Risk Factors for Orthostatic Hypertension in Children

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Objective To investigate the risk factors for orthostatic hypertension in children.

Study design Eighty children with orthostatic hypertension were enrolled in the group with orthostatic hypertension, and 51 healthy children served as the control group. Demographic characteristics, clinical history, daily water intake, nightly sleep duration, the results of the standing test, and complete blood count were recorded and compared between the 2 groups. The risk factors for pediatric orthostatic hypertension were determined by logistic regression analysis.

Results Body mass index and red blood cell distribution width were higher in the group with orthostatic hypertension than in healthy children, whereas daily water intake and sleep duration were lower. Logistic regression analyses showed that, if a child suffered from overweight, suffered from obesity, had a daily water intake of less than 800 mL, or had a red blood cell distribution width that was increased by 1%, the risk of orthostatic hypertension would be increased by 6.069 times (95% CI, 1.375-26.783; $P < .05$), 7.482 times (95% CI, 1.835-30.515; $P < .01$), 4.027 times (95% CI, 1.443-11.241; $P < .01$), or 4.008 times (95% CI, 1.698-9.461; $P < .01$), respectively. However, if the sleep duration was increased by 1 hour, the risk of developing orthostatic hypertension would be decreased by 74.3% (95% CI, 54.6%-85.4%, $P < .01$).

Conclusions Increased body mass index, inadequate water intake and sleep duration, and elevated red blood cell distribution width were identified as risk factors for pediatric orthostatic hypertension. *(J Pediatr 2020;227:212-7)*.

Orthostatic hypertension is characterized by abnormal blood pressure (BP) elevation from supine to upright or tilt, and it seems to be one of the causes of pediatric orthostatic intolerance, which refers to diverse symptoms occurring in the upright posture after the supine position, such as dizziness, headache, visual difficulties, fatigue, nausea, and syncope.[1] Kang et al reported that 23.8% of 2089 children with orthostatic intolerance symptoms showed orthostatic hypertension during the head-up tilt test.[2] Recurrent symptoms of orthostatic intolerance affect children's academic performance and quality of life and result in psychological burden for families.[3] Orthostatic hypertension is associated with masked hypertension and increases the risk of essential hypertension in young adults, but the risk factors for orthostatic hypertension in children have been unclear.[4-6]

Previous studies have reported that insufficient water intake and decreased sleep time are related to orthostatic intolerance in children and adolescents.[7] Comorbidity with allergic diseases in children with orthostatic intolerance is also not uncommon.[8] Overweight and obesity are currently recognized as risk factors for essential hypertension in children and adolescents.[9] Red blood cell distribution width (RDW), which reflects the extent of red blood cell volume heterogeneity, is associated with the prognosis of various cardiovascular diseases.[10] Compared with healthy children, children with neurally mediated syncope exhibited increased RDW levels.[11] This study aimed to investigate whether insufficient water intake, decreased sleep duration, comorbidity with allergic diseases, increased body mass index (BMI), and RDW could be risk factors for orthostatic hypertension in children.

Methods

Eighty patients with orthostatic hypertension were enrolled, and 51 healthy children served as the control group, all of whom were admitted to the Department

BMI	Body mass index
BP	Blood pressure
DBP	Diastolic blood pressure
HCT	Hematocrit
HR	Heart rate
MAP	Mean arterial pressure
RDW	Red blood cell distribution width
SBP	Systolic blood pressure

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of Pediatrics at Peking University First Hospital with orthostatic intolerance symptoms as their chief complaints. All patients were diagnosed with orthostatic hypertension according to the following criteria: orthostatic intolerance symptoms induced by predisposing factors, such as sudden postural changes or prolonged standing, with a positive response to the standing test; and the exclusion of other diseases, such as arrhythmias, structural heart diseases, or neurologic diseases.[12,13] Specifically, a positive orthostatic hypertension response to the standing test was defined as normal supine BP followed by either of the following during the initial 3 minutes of upright standing: increased systolic blood pressure (SBP) of 20 mm Hg or greater and/or an increased diastolic blood pressure (DBP) of 25 mm Hg or greater (in children 6-12 years old) or an increased DBP of 20 mm Hg or greater (in adolescents 13-18 years old), or a BP of 130/90 mm Hg or greater (in children 6-12 years old) or 140/90 mm Hg or greater (in adolescents 13-18 years old).[12,13] The supine BPs were considered normal if both SBP and DBP were in the 90th percentile or lower among children of the same sex, age, and height.[14,15] Children in the control group were recruited from primary and middle schools in 2 cities in China, including 25 boys and 26 girls aged 10-14 years. Orthostatic intolerance symptoms induced by position changes were assessed, and physical examination and standing tests were conducted for all participants in the control group. Those with a history of orthostatic intolerance symptoms or abnormal supine or upright BPs were excluded. None of the participants had an infection within 2 weeks before enrollment. This study was approved by the Ethics Committee of Peking University First Hospital, and informed consent was obtained from the parents of all participants.

The clinical data were collected and recorded by a questionnaire. Parents were asked to assist in the collection of medical history data. For all patients with orthostatic hypertension, details of their orthostatic intolerance symptoms were collected, including the predisposing factors, duration, modes of remission, and frequency of onset of each symptom. Orthostatic intolerance scores were calculated according to the following rules: for each orthostatic intolerance symptom (including palpitation, dizziness, headache, blurred vision, hands tremble, chest tightness, nausea, and syncope), 0 point indicates that the symptom has never occurred; 1 point indicates that the symptom occurs once every month on average; 2 points indicate the symptom's occurrence 2-4 times every month on average; 3 points represent its occurrence 2-7 times every week on average; and 4 points indicate its occurrence at least once every day. The sum of the scores for each symptom was counted as the orthostatic intolerance score for the participant.[16] Orthostatic intolerance symptoms were also investigated in the control group and orthostatic intolerance scores were also collected for them.

The personal and family histories of all participants were collected, including the average daily water intake and nightly sleep duration within the course of 1 week, history of car sickness and allergic diseases, and family history of primary hypertension and syncope in first-degree relatives. A measuring cup was provided as a reference for questions asked about daily water intake. According to the recommendations of the dietary guidelines for Chinese residents (2016), the daily water intake of children aged 10-14 years should be at least 800 mL.[17] Therefore, the minimum amount of 800 mL was selected to divide the daily water intake of the participants into 2 groups (<800 mL and ≥800 mL). Allergic diseases consisted of bronchial asthma and allergic rhinitis. Published guidelines were referred to when comorbidity with allergic diseases was identified.[18,19]

Weight and height were recorded for all participants, and BMI was calculated. In addition to the absolute value of BMI, the BMI percentile was also taken into account, and children with a BMI above the 85th percentile for children of the same sex and age were considered overweight, and those with a BMI above the 95th percentile were considered obese.[20]

A standing test was conducted for all participants in a quiet room. During the test, children were asked to lie on the testing bed for 10 minutes and then stand upright for another 10 minutes. At the same time, a Multi-lead Physiological Monitor (Dash 2000, General Electric, New York, New York) was used to take the heart rate (HR) and BP measures (including SBP, DBP, and mean arterial pressure [MAP]) of the participants. The HR and BP measured at 10 minutes in the supine position served as the supine HR and supine BP, and the HR and BP measured at 3 minutes after standing were recorded as the upright HR and upright BP.

On the day of admission to the hospital (for the group with orthostatic hypertension) or recruitment (for the control group), 2 mL of venous blood was drawn. A vacuum tube with ethylenediamine tetra-acetic acid was used for blood collection. After collection, the blood samples were stored at 4°C and sent for analysis within one hour. A complete blood count was then performed with an automated blood count instrument (XT-4000i, Sysmex, Kobe, Hyogo, Japan).

SPSS 20.0 (version for Windows) statistical analysis software (SPSS, Chicago, Illinois) was used for statistical analyses. Comparisons of proportions were performed with the χ^2 test. The Shapiro-Wilk test was adopted to judge whether data were normally distributed. Normally distributed variables were presented as mean ± SD, and differences were compared with the independent t test. Nonnormally distributed variables were expressed as medians (25th percentile, 75th percentile), and the Mann-Whitney U test was used for comparisons. The correlation of 2 normally distributed variables was evaluated by Pearson correlation analysis, whereas Spearman correlation analysis was used for the correlation of nonnormally distributed data. A binary logistic regression model was applied for the risk factor analysis for orthostatic hypertension in children. A 2-tailed P of less than .05 indicated a statistically significant difference.

Results

The 80 patients in the group with orthostatic hypertension included 43 boys aged 12.0 years (range, 11.0-13.0 years); the control group included 51 healthy children (25 boys) aged 12.0 years (range, 11.0-12.0 years). The sex ratio and age did not differ between the children with orthostatic hypertension and the controls ($P > .05$; Table I). However, the BMI of the group with orthostatic hypertension was greater than that of the control group ($P < .01$), and the proportions of overweight (BMI >85th percentile) and obesity (BMI >95th percentile) in children with orthostatic hypertension were both significantly higher than those in the control group (overweight, $P < .01$; obesity, $P < .01$; Table I).

The orthostatic intolerance scores of the children with orthostatic hypertension ranged from 1 to 8, with an average of 2 points (range, 1-3 points), and all the children in the control group had an orthostatic intolerance score of zero.

Compared with the control group, the group with orthostatic hypertension had a large number of children with a daily water intake of <800 mL (67.5% vs 47.1%; $P < .05$; Table I). In addition, the children with orthostatic hypertension slept less than the healthy controls did ($P < .01$; Table I). No significant difference between groups was observed in the proportion of participants with a positive history of car sickness ($P > .05$). There were 4 cases of allergic rhinitis, 2 cases of bronchial asthma, and 1 case of both bronchial asthma and allergic rhinitis in the group with orthostatic hypertension, and the control group had 5 participants with allergic rhinitis. The proportion of children with allergic diseases, however, did not show a significant difference between groups ($P > .05$).

The difference in the proportion of participants with a positive family history of syncope in first-degree relatives was not statistically significant between the 2 groups ($P > .05$). In addition, there were more children in the group with orthostatic hypertension with a family history of essential hypertension in first-degree relatives than in the control group (10.0% vs 0%; $P < .05$; Table I).

In the supine position, no significant difference was found in HR, SBP, or MAP between the 2 groups ($P > .05$). The supine DBP of the group with orthostatic hypertension was significantly lower than that of the healthy controls ($P < .01$; Figure). After standing, the group with orthostatic hypertension displayed significantly higher HR, SBP, DBP, and MAP than the healthy children did ($P < .01$ for all measures; Figure).

As shown in Table II, the hematocrit (HCT) and RDW were significantly higher in the group with orthostatic hypertension than in the control group (HCT, $P < .01$; RDW, $P < .01$; Table II). No significant difference was detected between the 2 groups in other variables in the complete blood count analysis, including the eosinophil counts ($P > .05$; Table II).

Spearman correlation analysis showed that BMI, nightly sleep duration, supine DBP, HCT, and RDW were all correlated with the severity of orthostatic hypertension. Specifically, as seen from Table III (available at www.jpeds.com), orthostatic intolerance scores were positively correlated with BMI, HCT, and RDW (BMI, $r = 0.402$ [$P < .01$]; HCT, $r = 0.243$ [$P < .01$]; RDW, $r = 0.324$ [$P < .01$]) for all participants and negatively correlated with sleep duration and supine DBP (sleep duration, $r = -0.416$ [$P < .01$]; supine DBP, $r = -0.284$ [$P < .01$]) in all participants. Moreover, the MAP elevations from supine to upright standing were positively correlated with BMI, HCT, and RDW (BMI, $r = 0.261$ [$P < .01$]; HCT, $r = 0.184$ [$P < .05$]; RDW, $r = 0.273$ [$P < .01$]) in all participants and negatively correlated with sleep duration and supine DBP (sleep duration, $r = -0.384$ [$P < .01$]; supine DBP, $r = -0.448$ [$P < .01$]) in all participants.

The initial regression model included sex, age, water intake, sleep duration, family history of primary hypertension, percentile of BMI (as ordinal categorical variable), supine DBP, HCT, and RDW. A forward stepwise selection was used for modeling, resulting in a final model including water intake, sleep duration, the percentile of BMI, and RDW, which were identified as the risk factors for orthostatic hypertension in children.

Table I. Characteristics of the study patients

Characteristics	Orthostatic hypertension group (n = 80)	Control group (n = 51)	Z/χ^2 value	*P* value
Males/females (n)	43/37	25/26	0.279	NS
Age (years)	12.0 (11.0, 13.0)	12.0 (11.0, 12.0)	1.592	NS
BMI (kg/m^2)	20.0 (17.8, 24.1)	18.0 (16.4, 19.7)	3.842	<.01
Overweight (BMI > 85th percentile; yes/no)	40/40	10/41	12.190	<.01
Obesity (BMI > 95th percentile; yes/no)	26/54	4/47	10.724	<.01
Water intake (<800/≥800 mL/d)	54/26	24/27	5.402	<.05
Sleeping hours (h/d)	7.5 (7.0, 8.0)	9.0 (8.0, 9.5)	−5.373	<.01
Car sickness (yes/no)	24/56	16/35	0.028	NS
Allergic diseases (yes/no)	7/73	5/46	0.042	NS
Family history of primary hypertension (yes/no)	8/72	0/51	5.432	<.05
Family history of syncope (yes/no)	5/75	1/50	1.311	NS

NS, no significance ($P > .05$); h/d, hours daily.
Variables are expressed as medians (25th percentile, 75th percentile).

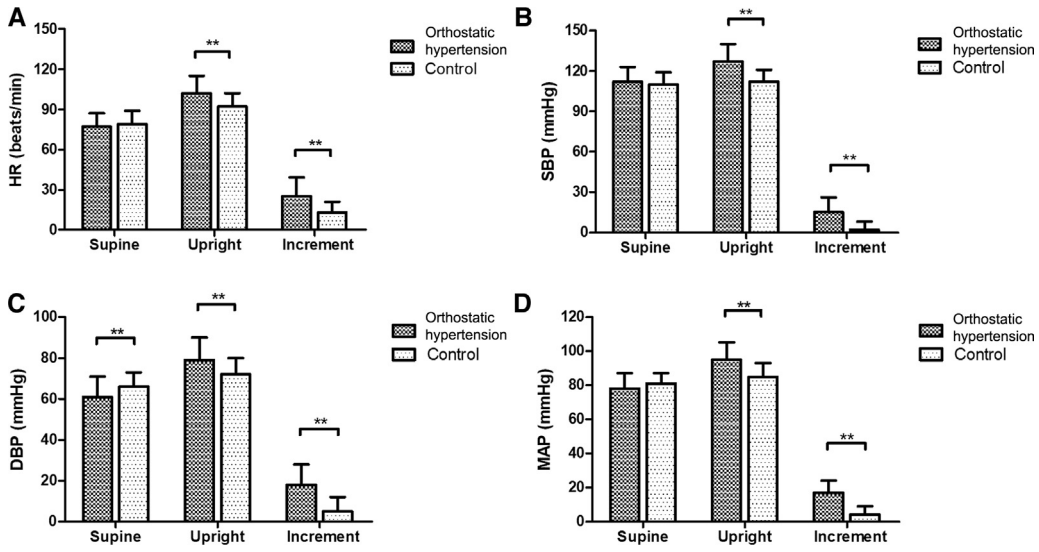

Figure. HR and BP changes in the study participants during the standing test. **A,** Changes of HR from supine to upright. **B,** Changes of SBP from supine to upright. **C,** Changes of DBP from supine to upright. **D,** Changes of MAP from supine to upright. Values are means ± SD. $^{**}P < .01$.

As seen from the logistic regression analysis (Table IV), if a child was overweight (BMI >85th percentile for children of the same sex and age) or obese (BMI >95th percentile), the risk of suffering from orthostatic hypertension would be increased by 6.069 times (95% CI, 1.375-26.783; $P < .05$) and 7.482 times (95% CI, 1.835-30.515; $P < .01$), respectively. If the daily water intake was less than 800 mL, the risk of suffering from orthostatic hypertension would be increased by 4.027 times (95% CI, 1.443-11.241; $P < .01$), and if the nightly sleep duration was increased by 1 hour, the risk of developing orthostatic hypertension would be decreased by 74.3% (95% CI, 54.6%-85.4%; $P < .01$). If the RDW was increased by 1%, the risk of suffering from orthostatic hypertension would be increased by 4.008 times (95% CI, 1.698-9.461; $P < .01$).

Discussion

In our study, the BMI of children with orthostatic hypertension was higher than that of the healthy controls. Previous studies indicated that the pathogenesis of orthostatic hypertension involved sympathetic overactivity and abnormal baroreflex.[21-23] Studies have reported enhanced sympathetic activity in patients with obesity, reflected by their increased plasma norepinephrine levels and increased norepinephrine spillover rates.[24-27] In addition, decreased baroreflex sensitivity was observed in children with obesity.[28] Children with orthostatic hypertension who are overweight or obese should have supine and upright BPs monitored.

We found that insufficient daily water intake (<800 mL/d) and lower supine DBP and higher HCT were associated with

Table II. Complete blood count results of the study participants

Results	Orthostatic hypertension group (n = 80)	Control group (n = 51)	Z value	*P* value
RBC (10^{12}/L)	4.79 (4.58, 5.05)	4.70 (4.38, 4.96)	1.926	NS
HCT (%)	40.6 (38.7, 43.0)	39.4 (38.0, 40.8)	2.707	<.01
HGB (g/L)	139 (132, 147)	134 (130, 144)	1.911	NS
MCV (fL)	84.3 (82.5, 87.2)	85.5 (83.1, 87.3)	−1.350	NS
MCH (pg)	29.1 (28.1, 30.1)	29.7 (28.8, 30.5)	−1.785	NS
MCHC (g/L)	343 (336, 351)	344 (338, 352)	−0.952	NS
RDW (%)	12.8 (12.5, 13.3)	12.0 (12.0, 13.0)	4.015	<.01
PLT (10^9/L)	266 ± 60	282 ± 55	−0.823	NS
MPV (fL)	10.5 (9.9, 11.0)	10.7 (9.9, 11.1)	−1.106	NS
PDW (%)	11.8 (11.1, 13.0)	12.1 (10.8, 13.1)	−0.014	NS
WBC (10^9/L)	6.41 ± 1.41	6.62 ± 1.39	−1.544	NS
EOS (10^9/L)	0.14 (0.09, 0.22)	0.10 (0.06, 0.21)	1.708	NS

EOS, eosinophilic granulocyte; *HGB*, hemoglobin; *MCH*, mean corpuscular hemoglobin; *MCHC*, mean corpuscular hemoglobin concentration; *MCV*, mean corpuscular volume; *MPV*, mean platelet volume; *PDW*, platelet distribution width; *PLT*, platelet; *RBC*, red blood cells; *WBC*, white blood cells.
Normally distributed variables are expressed as means ± SD; non-normally distributed variables are expressed as medians (25th percentile, 75th percentile).

Table IV. Logistic regression analysis of variables

Characteristics	B	Se	Wald	*P* value	OR (95% CI)
The percentile of BMI	–	–	11.102	<.01	–
Overweight (>85th percentile)	1.803	0.757	5.668	<.05	6.069 (1.375-26.783)
Obesity (>95th percentile)	2.013	0.717	7.874	<.01	7.482 (1.835-30.515)
Water intake <800 mL/d	1.393	0.524	7.073	<.01	4.027 (1.443-11.241)
Sleeping hours	−1.358	0.290	21.898	<.01	0.257 (0.146-0.454)
RDW	1.388	0.438	10.032	<.01	4.008 (1.698-9.461)
Constant	−7.342	5.382	1.861	–	–

orthostatic hypertension. Water intake, supine DBP, and HCT are all associated with circulating blood volume. Thus, there may be relatively low blood volume in children with orthostatic hypertension, and owing to gravity, returned blood volume is decreased after standing, leading to the reduction of upright cardiac output.[29] Decreased cardiac output after standing in patients with orthostatic hypertension has been reported by Streeten et al, who also proposed that cardiac output reduction was a trigger of sympathetic overactivation with an upright position and resulted in the elevation of BP.[21] Adequate water intake might also help to improve the symptoms of orthostatic intolerance in children and adolescents with orthostatic hypertension.

The present study showed that decreased sleep duration was associated with orthostatic hypertension. Studies have shown that a lack of sleep at night could lead to increased sympathetic nervous activity and be associated with the development of essential hypertension in children and adolescents.[30,31] Liu et al conducted 24-hour ambulatory BP monitoring on 43 children with orthostatic hypertension and discovered that most children with orthostatic hypertension were "nondippers," suggesting abnormal circadian rhythm of BP and increased sympathetic activity in children with orthostatic hypertension.[32] Thus, the mechanism by which sleep insufficiency increases the risk of orthostatic hypertension might involve increased sympathetic activity.

The RDW reflects the variability in the size of erythrocytes. The RDW of patients with essential hypertension, especially those of "nondippers," has been shown to be higher than that of the control group.[33,34] Our study showed that the RDW was significantly higher in children with orthostatic hypertension than in the control group. Similar to our findings, Zhang et al reported that the RDW values of children with neurally mediated syncope were significantly higher than those of healthy controls (13.1 ± 0.4% vs 12.4 ± 0.4%; $P < .001$).[11]

The underlying reasons for RDW elevation include vitamin D deficiency, reduced iron storage, and vitamin B_{12} deficiency; these are detected in children with orthostatic intolerance.[35-39]

There is a relationship between orthostatic intolerance and allergic diseases; mast cell activation in patients with postural tachycardia syndrome has been reported.[40] Liao et al studied found that syncope occurred more frequently in children with vasovagal syncope and allergies than in children with vasovagal syncope, but without allergies.[8] However, the prevalence of allergies did not differ significantly between the group with orthostatic hypertension and the healthy controls.

Based on our findings, advising children to drink enough water and obtain sufficient sleep, as well as encouraging overweight and obese children to lose weight, could contribute to the prevention of pediatric orthostatic hypertension.

This study has limitations. First, the mechanisms involved in RDW elevation in children with orthostatic hypertension need further examination. Second, although patients in the group with orthostatic hypertension complained of orthostatic intolerance symptoms, it is difficult to measure BP at the same time when they feel discomfort in daily life. Therefore, whether abnormal BP changes for orthostatic hypertension always co-occur with symptoms of orthostatic intolerance merits further study. Third, the regression model for risk factors in our study was built based on the patient data from one center, and the sample size was relatively small. ■

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Table III. Correlation analysis between examined variables and severity of orthostatic hypertension

	Correlation to MAP increment from supine to upright (n = 131)		Correlation to orthostatic intolerance symptom scores (n = 131)	
Items	**r**	***P* value**	**r**	***P* value**
BMI	0.261	<.01	0.402	<.01
Sleeping hours	−0.384	<.01	−0.416	<.01
Supine DBP	−0.448	<.01	−0.284	<.01
HCT	0.184	<.05	0.243	<.01
RDW	0.273	<.01	0.324	<.01