Clinical Prognostic Factors in Pediatric Patients With Orthostatic Intolerance

Global Pediatric Health
Volume 7: 1–9

DOI: 10.1177/2333794X20971980
journals.sagepub.com/home/gph
SAGE

Kazue Ishitsuka, MD, MPH, PhD[1], Kaori Yamawaki, MD[1,2], Miwako Horikawa, MD[1], Hisaya Nakadate, MD, PhD[1], Akira Nagai, MD, PhD[1], and Akira Ishiguro, MD, PhD[1]

Abstract

Midodrine is widely used for orthostatic intolerance (OI); however, little is known about the prognostic factors of OI after midodrine treatment. We retrospectively reviewed electronic medical charts to investigate clinical prognostic factors of OI on 159 OI patients aged 7 to 18 years who were treated with midodrine at a children's hospital. Logistic regression was conducted to clarify predictors for improving symptoms at the first month of the treatment. Patients with orthostatic uncomfortable feeling or fainting were significantly more likely to improve symptoms at the first month of the treatment (odds ratio [OR], 3.48; 95% confidence interval [95%CI], 1.36-8.89), but patients with underweight were significantly less likely to improve symptoms (OR, 0.19; 95%CI, 0.06-0.56). Our results suggest that predictive factors for OI by midodrine treatments are orthostatic symptoms and underweight in pediatric patients. These findings are useful to develop further studies for OI treatments.

Keywords

orthostatic intolerance, prognostic factors, children, adolescents, midodrine

Received March 12, 2020. Received revised October 9, 2020. Accepted for publication October 16, 2020.

Introduction

Orthostatic intolerance (OI) is a common disorder for children and adolescents in outpatient clinics that is characterized by orthostatic symptoms, palpitations, light-headedness, and fatigue.[1-3] Approximately 8.5% of children and adolescents at outpatient clinics have OI in Japan.[4] Meanwhile, at least 500 000 OI patients have been reported in the United States, which may be higher due to lack of clinical awareness of OI.[5] Symptoms vary among patients with OI.[6-10] Orthostatic tests, such as active standing tests or head-up tilt tests, identify the subtypes of OI, including orthostatic hypotension and postural orthostatic tachycardia (POTS).[3] Although most patients' quality of life and symptoms improve without medical treatment, some patients have severe symptoms and impaired quality of life, resulting in school absenteeism and social withdrawal.[6-10]

Patients with OI are prescribed drugs to expand plasma volume, to increase peripheral vasoconstriction, or to compensate for the high catecholamine levels.[2] Midodrine, an alpha-1 adrenergic agonist, has been the current standard of medication for orthostatic hypotension.[11] Recent studies outside of Japan have shown that midodrine is also effective for other types of OI, including POTS.[12,13] The Japanese guidelines recommend midodrine treatment as the first-line pharmacological treatment for OI.[4]

Although midodrine is widely used for patients with OI, the effectiveness of midodrine is limited. Previous studies showed that more than 20% to 30% of patients with OI did not improve their symptoms.[12-14] However, the information regarding prognostic factors in children and adolescents with OI is still limited.[14] Understanding clinical prognostic factors is important to improve choices for appropriate treatments in patients with OI.

We investigated clinical prognostic factors for children and adolescents with OI who were treated with midodrine.

[1]National Center for Child Health and Development, Tokyo, Japan
[2]Kyushu University, Fukuoka, Japan

Corresponding Author:
Kazue Ishitsuka, Center for Postgraduate Education and Training, National Center for Child Health and Development, 2-10-1 Okura, Setagaya-ku, Tokyo 185-8535, Japan.
Email: ishistuka-k@ncchd.go.jp

Materials and Methods

Data Source and Patients

The design of this study was a retrospective cohort study. The authors reviewed electronic medical records for outpatients who were treated with midodrine between April 2011 and March 2014 in the Department of General Pediatrics and Interdisciplinary Medicine at the National Center for Child Health and Development. We excluded patients with secondary OI.[15,16] OI was clinically diagnosed based on clinical symptoms and the active standing test.[2,4,17] In the active standing test, blood pressure was measured and an electrocardiogram taken in the supine position before the active standing test, immediately after standing, after 5 minutes, and after 10 minutes. When patients stated that they felt uncomfortable during the active standing test, the active standing test was suspended. Midodrine was prescribed after patients were diagnosed based on the symptoms of OI and results from the active standing test.

Outcomes and Predictors

Outcomes were assessed by improvement of symptoms at the first month after midodrine was initiated for patients. Outcomes were categorized as either improved (including completely resolved) after midodrine (Improvement group) or not improved after midodrine (No-improvement group). Outcomes were recorded in the medical chart by pediatricians after obtaining information from patients and parents.

To identify predictors, we collected information on patients' characteristics (age, sex, body mass index, school absenteeism), symptoms using an orthostatic checklist, and the results of the active standing test. Percentiles of body mass index were categorized into 3 groups: underweight ($<5\%$), normal (5%-84.9%), and overweight/obese ($\geq 85\%$) based on the literature.[18-20] Because there were few children with obesity, overweight/obese were combined into 1 group. School absenteeism was defined as missing 30 school days or more during the academic year based on the Ministry of Education, Culture, Sports, Science and Technology's definition.[21]

Symptoms were assessed using orthostatic checklists from the Japanese pediatric OI guidelines.[4] The following parameters from the active standing test were assessed: heart rate and systolic and diastolic blood pressure before, immediately after, 5 minutes after, and 10 minutes after the active standing test. Differences in heart rate and systolic and diastolic blood pressure after the standing test compared to being in the supine position were calculated. To consider age-dependent variations in the differences in heart rate and blood pressure after compared to before the active standing test, percentage differences were also calculated.[22-24]

Statistical Analyses

Statistical significance for unadjusted comparisons was determined using the Chi-square test for categorical variables. We present summary data of baseline characteristics in patients with OI as frequency (percentage) for categorical variables and mean (standard deviation) or median (interquartile range) for continuous variables. Differences in the results of the active standing test were assessed between the Improvement and No-improvement groups by using the Mann-Whitney U test. Univariate logistic regression was used to identify predictive factors of the improvement of symptoms after administration of midodrine after the first month. We used 95% confidence intervals of the odds ratio and $P < .05$ for assessment of statistical significance. All statistical analyses were conducted using Intercooled STATA, version 11.0 (Stata Corp., College Station, TX).

Ethical Approval and Informed Consent

This study was approved by the ethics committee at the National Center for Child Health and Development (#1069). Because this was a retrospective observational study reporting anonymized data, informed consent was not required.

Results

We identified 166 patients with OI who underwent the active standing test and received treatment with midodrine. There were no patients with secondary OI in the present study. Of 166 patients who were treated with midodrine after completing the standing test, 7 patients were excluded from the analysis because their symptoms were not described at 1 month of midodrine treatment. A total of 159 patients were included for this study. The mean age of these patients was 13.8 years (range 7-18), 88/159 (55%) patients were girls, and 109/159 (69%) patients had school absenteeism (Table 1). The most common symptoms were pallor (27/159 [17%]), followed by palpitations or dyspnea (24/259 [15%]), and loss of appetite (21/259 [13%]).

Table 1 also compares demographics and symptoms of OI patients before midodrine administration. Of 159 patients, the symptoms were improved in 134/159 (84%) patients; the symptoms were not improved in 25/159 (16%) patients. Patients in the Improvement group were

Table 1. Characteristics of Patients with Orthostatic Intolerance.

	All (n = 159)	Improvement group (n = 134)	No-improvement group (n = 25)	
	Mean or n (SD) or (%)	Mean or n (SD) or (%)	Mean or n (SD) or (%)	*P*[a]
Age (years) (mean, SD)	13.8 (1.9)	13.8 (2.0)	13.8 (1.5)	.898
Sex (n, %)				.421
Boys	71 (45)	58 (43)	13 (52)	
Girls	88 (55)	76 (57)	12 (48)	
Body mass index category (n, %)				<.05
Underweight	16 (10)	9 (7)	7 (28)	
Normal	130 (82)	115 (86)	15 (60)	
Overweight/obese	13 (8)	10 (8)	3 (12)	
School absenteeism (n, %)				
Yes	109 (69)	91 (68)	18 (72)	.780
No	50 (31)	68 (51)	141 (564)	
Symptoms[b] (n, %)				
Pallor				.210
Yes	27 (17)	24 (18)	3 (12)	
No	132 (83)	110 (82)	22 (88)	
Palpitations or dyspnea after mild exercise				.638
Yes	24 (15)	21 (16)	3 (12)	
No	135 (85)	113 (84)	22 (88)	
Loss of appetite				.363
Yes	21 (13)	16 (12)	5 (20)	
No	138 (87)	118 (88)	20 (80)	
Feel uncomfortable during standing position, sometimes, fainting				.04
Yes	19 (12)	13 (10)	6 (24)	
No	140 (88)	121 (90)	19 (76)	
Abdominal colic				.318
Yes	17 (11)	15 (11)	2 (8)	
No	142 (89)	119 (89)	23 (92)	
Morning sickness				.856
Yes	11 (7)	6 (4)	1 (4)	
No	148 (93)	124 (93)	24 (96)	
Motion sickness				.386
Yes	11 (7)	10 (7)	1 (4)	
No	148 (93)	124 (93)	24 (96)	
Nausea during taking bath, or nausea during unpleasant experiences				.699
Yes	8 (5)	15 (11)	4 (16)	
No	151 (95)	128 (96)	23 (92)	
Vertigo and dizziness when children and adolescents were standing				.620
Yes	7 (4)	6 (4)	1 (4)	
No	152 (96)	128 (96)	24 (96)	
Headache				.929
Yes	5 (3)	4 (3)	1 (4)	
No	154 (97)	130 (97)	24 (96)	
Fatigue				.450
Yes	3 (2)	2 (1)	1 (4)	
No	156 (98)	132 (99)	24 (96)	

Percentiles of body mass index were categorized into underweight (<5%), normal (5%-84.9%), and overweight/obese (≥85%).
Abbreviation: OI, orthostatic intolerance.
[a]*P* value was calculated using the Mann-Whitney *U* test.
[b]Symptoms were derived from the checklists for OI from the Japanese pediatric OI guidelines.

significantly less likely to be underweight than those in the No-improvement group (9/134 [7%] vs 7/25 [28%], $P < .05$) and those in the Improvement group were more likely to say initially that they "feel uncomfortable during standing position" than those in the No-improvement group (13/134 [10%] vs 6/25 [24%], $P < .05$).

Table 2 shows results of the active standing test in patients with OI. Systolic and diastolic blood pressures at 10 minutes were significantly lower in the Improvement group than those in the No-improvement group (systolic blood pressure: 104 mmHg vs 109 mmHg, $P < .05$; diastolic blood pressure: 69 mmHg vs 74 mmHg, $P < .05$). Change in diastolic blood pressure from before standing to diastolic blood pressure 10 minutes after standing was less in the Improvement group than that in the No-improvement group (8 mmHg vs 12 mmHg, $P < 0.05$).

Table 3 shows univariate logistic regression analysis on prognostic factors for the improvement of symptoms in OI patients after midodrine treatment. Patients in the Improvement group were significantly less likely to be underweight (odds ratio [OR], 0.16; 95% confidence interval [95%CI], 0.05-0.51) compared to the No-improvement group. Patients in the Improvement group were significantly more likely to say initially that they "feel uncomfortable during standing" (OR, 3.48; 95%CI, 1.36-8.89) and showed significantly lower changes in diastolic blood pressure from the supine position to 10 minutes after the standing position test than those in the No-improvement group (OR, 0.93; 95%CI, 0.87-0.98).

Discussion

We found that approximately 80% of patients had improved symptoms after midodrine use. Our findings indicate that the predictors of improvement of symptoms after midodrine treatment were low diastolic blood pressure after standing and orthostatic symptoms. Patients with underweight had significantly less improvement than patients without underweight. To our knowledge, this may be the first study to investigate clinical predictors in pediatric patients with OI.

Studies from outside of Japan have shown that midodrine is recommended for OI types other than orthostatic hypotension, including POTS.[12,13] Midodrine was the first-line pharmacological treatment administered to patients diagnosed based on symptoms of OI and the results of the active standing test in the present study. Patients with OI had various types of symptoms, including orthostatic symptoms, palpitations, light-headedness, and fatigue.[1-3] Due to the variability in symptoms, identifying those that show recovery following treatment with midodrine will be useful for improving medication choice. We found that the clinical symptom that may be useful for predicting improvements in OI patients after midodrine treatment was "patients feel uncomfortable during standing position, sometimes, fainting". Other orthostatic symptoms, such as dizziness did not affect prognosis. Midodrine may therefore be a better choice for patients who feel uncomfortable in the standing position who sometimes faint.

Results from the active standing test showed that a larger drop in blood pressure measured 10 minutes after the active standing test was a predictor of improved outcomes in OI patients. A study in China showed that lower blood pressure in the orthostatic test was linked to a poor prognosis in patients with POTS, which is consistent with our results.[14] We think that midodrine treatment may be more likely to improve patients with delayed orthostatic hypotension than those with other types of OI. These findings may be explained by the pharmacological effects of midodrine. Midodrine treatment improves orthostatic blood pressure through vasoconstriction of arterioles and venous capacitance vessels.[24] Our results suggest that midodrine is the most suitable medication for delayed orthostatic hypotension.

Another finding indicates that underweight was associated with no improvement of symptoms after midodrine use. Earlier studies have shown that autonomic dysfunction of the cardiovascular system was reported in anorexia nervosa because of low body weight.[25,26] Studies reported that body mass index was associated with postural hypotension in adults.[27,28] Although underweight was associated with orthostatic intolerance, midodrine may not be effective for orthostatic intolerance under these conditions.

In cases where midodrine is not effective, the Japanese guidelines recommend administering amezinium metilsulfate for OI.[4,29] To expand plasma volume, fludrocortisone is also an option for initial orthostatic hypotension and hyperadrenergic POTS, subtypes of OI.[2,3] For POTS, a beta blocker is recommended.[2-4,30] International consensus guidelines for treatment of pediatric OI are lacking. Further clinical studies are required to establish international guidelines for pediatric OI.

Several limitations of the present study should be acknowledged. First, improvements of symptoms in patients with OI were assessed by pediatricians during clinical visits. We did not assess through standardized questionnaires. Second, improvement of symptoms was assessed at the first month after midodrine treatment, and some patients who improved did not visit the clinic. Long-term outcomes remain unknown, although orthostatic symptoms could be chronic and recurrent. Third,

Table 2. Results of Orthostatic Intolerance Test Compared in Patients With No-improvement and Improvement After Midodrine Treatment.

	Improvement group	No-improvement group	
	Median (interquartile range)	Median (interquartile range)	*P*[a]
HR (bpm)			
Pre-standing	68 (59, 77)	64 (59, 72)	.291
Immediately after standing	98 (88, 107)	91 (83, 103)	.559
5 minutes after standing	94 (86, 104)	87 (82, 102)	.140
10 minutes after standing	96 (86, 111)	88 (79, 115)	.204
SBP (mmHg)			
Pre-standing	103 (97, 110)	104 (97, 112)	.735
Immediately after standing	107 (99, 113)	107 (102, 117)	.850
5 minutes after standing	105 (98, 113)	111 (103, 116)	.181
10 minutes after standing	104 (99, 112)	109 (104, 118)	<.05
DBP (mmHg)			
Pre-standing	62 (58, 68)	62 (56, 64)	.735
Immediately after standing	68 (65, 73)	69 (64, 74)	.831
5 minutes after standing	69 (64, 74)	72 (65, 76)	.849
10 minutes after standing	69 (65, 75)	74 (70, 78)	<.05
Changes from supine position to standing			
HR (bpm)[b]			
Immediately after standing	30 (20, 38)	22 (32, 45)	.671
5 minutes after standing	27 (17, 39)	13 (24, 34)	.374
10 minutes after standing	30 (21, 42)	18 (25, 36)	.970
SBP (mmHg)[c]			
Immediately after standing	4 (−1, 9)	3 (−1, 7)	.449
5 minutes after standing	7 (2, 12)	7 (2, 12)	.517
10 minutes after standing	8 (2, 13)	12 (6, 18)	.828
DBP (mmHg)[d]			
Immediately after standing	7 (2, 12)	7 (2, 12)	.210
5 minutes after standing	8 (3, 13)	9 (3, 13)	.087
10 minutes after standing	8 (2, 13)	12 (6, 18)	<.05
Percent change from supine position to standing			
HR (%)[e]			
Immediately after standing	42 (27, 55)	49 (29, 60)	.383
5 minutes after standing	36 (20, 62)	45 (29, 61)	.073
10 minutes after standing	45 (27, 67)	46 (31, 63)	.755
SBP (%)[f]			
Immediately after standing	−6 (−12, 2)	−7 (−13, 2)	.526
5 minutes after standing	−5 (−13, 2)	−4 (−10, 6)	.504
10 minutes after standing	−6 (−15, −0.7)	−2 (−12, 5)	.173
DBP (%)[g]			
Immediately after standing	−9 (−15, −2)	−11 (−21, −3)	.654
5 minutes after standing	−12 (−20, −4)	−10 (−22, −5)	.573
10 minutes after standing	−15 (−21, −7)	−12 (−22, −3)	<.05

Abbreviations:HR, heart rate; DBP, diastolic blood pressure; SBP, systolic blood pressure.
[a]*P* value was calculated using the Mann-Whitney *U* test.
[b]Changes of HR from supine position to standing = HR after standing − HR before standing.
[c]Changes of SBP from supine position to standing = SBP after standing − SBP before standing.
[d]Changes of DBP from supine position to standing = DBP after standing − DBP before standing.
[e]Percent change in HR from supine position to standing = (HR after standing − HR before standing)/HR before standing × 100.
[f]Percent change in SBP from supine position to standing = (SBP after standing − SBP before standing)/SBP before standing × 100.
[g]Percent change in DBP from supine position to standing = (DBP after standing − DBP before standing)/DBP before standing × 100.

Table 3. Odds ratios for improvement of symptoms in patients with orthostatic intolerance, using logistic regression.

	Odds ratio[a] (95%CI)	*P*
Age	0.99 (0.79, 1.23)	.897
Sex		
Boys	Reference	
Girls	1.42 (0.60, 3.34)	.422
Body mass index category		
Underweight	0.16 (0.05, 0.51)	<.05
Normal	Reference	
Overweight/obese	0.41 (0.10, 1.71)	.222
Symptoms[b]		
Pallor		
Yes	0.99 (0.37, 2.65)	.986
No	Reference	
Palpitations or dyspnea after mild exercise		
Yes	1.25 (0.48, 3.28)	.654
No	Reference	
Loss of appetite		
Yes	1.62 (0.63, 4.19)	.317
No	Reference	
Feel uncomfortable during standing position, sometimes, fainting		
Yes	3.48 (1.36, 8.89)	<.05
No	Reference	
Abdominal colic		
Yes	1.10 (0.43, 2.83)	.845
No	Reference	
Morning sickness		
Yes	1.50 (0.45, 5.03)	.514
No	Reference	
Motion sickness		
Yes	0.83 (0.27, 2.55)	.749
No	Reference	
Nausea during taking bath, or nausea during unpleasant experiences		
Yes	0.91 (0.35, 2.34)	.843
No	Reference	
Vertigo and dizziness when children and adolescents were standing		
Yes	1.26 (0.42, 3.73)	.681
No	Reference	
Headache		
Yes	1.39 (0.42, 4.64)	.593
No	Reference	
Fatigue		
Yes	2.93 (0.90, 9.53)	.075
No	Reference	
Standing test[c]		
HR		
Pre-standing	1.01 (0.98, 1.05)	.522
Immediately after standing	1.00 (0.98, 1.03)	.914
5 minutes after standing	1.02 (0.99, 1.05)	.276
10 minutes after standing	1.01 (0.98, 1.04)	.371
SBP		
Pre-standing	0.99 (0.96, 1.03)	.706
Immediately after standing	0.99 (0.96, 1.03)	.706

(continued)

Table 3. (continued)

	Odds ratio[a] (95%CI)	*P*
5 minutes after standing	0.99 (0.96, 1.02)	.466
10 minutes after standing	0.98 (0.94, 1.01)	.148
DBP		
Pre-standing	1.03 (0.97, 1.10)	.325
Immediately after standing	1.03 (0.97, 1.10)	.325
5 minutes after standing	1.00 (0.96, 1.05)	1.000
10 minutes after standing	1.00 (0.95, 1.05)	.853
Changes from supine position to standing		
HR[c]		
Immediately after standing	1.00 (0.99, 1.01)	.799
5 minutes after standing	0.99 (0.97, 1.02)	.554
10 minutes after standing	1.01 (0.98, 1.04)	.536
SBP[d]		
Immediately after standing	1.00 (0.95, 1.04)	.903
5 minutes after standing	0.99 (0.94, 1.03)	.568
10 minutes after standing	0.98 (0.93, 1.03)	.406
DBP[e]		
Immediately after standing	0.98 (0.93, 1.03)	.422
5 minutes after standing	0.97 (0.93, 1.02)	.269
10 minutes after standing	0.93 (0.87, 0.98)	<.05
Percent change from supine position to standing		
HR[f]		
Immediately after standing	0.99 (0.97, 1.01)	.439
5 minutes after standing	1.00 (0.99, 1.02)	.619
10 minutes after standing	0.99 (0.98, 1.01)	.458
SBP[g]		
Immediately after standing	1.00 (0.98, 1.03)	.811
5 minutes after standing	1.01 (0.98, 1.04)	.498
10 minutes after standing	1.02 (0.99, 1.05)	.241
DBP[h]		
Immediately after standing	1.02 (0.98, 1.05)	.363
5 minutes after standing	1.02 (0.99, 1.05)	.314
10 minutes after standing	1.05 (1.01, 1.09)	<.05

Abbreviations:CI, confidence interval; HR, heart rate; SBP, systolic blood pressure, DBP; diastolic blood pressure.
[a]Odds ratios were calculated using univariate logistic regression. Age, HR, DBP, and SBP were treated as continuous variables. Those other than these variables were treated as categorical variables.
[b]Symptoms were assessed using the checklists for OI from the Japanese pediatric OI guidelines.
[c]Changes of HR from supine position to standing = HR after standing − HR before standing
[d]Changes of SBP from supine position to standing = SBP after standing − SBP before standing
[e]Changes of DBP from supine position to standing = DBP after standing − DBP before standing
[f]Percent change in HR from supine position to standing = (HR after standing − HR before standing)/HR before standing × 100
[g]Percent change in SBP from supine position to standing = (SBP after standing − SBP before standing)/SBP before standing × 100
[h]Percent change in DBP from supine position to standing = (DBP after standing − DBP before standing)/DBP before standing × 100

we investigated the predictors of effectiveness of midodrine; however, the results of effectiveness of midodrine should be interpreted with caution because of the lack of a control group. Predictors of improvements among patients who were not administered midodrine remain unknown. Fourth, some items in the OI assessment tool comprise 2 symptoms, such as palpitations and dyspnea.[4] Although the 2 symptoms may be derived from related organs, each symptom should be assessed separately. Fifth, the cut-off point of BMI percentile for underweight has not been well established. In the present study, the fifth percentile of BMI was defined as severely underweight that can affect prognosis of OI.[20] However, milder underweight may also affect prognosis of OI.

In summary, we investigated predictors of OI in children and adolescents who received midodrine, a widely

used drug for OI. Our results suggest that midodrine is more effective for delayed orthostatic hypotension than other types of OI. These findings should be helpful to further studies for the choice of treatment in patients with OI.

Acknowledgment

The authors thank the Medical English editor in the Division of Education for Clinical Research at the National Center for Child Health and Development for editing this manuscript.

Author Contributions

KI: developed a conception of the study design, collected and analyzed data, interpreted the results, and drafted the manuscripts.
KY: contributed to collecting and analyzing data.
MH, HN and AN: contributed to collecting data and interpreting the results.
AI: contributed to the interpretation of data and drafting manuscript.
All authors performed critically revised the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Kazue Ishitsuka https://orcid.org/0000-0002-2944-7012
Kaori Yamawaki https://orcid.org/0000-0001-6759-2643
Akira Ishiguro https://orcid.org/0000-0002-3896-5313

References

1. Sukul D, Chelimsky TC, Chelimsky G. Pediatric autonomic testing: retrospective review of a large series. *Clin Pediatr (Phila)*. 2012;51:17-22.
2. Stewart JM. Common syndromes of orthostatic intolerance. *Pediatrics*. 2013;131:968-980.
3. Stewart JM, Boris JR, Chelimsky G, et al. Pediatric disorders of orthostatic intolerance. *Pediatrics*. 2018;141:e20171673.
4. Tanaka H, Fujita Y, Takenaka Y, et al. Japanese clinical guidelines for juvenile orthostatic dysregulation version 1. *Pediatr Int*. 2009;51:169-179.
5. Robertson D. The epidemic of orthostatic tachycardia and orthostatic intolerance. *Am J Med Sci*. 1999;317:75-77.
6. Moon J, Kim D-Y, Byun J-I, et al. Orthostatic intolerance symptoms are associated with depression and diminished quality of life in patients with postural tachycardia syndrome. *Health Qual Life Outcomes*. 2016;14:144.
7. Low PA, Opfer-gehrking TL, Textor SC, et al. Autonomic nervous system comparison of the postural tachycardia syndrome (POTS) with orthostatic hypotension due to autonomic failure. *J Auton Nerv Syst*. 1994;50:181-188.
8. McDonald C, Koshi S, Busner L, et al. Postural tachycardia syndrome is associated with significant symptoms and functional impairment predominantly affecting young women: a UK perspective. *BMJ Open*. 2014;4:1-8.
9. Ojha A, Chelimsky TC, Chelimsky G. Comorbidities in pediatric patients with postural orthostatic tachycardia syndrome. *J Pediatr*. 2011;158:20-23.
10. Parsaik AK, Singer W, Allison TG, et al. Orthostatic intolerance without postural tachycardia: how much dysautonomia ? *Clin Auton Res*. 2013;23(4):181-188.
11. Hale GM, Valdes J, Brenner M. The treatment of primary orthostatic hypotension. *Ann Pharmacother*. 2017;51:417-428.
12. Lai CC, Fischer PR, Brands CK, et al. Outcomes in adolescents with postural orthostatic tachycardia syndrome treated with midodrine and beta-blockers. *Pacing Clin Electrophysiol*. 2009;32:234-238.
13. Chen L, Wang L, Sun J, et al. Midodrine hydrochloride is effective in the treatment of children with postural orthostatic tachycardia syndrome. *Circ J*. 2011;75:927-931.
14. Deng W, Liu Y, Liu AD, et al. Difference between supine and upright blood pressure associates to the efficacy of midodrine on postural orthostatic tachycardia syndrome (POTS) in children. *Pediatr Cardiol*. 2014;35:719-725.
15. Perlmuter LC, Sarda G, Casavant V, et al. A review of the etiology, associated comorbidities, and treatment of orthostatic hypotension. *Am J Ther*. 2013;20:279-291.
16. Tang M, Donaghue KC, Cho YH, Craig ME. Autonomic neuropathy in young people with type 1 diabetes: a systematic review. *Pediatr Diabetes*. 2013;14:239-248.
17. Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Auton Neurosci*. 2011;161:46-48.
18. Kato N, Takimoto H, Sudo N. The cubic functions for spline smoothed L, S and M values for BMI reference data of Japanese children. *Clin Pediatr Endocrinol*. 2011;20:47-49.
19. Ogden CL, Flegal KM. Changes in terminology for childhood overweight and obesity. *Natl Health Stat Report*. 2010;25:1-5.
20. Al-Adawia S, Bax B, Bryant-Waugh R, et al. Revision of ICD–status update on feeding and eating disorders. *Adv Eat Disord*. 2013;1:10-20
21. Shimizu K. Defining and interpreting absence from school in contemporary Japan: how the ministry of education has framed school non-attendance. *SSJJ*. 2011;14:165-187.
22. Skinner JE, Driscoll SW, Porter CB, et al. Orthostatic heart rate and blood pressure in adolescents: reference ranges. *J Child Neurol*. 2010;25:1210-1215.
23. Tanaka H, Thulesius O, Borres M, Yamaguchi H, Mino M. Blood pressure responses in Japanese and Swedish children in the supine and standing position. *Eur Heart J*. 1994;15:1011-1019.

24. Singer W, Sletten DM, Opfer-Gehrking TL, Brands CK, Fischer PR, Low PA. Postural tachycardia in children and adolescents: what is abnormal? *J Pediatr*. 2012;160:222-226.
25. McClellan KJ, Wiseman LR, Wilde MI. Midodrine. A review of its therapeutic use in the management of orthostatic hypotension. *Drugs Aging*. 1998;12(1):76-86.
26. Mehler PS, Brown C. Anorexia nervosa–medical complications. *J Eat Disord*. 2015;3:11.
27. Takimoto Y, Yoshiuchi K. Autonomic dysfunction responses to head-up tilt in anorexia nervosa. *Clin Auton Res*. 2014;24:175-181.
28. Florian JP, Baisch FJ, Heer M, Pawelczyk JA. Caloric restriction decreases orthostatic tolerance independently from 6 head-down bedrest. *PLoS One*. 2015;10:e011 8812.
29. Task Force of Clinical Guidelines for Juvenile Orthostatic Dysregulation. *Japanese Clinical Guidelines for Juvenile Orthostatic Dysregulation Version 2*. Nankodo; 2015 (in Japanese).
30. Kizilbash SJ, Ahrens SP, Bruce BK, et al. Adolescent fatigue, POTS, and recovery: a guide for clinicians. *Curr Probl Pediatr Adolesc Health Care*. 2014;44: 108-133.