptoms. Tryptase is the most specific mediator of mast cells [8–10]. Values above 15 ng/ml are considered high for the tryptase level [11]. Basal tryptase levels are measured in clinically suspected patients.

There are few studies in the literature on the relationship between MCA and POTS in adulthood. Adult studies showed MCA in patients with POTS and the resolution of their symptoms after treatment with mast cell mediators [5]. However, data on children and adolescents are limited. Herein, we aim to evaluate whether MCA is a potential underlying factor in the pathogenesis of POTS. To assess our hypothesis, we measured tryptase levels, which are a specific marker for MCA in patients diagnosed with POTS.

MATERIALS AND METHODS

This prospective study was conducted between November 2018 and August 2019. Patients who were admit-

Highlight key points

- Postural orthostatic tachycardia syndrome (POTS) is one of the orthostatic intolerance syndromes.
- Mast cell activation (MCA) is one of the underlying mechanisms leading to POTS.
- Mast cell mediators and their metabolites may be used to evaluate MCA.

ted to the Pediatric Cardiology Outpatient Clinic for complaints of presyncope or syncope and underwent the TILT-table test were enrolled in the study. Patients aged between 10 and 18 years participated in the study. Patients with structural heart disease, chronic disease, allergic diseases, a previous history of peripheral neuropathy, or taking any medication impairing autonomic reflexes were excluded from the study.

Patients' gender, age, height, weight, body mass index (BMI), complaint at admission, prodromal symptoms, symptoms during and after the event, symptoms related to MCA, vital signs at the time of admission (heartbeat, blood pressure [BP], oxygen saturation measured by pulse oximetry), and physical examination findings were evaluated. Patients' complete blood count, biochemistry, thyroid function tests, serum B12, ferritin, tryptase levels, electrocardiography (ECG), and echocardiography (ECHO) were recorded retrospectively.

TILT-Table Test

Patients were divided into two groups according to the results of the TILT-table test. The Italian Protocol [12], which is the protocol accepted in international studies, was implemented as a TILT test protocol. Initially, before the test, basal serum tryptase levels were obtained from all patients. Blood samples were taken from the cubital veins. A total of 5 cc of blood was taken and centrifuged at 5000 rpm for 10 minutes. Serum samples were stored at -20 °C for 3 months. Then patients rested for 10 minutes in the supine position. Subsequently, the table was brought to the 70-degree inclination position, and the non-provocative (passive) phase was applied for 20 minutes. According to the directive published by the European Society of Cardiology (ESC) in 2018, during the TILT-table test, patients who had experienced an increased heart rate of ≥ 30 beats/min (>40 beats/min increase in individuals between the ages of 12 and 19) or a heart rate of ≥ 120 beats/min with no orthostatic hypotension (no decrease in systolic blood pressure more than 20 mmHg) for more than 30 seconds within the

first 10 minutes after moving from supine to upright position were diagnosed with POTS [13, 14]. Patients who were diagnosed with POTS in the passive phase were included in Group 1, and 45–60 minutes later, a second serum tryptase sample was taken from these patients and kept at -20°C . Tryptase levels were measured using a commercial fluoroenzyme immunoassay kit (Immuno-cap Tryptase Kit, Sweden).

The remaining patients who had no symptoms and were not diagnosed with POTS were included in Group 2. Group 2 consisted of patients who had presyncope or syncope but were not diagnosed with POTS in the TILT-table test. Thus, the test was moved to the second phase (provocative or active phase) in Group 2. The patients in Group 2 were placed in a supine position, and sublingual nitroglycerin was given and brought back to the 70-degree inclination position. The test continued for 20 minutes. Blood pressure and heart rate were measured before, during, and after the test. The results were recorded. However, control tryptase levels from patients (Group 2) were not obtained after the active phase.

Approval was received from the Kocaeli University Faculty of Medicine Clinical Research Ethics Committee for our research on November 28, 2018, under Project Number 2018/339. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Informal consent from both parents and patients was obtained.

Statistical Analysis

All statistical analyses were performed using IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA). Compatibility with a normal distribution was evaluated with a Kolmogorov-Smirnov test. Numeric variables with a normal distribution were assigned as mean \pm standard deviation, numerical variables without a normal distribution were assigned as median (25th–75th percentile), and categorical variables as frequency (percent). Student-T tests were used to identify differences between the groups for numerical variables with a normal distribution and Mann-Whitney U tests for numerical variables without a normal distribution.

A Chi-squared analysis was used to evaluate the relationships between categorical variables. A paired sample T-test and Friedman two-way analysis of variance were used to compare measurements that were obtained at different times. In the two-tailed hypothesis test, $p < 0.05$ was considered statistically significant.

TABLE 1. Demographic features of patients

	Group1 (n=28) Mean \pm SD	Group 2 (n=30) Mean \pm SD	p
Age	14.49 \pm 1.97	14.43 \pm 2.05	0.876
Weight (percentile)	38.59 \pm 26.81	43.19 \pm 31.75	0.697
Weight (SDS)	-0.34 \pm 0.81	-0.25 \pm 1.15	0.697
Height (percentile)	65.96 \pm 25.22	44.13 \pm 29.57	0.006
Height (SDS)	0.58 \pm 0.95	-0.09 \pm 1.15	0.006
BMI (kg/m ²)	18.88 \pm 2.23	20.28 \pm 3.3	0.068
BMI (percentile)	27.38 \pm 22.23	43.50 \pm 30.59	0.034
BMI (SDS)	-0.76 \pm 0.79	-0.22 \pm 1.19	0.034
Gender, (%)			0.640
Female	60.7	70	
Male	39.3	30	
Female/Male	1.55/1	2.33/1	
Family story, (%)	10.7	16.7	0.707

SD: Standard deviation; POTS: Postural orthostatic tachycardia syndrome; BMI: Body mass index.

RESULTS

Fifty-eight patients were enrolled in the study. Of them, 38 were (65.5%) female and 20 were (34.5%) male. The female-male ratio was 1.9. The mean age of patients was 14.46 ± 2 years. The mean body weight, height, and BMI were 51.7 ± 10.45 kg, 161.8 ± 10.09 cm, and 19.61 ± 2.9 kg/m², respectively. No structural or functional heart disease was detected in the echocardiograms of all patients. As a result of the TILT-table test, 28 (48.2%) patients were diagnosed with POTS and included in Group 1. The remaining 30 (51.7%) patients were not diagnosed with POTS in the TILT-table test and were included in Group 2. Of these 30 patients (Group 2), 7 were diagnosed with vasovagal syncope during the TILT-table test. Among the 7 patients with vasovagal syncope, 4 were diagnosed in the non-provocation phase and 3 in the provocation phase. The TILT-table test of the remaining 23 patients in Group 2 revealed normal results. Even if the tests were normal in these 23 patients, the diagnosis of vasovagal syncope was made clinically. Unlike tachycardia in POTS, vasovagal syncope was defined as the presence of bradycardia and hypotension (Table 1).

Of the patients diagnosed with POTS, 17 (60.7%) were female and 11 (39.3%) were male. The female/male ratio was 1.55/1. The mean age of these patients was

TABLE 2. Conditions at the onset of attacks and symptoms of mast cell diseases in the history

	Group 1 (n=28) (%)	Group 2 (n=30) (%)	p
Gastrointestinal symptoms			
Nausea	35.7	36.7	1.000
Abdominal pain	10.7	6.7	0.665
Diarrhea	10.7	0	0.106
Vomiting	3.6	6.7	0.492
Skin findings			
Flushing	25	20	0.888
Urticaria-angioedema	10.7	10	1.000
Cardiovascular symptoms			
Palpitation	39.3	50	0.578
Hypotension	21.4	10	0.290
Sweating	17.9	16.7	1.000
Respiratory symptoms			
The feeling of hanging in the thorax	14.3	3.3	0.187
Shortness of breath	14.3	30	0.263
Wheezing	10.7	6.7	0.665
Hoarseness of voice	0	13.3	0.113
Nazo-ocular findings			
Naso congestion	28.6	30	1.000
Runny nose	17.9	23.3	0.849
Itchy nose	14.3	20	0.732
Itching	14.3	20	0.732
Eye itch	7.1	23.3	0.147
Eye discharge	3.6	6.7	1.000
Other findings			
Dizziness	78.6	83.3	0.440
Blurring in vision	71.4	76.7	0.899
Tiredness	46.4	53.3	0.877
Feeling cold	21.4	13.3	0.793
Headache	32.1	56.7	0.499
Pain in the neck	10.7	23.3	0.107
Anaphylaxis	0	0	0.301

14.47±1.91 years. The mean body weight, height, and BMI percentiles were 38.59±26.81, 65.96±25.22, and 27.38±22.23, respectively. Height percentiles were higher and BMI percentiles were lower in Group 1 compared to Group 2 (p=0.006 vs. 0.034). The remaining demographic findings were similar between the two groups. Furthermore, there were no statistically significant differences between the two groups in terms of general symp-

TABLE 3. Symptoms developing during the test

	Group 1 (n=28) (%)	Group 2 (n=30) (%)	p
Syncope/presyncope	32.1	60	0.063
Dizziness	46.4	46.7	1.000
Nausea	39.3	36.7	1.000
Tiredness	28.5	36.7	0.683
Blackout	21.4	43.3	0.135
Headache	7.1	23.3	0.147
Numbness in the feet	7.1	3.3	0.605
Sweating	3.6	10	0.612
Shortness of breath	3.6	3.3	1.000
Abdominal pain	3.6	3.3	1.000

toms related to syncope and mast cell activation (Table 2). Anaphylaxis wasn't observed in any patients. During the test, the most common symptom in Group 1 was dizziness, which was observed in 13 patients (46.4%). Other common symptoms in Group 1 patients were nausea, fatigue, feeling bad, and blackouts (Table 3).

In Group 1, POTS symptoms developed for an average of 4.92±3.26 minutes during the TILT-table test. At that time, the mean heart rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were 120±9/min, 109±17 mm Hg, and 70±9 mm Hg, respectively. An average increase of 38±6 (47%) beats/min was observed in heart rate compared to baseline heart rate.

In the laboratory, the complete blood count, blood biochemistry, thyroid function tests, serum B12, and ferritin levels of patients were investigated. There were no significant differences between these two groups in terms of laboratory parameters except neutrophil count (Table 4). The median neutrophil counts were lower in Group 1 compared to Group 2 (3029/mm³ vs. 3762/mm³, p=0.009).

The mean baseline tryptase levels were 3.2±1.3 ng/ml in patients with POTS (Group 1) and 3.84±1.78 ng/ml in patients with non-POTS (Group 2) (p=0.129). Interestingly, serum tryptase levels (both baseline [3.19±1.37 ng/ml vs. 2.99±1.18 ng/ml] and after 45–60 min of the TILT-table test [3.32±1.38 ng/ml vs. 2.799±1.12 ng/ml]) were higher in patients presenting with symptoms related to MCA compared to others. However, these differences did not reach statistical significance.

TABLE 4. Laboratory findings of patients

	Group 1 (n=28)	Group 2 (n=30)	p
Hemoglobin (g/dL), Mean±SD	13.19±1.1	13.4±1.5	0.567
Hematocrit (%), Mean±SD	39.39±3.16	39.81±4.2	0.684
White blood cell (/mm ³), Median (25–75 p)	6275 (5343–6843)	7.084 (5.576–8.200)	0.145
Neutrophil (/mm ³), Median (25–75 p)	3.029 (2.423–3.773)	3.762.5 (3.127.5–4.607)	0.009
Lymphocyte (/mm ³), Median (25–75 p)	6.275 (5.343.5–6.843.5)	7.084 (5.576–8.200)	0.947
Platelet (/mm ³), Median (25–75 p)	250300 (201.100–318675)	276.000 (236.000–326.225)	0.563
MCV (fL), Mean±SD	82.75±5.45	84.1±5.88	0.398
Eosinophil (%), Median (25–75 p)	1.94 (1.23–4.59)	1.51 (1–3.01)	0.184
Fasting blood sugar (mg/dL), Mean±SD	94.08±13.67	89.84±15.52	0.325
Sodium (mmol/L), Mean±SD	140.66±2.22	140.21±3.61	0.580
Potassium (mmol/L), Mean±SD	4.24±0.4	4.39±0.42	0.189
Calcium (mg/dL), Mean±SD	9.83±0.36	9.83±0.46	0.991
B12 (pg/mL), Median (25–75 p)	225 (171–313.25)	209 (132.5–277.5)	0.304
Ferritin (ng/mL), Mean±SD	25.22±13.78	22.65±15.57	0.532
T4 (ng/dL)	0.91±0.33	0.9±0.2	0.836
TSH (μU/mL)	1.56 (1.23–2.25)	1.3 (1.08–1.89)	0.166

SD: Standard deviation; TSH: Thyroid stimulating hormone; MCV: Mean cell volume; T4: Thyroxine.

DISCUSSION

Herein, we evaluated 58 patients suffering from syncope or presyncope. POTS is one of the underlying etiologies of syncope, which commonly affects young females and is characterized by dizziness and tachycardia without developing hypotension [1]. Many mechanisms have been defined in POTS etiology, such as autonomic denervation, hypovolemia, hyperadrenergic stimulation, and hypervigilance [4]. However, it is not clear if MCA is another mechanism implicated in the etiology. Supporting this hypothesis, Shibao et al. [5] showed abnormal MCA in adults with POTS. Yet, there was no study focusing on the role of MCA in pediatric POTS patients. In the present study, we evaluated the potential role of MCA in POTS. According to our findings in the adult study, patients who present with symptoms associated with MCA have higher serum tryptase levels (at both baseline and 45–60 minutes following TILT-table testing). POTS is a complex disease, and different mechanisms may participate in its pathogenesis. However, MCA is not the sole problem in the process of POTS; it may be implicated in pathogenesis in some patients.

Although POTS affects all ages, it is more common in the adolescent and young adult age groups [15]. In our study, the mean age of POTS cases was 14.47±1.91 years,

which was compatible with the literature. Adult studies have shown that POTS is 4–5 times higher in women [16–18]. The demographic characteristics of the disease may be different in children compared to adults. However, there are a limited number of pediatric studies on POTS. For instance, in one study [19] of 37 children and adolescents with POTS, unlike adult studies, the female/male ratio was 1.64, which was consistent with our results. Furthermore, people with a low BMI are more prone to vasovagal syncope, or POTS. Lin et al. [20] showed lower BMI in children and adolescents with POTS and vasovagal syncope. Correspondingly, in the present study, we found a lower BMI in patients with POTS.

The most common symptoms of POTS are dizziness and palpitations. In a study of 39 adult patients with POTS conducted by Deb et al. [21], the most common complaints were palpitations (92%), fatigue (90%), and dizziness (87%). As further evidence, Zhang et al. [19] evaluated 37 children and adolescents with POTS, finding that dizziness was the most commonly reported symptom (100%) followed by fatigue (85%). Consistent with Zhang's study, the most common symptom was dizziness (78.6%) in our study. Despite dizziness and palpitations, patients with POTS may experience additional symptoms of MCA, such as gastrointestinal symptoms,

urticaria, and a runny nose. In the present study, we also observed some symptoms related to mast cell activation. For instance, gastrointestinal symptoms (35.7% nausea, 10.7% abdominal pain, 10.7% diarrhea, and 3.6% vomiting) were present in one-third of our patients.

In the study of laboratory findings, the neutrophil count of Group 1 (the POTS group) was significantly lower than that of Group 2 (the non-POTS group), while no statistical significance was found for other laboratory parameters. Both mast cells and eosinophils originate from the same pluripotent hematopoietic stem cells (CD 34+, CD 117+). However, the number of baseline eosinophil values did not differ between Group 1 and Group 2.

The mediators released from mast cells result in postural tachycardia, lightheadedness, flushing, nasal congestion, vomiting, and diarrhea, which are also suggestive symptoms of POTS. The fact that POTS and MCA share some of the same clinical findings has led to the hypothesis that mast cells may have a role in POTS pathogenesis. It is possible to document MCA based on mast cell mediators and their metabolites, such as plasma tryptase, plasma and urine prostaglandins, plasma histamine, and plasma methylhistamine. Firstly, Shibao et al. [5] tested this hypothesis in adult patients with POTS. They showed increased urine methylhistamine levels in POTS patients presenting with clinical findings similar to MCA. Methylhistamine is the major metabolite of histamine, and increased urine levels of N-methylhistamine indicate mast cell activity. However, in the aforementioned study, urine methylhistamine levels did not differ in isolated POTS patients compared to healthy controls. They concluded that MCA should be considered in POTS patients with suggestive symptoms of MCA, and these patients may benefit from inhibitors of mast cell mediators. Plasma tryptase level is a valuable biomarker to confirm MCA [22]. For this purpose, Kohno et al. [23] tested the mediators of MCA (prostaglandins, histamine, methyl histamine, and tryptase) in 69 patients with POTS. Of these 69 patients, 44 expressed additional symptoms suggesting MCA. Among them, 29 (66%) patients exhibited at least one laboratory abnormality related to MCA. Elevated plasma histamine or 24-hour urine n-methylhistamine levels were detected in 23 patients, elevated prostaglandins in 16, and elevated plasma tryptase in 2 patients. In the present study, which did not reach statistical significance, serum tryptase levels (both baseline and after 45–60 min of the TILT-table test) were higher in patients present-

ing with symptoms related to MCA compared to others. Therefore, the activation of mast cells should be kept in mind in POTS patients when MCA-related symptoms are present. Understanding POTS mechanisms may help guide treatment.

The main limitations of the study are its single-center design and the small number of patients. Another limitation is that tryptase is not always elevated in all conditions of MCA. However, our findings are quite important due to the fact that this is the first study on the role of MCA in childhood POTS.

Conclusion

In conclusion, we suggest that clinicians question the symptoms related to MCA in suspicious cases. Further studies are required to test the effectiveness of mast cell-targeted therapies in these patients.

Ethics Committee Approval: The Kocaeli University Faculty of Medicine Non-interventional Clinical Research Ethics Committee granted approval for this study (date: 28.11.2018, number: KU GO-KAEK 2018/18.20).

Authorship Contributions: Concept – YEB, AB, IES; Design – YEB, AB; Supervision – YEB, AB, MA; Fundings – YEB, AB, MA; Materials – YEB, AB, EZB; Data collection and/or processing – YEB, AB, EZB; Analysis and/or interpretation – YEB, AB, OK; Literature review – YEB, AB, OK; Writing – YEB, AB, IES; Critical review – YEB, AB, MA.

Conflict of Interest: No conflict of interest was declared by the authors.

Use of AI for Writing Assistance: Not declared.

Financial Disclosure: This study was funded by Kocaeli University BAP (approval number: 2019/005).

Peer-review: Externally peer-reviewed.

REFERENCES

1. Raj SR. Postural tachycardia syndrome (POTS). *Circulation* 2013;127:2336–42. [CrossRef]
2. Rea NA, Campbell CL, Cortez MM. Quantitative assessment of autonomic symptom burden in postural tachycardia syndrome (POTS). *J Neurol Sci* 2017;377:35–41. [CrossRef]
3. Garland EM, Celedonio JE, Raj SR. Postural tachycardia syndrome: beyond orthostatic intolerance. *Curr Neurol Neurosci Rep* 2015;15:60. [CrossRef]
4. Benarroch EE. Postural tachycardia syndrome: a heterogeneous and multifactorial disorder. *Mayo Clin Proc* 2012;87:1214–25. [CrossRef]
5. Shibao C, Arzubiaga C, Roberts LJ 2nd, Raj S, Black B, Harris P, et al. Hyperadrenergic postural tachycardia syndrome in mast cell activation disorders. *Hypertension* 2005;45:385–90. [CrossRef]
6. Doherty TA, White AA. Postural orthostatic tachycardia syndrome and the potential role of mast cell activation. *Auton Neurosci* 2018;215:83–8. [CrossRef]

7. Akin C, Metcalfe DD. Systemic mastocytosis. *Annu Rev Med* 2004;55:419–32. [\[CrossRef\]](#)
8. Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: proposed diagnostic criteria. *J Allergy Clin Immunol* 2010;126:1099–104. [\[CrossRef\]](#)
9. Valent P, Akin C, Arock M, Brockow K, Butterfield JH, Carter MC, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. *Int Arch Allergy Immunol* 2012;157:215–25. [\[CrossRef\]](#)
10. Metcalfe DD, Pawankar R, Ackerman SJ, Akin C, Clayton F, Falcone FH, et al. Biomarkers of the involvement of mast cells, basophils and eosinophils in asthma and allergic diseases. *World Allergy Organ J* 2016;9:7. [\[CrossRef\]](#)
11. Frieri M, Patel R, Celestin J. Mast cell activation syndrome: a review. *Curr Allergy Asthma Rep* 2013;13:27–32. [\[CrossRef\]](#)
12. Bartoletti A, Alboni P, Ammirati F, Brignole M, Del Rosso A, Foglia Manzillo G, et al. ‘The Italian Protocol’: a simplified head-up tilt testing potentiated with oral nitroglycerin to assess patients with unexplained syncope. *Europace* 2000;2:339–42. [\[CrossRef\]](#)
13. Sheldon RS, Grubb BP 2nd, Olshansky B, Shen WK, Calkins H, Brignole M, et al. 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *Heart Rhythm* 2015;12:e41–63. [\[CrossRef\]](#)
14. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, et al; ESC Scientific Document Group. 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J* 2018;39:1883–48. [\[CrossRef\]](#)
15. Robertson D. The epidemic of orthostatic tachycardia and orthostatic intolerance. *Am J Med Sci* 1999;317:75–7. [\[CrossRef\]](#)
16. Jacob G, Biaggioni I. Idiopathic orthostatic intolerance and postural tachycardia syndromes. *Am J Med Sci* 1999;317:88–101. [\[CrossRef\]](#)
17. Thieben MJ, Sandroni P, Sletten DM, Benrud-Larson LM, Fealey RD, Vernino S, et al. Postural orthostatic tachycardia syndrome: the Mayo clinic experience. *Mayo Clin Proc* 2007;82:308–13. [\[CrossRef\]](#)
18. Kimpinski K, Figueroa JJ, Singer W, Sletten DM, Iodice V, Sandroni P, et al. A prospective, 1-year follow-up study of postural tachycardia syndrome. *Mayo Clin Proc* 2012;87:746–52. [\[CrossRef\]](#)
19. Zhang Q, Chen X, Li J, Du J. Clinical features of hyperadrenergic postural tachycardia syndrome in children. *Pediatr Int* 2014;56:813–6. [\[CrossRef\]](#)
20. Lin J, Zhao H, Ma L, Jiao F. Body mass index is decreased in children and adolescents with postural tachycardia syndrome. *Turk J Pediatr* 2019;61:52–8. [\[CrossRef\]](#)
21. Deb A, Morgenshtern K, Culbertson CJ, Wang LB, Hohler AD. A survey-based analysis of symptoms in patients with postural orthostatic tachycardia syndrome. *Proc (Bayl Univ Med Cent)* 2015;28:157–9. [\[CrossRef\]](#)
22. Valent P, Akin C, Bonadonna P, Hartmann K, Brockow K, Niedoszytko M, et al. Proposed diagnostic algorithm for patients with suspected mast cell activation syndrome. *J Allergy Clin Immunol Pract* 2019;7:1125–33. [\[CrossRef\]](#)
23. Kohno R, Cannon DS, Olshansky B, Xi SC, Krishnappa D, Adkisson WO, et al. Mast cell activation disorder and postural orthostatic tachycardia syndrome: a clinical association. *J Am Heart Assoc* 2021;10:021002. [\[CrossRef\]](#)