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Clinical and laboratory characteristics of pediatric orthostatic hypertension: a retrospective study

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ABSTRACT

Aims: Orthostatic hypertension (OHT) is an underrecognized condition in the pediatric population, characterized by an abnormal rise in blood pressure upon standing. Given its potential long-term implications, including cardiovascular remodeling and end-organ damage, early identification and management of OHT are crucial. This study aims to evaluate the clinical and laboratory characteristics of children diagnosed with OHT, providing insights into potential risk factors and associated conditions.

Methods: A retrospective, cross-sectional study was conducted at Ankara Training and Research Hospital between September 2022 and August 2024. A total of 111 pediatric patients diagnosed with OHT based on an active standing test were included. Demographic data, presenting symptoms, laboratory parameters (including vitamin B12, ferritin, and vitamin D levels) were analyzed.

Results: The median age of the cohort was 15.3 years (range: 6.8–17.9), with a female predominance (63%). Nearly half of the patients (46%) were overweight or obese, and 22% had a family history of hypertension. Cardiovascular symptoms were the most common (36%), followed by cerebral hypoperfusion symptoms (35%) and other symptoms, including fatigue and concentration issues (27%). A significant proportion of the patients exhibited vitamin D deficiency (41%), vitamin B12 borderline levels (45%), and iron deficiency anemia (15%). Additionally, postural orthostatic tachycardia syndrome (POTS) was present in 24% of patients, with a notable association between POTS and low body weight (p=0.037).

Conclusion: The descriptive findings of this study illustrate a range of clinical and laboratory characteristics in children with OHT, hinting at potential areas for future investigation. Although associations with pubertal status, obesity, and vitamin deficiencies were observed, the study's design limits causal inference. Future research, including control groups and prospective approaches, is crucial to understand the clinical importance of these observations.

Keywords: Orthostatic hypertension, autonomic dysfunction, pediatric population, active standing test

INTRODUCTION

Orthostatic hypertension (OHT) is characterized by an abnormal increase in blood pressure (BP) upon transitioning from a lying to a standing position, resulting from disrupted autoregulatory mechanism.[1] Identifying OHT in children is essential due to the potential risks of hypertension, such as stroke, end-organ damage, and cardiovascular complications.[2] Given the dangers of target organ damage in adulthood, it is critical to precisely identify patients at heightened risk and establish preventive strategies from an early age to help mitigate endothelial dysfunction and vascular remodeling.[3]

The diagnosis of OHT relies on the activate standing test or tilt testing response of patients exhibiting orthostatic symptoms, following the exclusion of structural cardiac and neurological disorders, and in the absence of pheochromocytoma, central nervous system illness or diabetes mellitus.[3] According to Zhao's[4] study on the response measured at the third minute of the active standing test, OHT can be defined as follows: a) for children aged 6 to 12 years, it is characterized by a systolic pressure increase of 20 mmHg and a diastolic pressure increase of 25 mmHg, or a BP exceeding 130/90 mmHg; b) for those aged 13 to 18 years, it is defined by a systolic and diastolic pressure increase of 20 mmHg, or a BP above 140/90 mmHg.

A limited number of research have been conducted to investigate the clinical characteristics and pathogenesis of OHT, which is an underexplored disorder in the pediatric

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population. To enhance early diagnosis and management strategies, gaining insight into the cardiovascular and autonomic characteristics of OHT in children would be highly beneficial. The aim of the study is to evaluate children with OHT by analyzing their clinical findings and laboratory parameters.

METHODS

The present study was conducted as a retrospective investigation at Ankara Training and Research Hospital from September 2022 to August 2024 to identify the findings of the clinical presentation, physical examination findings, laboratory results and echocardiographic findings in children diagnosed with OHT. The ethical approval of this cross-sectional study was obtained from the Ankara Training and Research Hospital Scientific Researches Ethics Committee (Date: 21.08.2024, Decision No: 217/2024). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Predesignated demographic, clinical characteristics and diagnostic findings pertaining to children were searched through the medical archive of the hospital. The study group comprised children who presented at the outpatient clinic exhibiting symptoms suggestive of orthostatic intolerance, such as dizziness, syncope, headache, or palpitations. The active standing test was performed as a component of their clinical assessment to explore the possibility of autonomic dysfunction within this population. All participants underwent a thorough clinical evaluation. Patients with known endocrinological, cardiovascular, allergic, psychological, or neurological conditions that could potentially confound the interpretation of their symptoms were excluded. In addition to routine laboratory tests (e.g., hemogram, electrolytes, renal and liver function tests), further investigations such as thyroid function test, adrenal hormones or metabolic hormones were performed when atypical findings during clinical evaluation. When necessary, patients were referred to relevant departments (e.g., suspected allergic etiology, neurological concerns) for additional evaluations. Children with a history of chronic illness or follow-up for other medical conditions were not included in the study. For each participant, office BP was measured on the right arm using the auscultatory method by a physician with a correctly sized cuff, following a minimum 20-minute rest period. BP values were interpreted according to the guidelines from the American Academy of Pediatrics.[5]

The evaluation of orthostatic responses in this study relied solely on "the active standing test". The active standing test was conducted after the patients had rested lying down for 10 minutes and then again at 3 and 10 minutes after quickly standing up. The active standing test was performed in a quiet room with a temperature of 22 to 24 °C, and it was ensured that the patients had fasted for 2 h and had not taken any medications. OHT was defined according to BP alterations noted during the standing test. In children aged 6 to 12 years, the condition was characterized by a systolic BP increase of 20 mmHg or greater, accompanied by a diastolic BP increase of 25 mmHg or greater. For children older than 12 years, a systolic BP elevation of 20 mmHg or more was considered sufficient for the diagnosis. Postural orthostatic tachycardia syndrome (POTS) was defined based on cardiovascular responses during orthostatic testing, indicated by either a sustained increase in heart rate of ≥40 bpm from the supine baseline or above 130 bpm in children aged 6 to 12, or above 125 bpm in those older than 13 within 10 minutes of standing.[6]

The initial presenting complaints were categorized into four groups: central nervous system symptoms (dizziness, headache, syncope), cardiovascular system symptoms (chest pain, palpitations), gastrointestinal system symptoms (nausea, abdominal pain) and other (impaired concentration, fatigue). Vitamin B12 deficiency was defined as values below 200 pg/ml, and borderline B12 level ranged from 200 to 300 pmol/L. A vitamin D level below 12 ng/dl was classified as a deficiency, levels between 12 and 20 ng/ml were considered insufficient while levels above 20 ng/ml are regarded as sufficient.[7] Ferritin levels below 12 ng/ml below the age of 5 years and 15 ng/ml above the age of 5 years were considered iron deficiency.[8]

Statistical Analysis

The data analysis was performed using IBM-SPSS Statistics for Windows 22.0 (IBM Corp., Armonk, NY, USA). The distribution properties of the continuous variables were assessed using the Kolmogorov-Smirnov test. The descriptive statistics utilized the mean (SD) for the normally distributed data, and the median and range for the non-normally distributed data. Results for the continuous and categorical variables with normally distributed distributions were assessed using the paired samples t test and chi-squared test. $p<0.05$ was considered statistically significant.

RESULTS

All 111 children participating in the study were diagnosed with OHT, with a median age of 15.3 years (range from 6.8 to 17.9 years). Notably, 27 of these patients also fulfilled the diagnostic criteria for POTS, reflecting a co-occurrence of both conditions. Seven patients (6%) were younger than 11 years and 104 patients (93%) were older than 11 years. A thorough analysis of the demographic and clinical data, as well as the laboratory and diagnostic parameters, was seen in **Table 1**. There was a female gender predominance in the patients 63% of were female, 37% were male. There were 25 (22.5%) patients with a family history of hypertension. In all, 51 patients (46%) were overweight or obese. Besides, 7 patients were underweighted.

A total of 24 (22%) patients displayed high BP or hypertension during the rest. Cardiovascular findings were the most common, observed in 40 (36%) of patients, followed by cerebral hypoperfusion findings in 39 (35%) and gastrointestinal findings in 2 (2%), with 30 (27%) of children presenting with other findings involving fatigue, concentration problems. In response to the active standing test, BP was 123.2/74.0 mmHg (16.7/9.8), and heart rate was 99.2 bpm (15.4) at 3 minutes of standing. At 10 minutes, BP was 122.4±15.3/75.6±9.1 mmHg, and heart rate was 101.2±16.4 bpm.

Ten patients exhibited vitamin B12 deficiency. Fifty patients revealed borderline vitamin B12 levels. Twenty-seven patients (24%) were accompanied by POTS. Seventeen patients were

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Table 1. Baseline demographic, clinical, and laboratory characteristics of the children with orthostatic hypertension

Patients number	111
Age* (year)	15.3 (6.8-17.9)
Gender (F/M)	70 (63%)/41 (37%)
Antropometric measurements	
Weight (kg)*	65.0 (35.6-118.0)
Weight sds *	1.5 (-3-+5.1)
Height (cm) *	162.0 (135.0-190.0)
Height sds+	0.33±1.3
Body-mass index (kg/m^2) *	25.7 (14.6-41.0)
Body-mass index percentile*	87.3 (0.01-99.9)
Blood pressure	
Systolic blood pressure (mmHg)+	115.9±16.3
Diastolic blood pressure (mmHg)+	58.7±8.7
Heart rate+	81.1±14.1
SBP percentile*	71.0 (1.0-99.9)
DBP percentile*	25.0 (1.0-99.9)
Systolic orthostatic hypertension	20 (18%)
Diastolic orthostatic hypertension	64 (57%)
Both systolic and diastolic hypertension	27 (24%)
Laboratory	
Hemoglobin (g/dl) +	13.7±1.4
Creatinine +	0.65±0.13
Albumin*	48.0 (40-55)
Vitamin B12*	289 (116-759)
Ferritin*	31.5 (5.7-160)
Vitamin D*	14.4 (5.3-60)

* Indicates median (minimum to maximum), + Indicates mean (SD), F: Famale, M: Male, SD: Standard deviation

Table 2. Comparative results of children with and without postural orthostatic tachycardia syndrome

	Orthostatic hypertension without POTS (n:84)	Orthostatic hypertension with POTS (n:27)	p value
Age*	14.9±2.1	14.5±1.9	0.584
BMI*	25.7±5.9	24.8±7.2	0.500
Family history	19 (22.6%)	6 (22.2%)	0.966
Obesity	41 (48.8%)	10 (37.0%)	0.286
Low weight	3 (3.6%)	4 (14.8%)	0.037
Hypertension	16 (19%)	8 (29.6%)	0.245
Baseline (mmHg)			
SBP*	114.6±15.2	119.0±19.0	0.185
DBP*	57.4±7.7	63.3±10.4	0.002
Standing after 3 min (mmHg)			
SBP*	121.1±13.7	128±23.4	0.141
DBP*	74.6±8.9	78.7±11.2	0.005
Standing after 10 min (mmHg)			
SBP*	121.4±14.3	124.9±18.2	0.310
DBP*	74.8±9.5	78.4±7.1	0.074

* Indicates median mean±SD, POTS: Postural orthostatic tachycardia syndrome, BMI: Body-mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

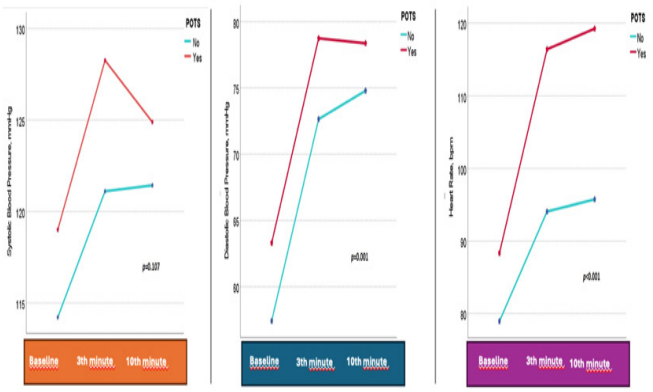

Figure. Changes in systolic blood pressure (ΔSBP) (left), diastolic blood pressure (ΔDBP) (middle), and heart rate (ΔHR) (right) during the active standing test in children with and without postural orthostatic tachycardia syndrome. Measurements were recorded at baseline, 3rd minute, and 10th minute of standing. Repeated measures ANOVA was applied to examine differences in hemodynamic parameters
POTS: Postural orthostatic tachycardia syndrome

diagnosed with iron deficiency anemia. Forty-six patients (41%) exhibited vitamin D deficiency, and another forty-six (41%) presented with vitamin D insufficiency.

POTS has been detected in 27 (24%) patients together with OHT (**Table 2**). The mean age of patients with POTS was 14.5±1.9 years, with the mean of BMI was 24.8±7.2. Among the patients, 8 (30%) were male and 19 (70%) were female. POTS patients predominantly had central nervous system manifestations (40%). Subsequently, the cardiovascular system symptoms accounted for 30%, other symptoms constituted 26%, and gastrointestinal symptoms represented 4%. No significant difference in clinical presentation was observed between patients with OHT with and without POTS (p value 0.692). Furthermore, there was no significant difference between the two groups for the presence of obesity and hypertension (p value 0.286 and 0.245 respectively). Nonetheless, an important statistical difference was noted for low weight. Fifteen percent of the POTS cohort exhibited low body weight, whereas this prevalence was 4% in the cohort without POTS (p value 0.037). Despite a trend towards a larger systolic BP increase in the POTS+OHT group (p=0.107), this difference was not statistically significant. However, the POTS+OHT group demonstrated significantly higher heart rate and diastolic BP values compared to the non-POTS group (p<0.001 and p=0.001, respectively) (**Figure**).

DISCUSSION

According to the findings of this study, approximately half of the children were overweight or obese, suggesting a potential link between altered cardiovascular regulation and orthostatic BP dysregulation in this population. The majority of patients were female, demonstrating a notable gender predominance among the cohort. Furthermore, a significant proportion of the study population was in the pubertal period. One-fourth of the children had a history of hypertension in their family. Taking these findings into consideration, the development of OHT may be attributed to a multifactorial interplay, including genetics, sex-specific characteristics, obesity, and genetic predisposition.

The existing literature does not provide evidence of a clear gender dominance.[9] In contrast, our study revealed a significant predominance of female patients. Research suggests the incidence rises during the pubertal period.[3] Consistent with this in our study, the mean age of the patients showed dominantly pubertal period. In their study, Zhao et al.[4] reported a 67% prevalence of pubertal patients, whereas our research found a significantly higher rate of 93%. This may pertain to neurohormonal dysregulation due to accelerated somatic growth together with relatively slower neurological maturation.[3] Approximately 50% of our patient population fell within the overweight or obese categories. Evidence indicates that these conditions are linked to a heightened risk of OHT.[10]

Moreover, those who have a family history of hypertension may face a greater likelihood of experiencing OHT. A quarter of our patients reported a family history of hypertension. This finding suggests that OHT may be linked to the possibility of genetic inheritance.

Vitamin D influences the arterial wall by reducing its compliance and contributing to vascular stiffness. Furthermore, it may influence the baroreflex and the renin-angiotensin-aldosterone system, potentially disrupting autonomic regulation and contributing to the development of hypertension.[11] Kovalchuk et al.[12] reported reduced levels of 25(OH) in children experiencing vasovagal syncope and orthostatic hypotension. Xiao et al.[13] also detected reduced vitamin D levels in children with orthostatic intolerance. Zhang et al.[14] reported that autonomic dysfunction may occur in children with vasovagal syncope because of vitamin D deficiency. Our investigation also revealed significant amounts of vitamin D deficiency and insufficiency. Given the well-documented high prevalence of vitamin D deficiency and insufficiency in the general pediatric population of our country, shaped by factors such as limited sun exposure, dietary habits, and lifestyle, the similarly high prevalence observed in our OHT cohort warrants cautious interpretation.[15] In the absence of a matched control group, it remains unclear whether this finding reflects a direct etiological role in the pathophysiology of OHT or represents a coincidental association. Therefore, further controlled studies are needed to clarify the potential contribution of vitamin D deficiency to autonomic dysregulation and increased vascular tone in pediatric OHT.

Autonomic dysfunction has been occasionally associated with cobalamin deficiency.[16] Vitamin B12 assumes a pivotal role in the process of myelinogenesis and the maintenance of sympathetic postganglionic fiber functionality.[16-18] Consequently, its deficiency has been correlated with a decrement in both sympathetic and parasympathetic nervous system activity. A study conducted with Öner and her colleagues[19] reported that 62.8% of POTS cases were associated with B12 deficiency. In their findings, Pektaş et al.[20] indicated that vitamin B12 deficiency was observed more often in patients diagnosed with POTS than in those exhibiting a vasodepressor response. The relationship between vitamin B12 deficiency and autonomic dysfunction has been noted in various orthostatic syndromes; however, the specific role of B12 deficiency in the pathophysiological processes of OHT is an area requiring further investigation. For a more comprehensive understanding of the nutritional and metabolic effects, it is essential to conduct long-term studies that not only compare patients with OHT to a control group but also include comparisons with other orthostatic pathologies. These investigations would clarify potential variations in metabolic profiles, nutritional status, and related risk factors, so offering profound insights into the underlying mechanisms and informing more effective approaches to management.

In accordance with the other studies, POTS was linked to approximately one-fourth of patients exhibiting OHT in this study.[2,21] In Zhang's[2] study, no significant statistical difference in gender was observed regarding the connection of OHT and POTS, but our study exhibited a female predominance. The Zhang study identified headache as the prevalent symptom. In support of this, central nervous system symptoms were the main clinical presentation symptom in our investigation. The pathophysiology of POTS is recognized to involve increased sympathetic activity, dysfunctional sympathetic-related vasoconstriction or altered renin angiotension aldosterone regulation.[22,23] Notably, neurovascular and neurohormonal responses can present with overlap in both OHT and POTS. Aligning with the established hyperadrenergic state in POTS, our findings also revealed significantly elevated heart rate and diastolic BP in the POTS+OHT group, further substantiating the role of sympathetic overactivity in shaping their hemodynamic profile. Of interest, a greater proportion of POTS patients exhibited low body weight, a finding that could be associated with dysregulation of fluid volume and ineffective autonomic compensation, both acknowledged as contributing factors to the pathogenesis of POTS.

Limitations

These findings, however, need to be interpreted with the greatest caution, and there are a few limitations that need to be taken into consideration. The inherent limitations of a single-center study design, further compounded by the exclusion of a healthy control group, impede the generalizability of the reported outcomes and complicate the attribution of specificity to the observed clinical characteristics. The prevalence of nutritional inadequacies, the apparent predominance of pubertal development, and the identified patterns of autonomic response within the OHT cohort may not be distinct from those observed in the general pediatric population, thus precluding the definitive establishment of causal associations. However, given the limited research on pediatric OHT, the results provide valuable insights that enhance clinical awareness and guide future research. The assessment of the patients' self-reported symptoms suggests that recall bias, exaggeration, and selective remembering may have an impact on the patients. Employing autonomic symptom assessments scales in future study may produce more accurate and reliable results. Moreover, the study did not evaluate the children's eating habits, physical activity levels, or emotional health. Further research is required to design metrics that can precisely evaluate both physical activity levels and mental well-being. The limitations of this study will provide valuable insights for designing similar studies in the future. The interpretation of our findings is also potentially limited by the adoption of the active standing test as the sole diagnostic modality for orthostatic responses. Despite its simplicity and feasibility in outpatient settings, the absence of established, large-scale normative data and standardized protocols for the pediatric age group necessitates a cautious approach to the interpretation of the observed orthostatic changes. Therefore, while valuable for detecting responses within our study population, the broad applicability and clinical relevance of these results require corroboration through future research employing validated pediatric orthostatic testing paradigms.

CONCLUSION

The clinical, demographic and laboratory features of pediatric population with OHT have been identified in this study. According to results, a family history of hypertension, obesity, pubertal age, and female predominance might all be contributing to OHT in children. Remarkably, a significant percentage of children had iron, vitamin B12, and vitamin D deficiencies, suggesting that these conditions may be metabolic and nutritional factors contributing to autonomic dysfunction. While the pathophysiological mechanisms underlying these associations require further investigation, our study underscores the need for early identification and comprehensive management of pediatric OHT to mitigate potential long-term cardiovascular risks Future research with larger sample sizes and longitudinal follow-ups is warranted to explore the causal relationships and potential therapeutic interventions for this condition.

ETHICAL DECLARATIONS

Ethics Committee Approval

The ethical approval of this cross-sectional study was obtained from the Ankara Training and Research Hospital Scientific Researches Ethics Committee (Date: 21.08.2024, Decision No: 217/2024).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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