ORIGINAL ARTICLE

Autonomic Disturbances in Children with Nutcracker Syndrome: A Case Control Study

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ABSTRACT

Objective: To describe the autonomic nervous system abnormalities including frequency of orthostatic symptoms, orthostatic response to the active standing test and impairment in heart rate variabilitity (HRV) parameters in children with Nutcracker syndrome (NCS).

Methods: A case-control study was conducted between May and November 2023. We included children with NCS and healthy age- and sex-matched healthy controls. Children were evaluated for autonomic system disturbances by history for orthostatic symptoms, performance in an active standing test, 24-hour holter monitoring to determine the HRV, maximum and minimum heart rates, and the average heart rate and urine analysis for orthostatic proteinuria and hematuria.

Results: 45 children with NCS and 47 age-matched healthy controls were included. Orthostatic symptoms were observed in 55.5% of the NCS patients, with dizziness being the predominant complaint (37%), followed by fatigue (20%), palpitation (13%), headache (11%), vision disturbances (11%), syncope (6%), chest discomfort (4%), and diaphoresis (2%). In the 24-h holter monitoring of 24 patients, a decrease in the standard deviation of the NN intervals (SDNN), root mean square of successive R-wave peak to R-wave peak (RR) interval differences (rMSSD) was observed. SDNN was significantly lower in NCS compared to the control group; 135.5 (42.3) vs 155.9 (35.2), $P = 0.039$. rMSDD was also significantly lower in the NCS compared to control group; 46.2 (19.7) vs 61.3 (26.6), $P = 0.020$. The mean (SD) maximum heart rate was higher in NCS compared to control group; 172.3 (28.4) vs 159.4 (14.6), $P = 0.015$.

Conclusion: Autonomic nervous system dysfunction and orthostatic disturbances may be seen in children with NCS.

Keywords: *Autonomic nervous system, Compression, Entrapment, Heart rate variability, Renal vein*

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INTRODUCTION

Compression of the left renal vein is known as Nutcracker Syndrome (NCS). A wide variety of symptoms, ranging from asymptomatic to macroscopic hematuria or orthostatic proteinuria, and severe pain, can result from the elevated pressure in the left renal vein, or alterations in renal perfusion and collateral formation [1,2]. There is a lack of agreed-upon diagnostic and laboratory criteria and the variability in symptoms at presentation which makes the diagnosis challenging.

Orthostatic problems are believed to arise from alterations in the renal flow, resistance in arterioles and immunological cascade leading to inflammation and disruptions in the noradrenaline and renin-angiotensin system [3,4]. There is a lack of knowledge on the impact of NCS on the autonomic nervous system, despite some research being conducted on the chronic fatigue and orthostatic symptoms associated with NCS. Also, the prevalence of orthostatic problems in NCS is not currently known. The aim of this study was to evaluate the autonomic system abnormalities including the frequency of orthostatic symptoms and orthostatic response in children with NCS.

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MATERIAL AND METHODS

A case-control study was conducted between May and November 2023 in the Pediatric Cardiology Outpatient Clinic of Van Training and Research Hospital, Van, Turkey, wherein children under 18 years of age were enrolled after obtaining a written consent from parents/ caregivers and an assent as applicable. We also obtained a prior approval from the institutional ethics committee for the study.

The cases comprised of 45 children diagnosed with NCS and 47 age- and sex-matched healthy controls. NCS was diagnosed based on the presence of all of the following on sonography: an aortomesenteric/renal hilum peak velocity greater than 5:1, a renal hilum/aortomesenteric ratio greater than 5:1, and superior mesenteric artery angle smaller than 35° [5]. The control group consisted of healthy children without any underlying structural heart disease or any other chronic illness who were evaluated at the Pediatric Cardiology Outpatient Clinic for murmurs.

We obtained the patients' demographics, medical history including history suggestive of orthostatic abnormalities, and clinical characteristics. A detailed anthropometric assessment including weight and height were recorded for each child as per standard technique. A computer program was used for z score calculation. (*https://www.ceddcozum.com/*) which uses the Neyzi growth charts standardised for the Turkish population [6]. An abdominal sonogram was performed by the same experienced radiologist who was blinded to the fact whether the child had hematuria or orthostatic proteinuria or was a healthy control; the mesenteric angle, left renal vein diameter, and peak velocity were measured in both the supine and upright positions in all of the patients. The anteroposterior diameter and peak velocity were measured at the proximal portion of the left renal vein near the hilum and the aortomesenteric portion.

Of the 45 children with NCS, 24 underwent 24-h holter monitoring to determine the heart rate variability (HRV), maximum and minimum heart rates, and the average heart rate. The holter recordings were interpreted by a single pediatric cardiologist. In the HRV analysis, the time domain was analyzed. These parameters comprised the standard deviation (SD) of the normal-to-normal (NN) intervals (SDNN), mean of the SD of all of the NN intervals for each 5 min segment of a 24-h HRV recording (SDNNi), SD of the average of the NN intervals (SDANN), root mean square of successive R-wave peak to R-wave peak (RR) interval differences (rMSSD), percentage of successive RR intervals that differ by more than 50 ms (pNN50). The active standing test was used to monitor the child's autonomic reactions determined by the blood pressure and heart rate after 10 min of lying down and 5 min after rapidly 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. The diagnosis of orthostatic hypotension, orthostatic intolerance, orthostatic hypertension, or postural orthostatic tachycardia syndrome (PoTS) was established according to the symptoms, blood pressure, and heart rate values while in a supine or standing position [7,8]. Orthostatic hypotension was diagnosed in case of more than 20 mmHg drop in systolic and more than 10 mmHg in diastolic blood pressure. Postural orthostatic tachycardia syndrome was diagnosed in case of an increase in standing heart rate of 40 or 120 bpm from baseline and the absence of hypotension [9]. Orthostatic hypertension was diagnosed in more than 20 mmHg increase in systolic and more than 20 mmHg in diastolic blood pressure.

Statistical analysis: The statistical 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 Shapiro–Wilk test. The descriptive statistics utilized the mean (SD) for the normally distributed data, and the median and range for the non-normally distributed data. The continuous and categorical variables with normal distribution were compared using the paired samples t-test and chi-square test. $P < 0.05$ was considered statistically significant.

RESULTS

The baseline characteristics of children with NCS ($n = 45$) and the controls ($n = 47$) are shown in **Table I**. There were no statistically significant differences between the case and control groups in terms of sex or age. Anthropometric measurements revealed no significant differences in the height and height-for-age z score. However, statistically significant differences were seen in the weight weight-for-age z score, body mass index (BMI) and BMI-for-age z score.

No significant disparity was observed in the levels of blood urea, serum albumin, hemoglobin, and mean corpuscular volume between the groups. However, the NCS patients exhibited a lower creatinine concentration ($P = 0.008$) (**Table I**). BMIZ < –2 was seen in 3 children with NCS and they were considered skinny; 1 of them had severe thinness (BMIZ < –3). WAZ < –2 SD and HAZ < –2 was seen in 5 and 2 children with NCS, respectively. Three children with NCS had systemic blood pressure exceeding the 95th percentile.

Orthostatic proteinuria (42%) was the most prevalent finding in the urine of children with NCS (**Table II**). Hematuria and both proteinuria and hematuria were present in 28% and 13% of the children with NCS, respectively. The urinary results of 7 patients were normal. **Table II** contains the comprehensive results of the urine analysis and the renal doppler ultrasonography. The posterior type of NCS was found in 2 patients, while the others had the classical type.

Symptoms of orthostatic disturbances were found in 25 (55.5%) patients (**Table II**). The most common

Table I Baseline Characteristics of Study Participants

	Children with NCS (n = 45)	*Controls (n = 47)*	*P value*
Age (years)[a]	11.3 (3.7)	12.3 (3.5)	0.195
Female/male (*n*)	28/17	28/19	0.795
Weight (kg)[a]	37 (15.6)	42 (13.9)	0.070
WAZ[a]	–0.75 (–0.99)	–0.38 (0.80)	0.058
Height (cm)[a]	144.1 (21.9)	150.4 (18.7)	0.142
HAZ[a]	–0.22 (1.1)	–0.32 (0.76)	0.372
BMI (kg/m^2)[a]	16.8 (2.6)	18.2 (2.4)	0.011
BMIZ[a]	–0.82 (0.87)	–0.46 (0.9)	0.058
Blood urea (mg/dL)[a]	23.4 (7.3)	24.4 (5.5)	0.465
Serum creatinine (mg/dL)[a]	0.54 (0.15)	0.62 (0.13)	0.008
Serum albumin (mg/dL)[a]	4.5 (0.7)	5.6 (0.6)	0.261
Hemoglobin (g/dL)[a]	13.9 (1.3)	13.8 (0.9)	0.900
MCV (fL)[a]	84.7 (5.9)	83.4 (4)	0.258

Values expressed as [a]mean (SD)
BMIZ Body mass index-for-age z score, HAZ Height-for-age z score, MCV Mean corpuscular volume, NCS Nutcracker syndrome, WAZ Weight-for-age z score

symptom was dizziness (37%), followed by fatigue (20%), palpitation (13%), headache (11%), vision disturbances (11%), syncope (6%), chest discomfort (4%), and diaphoresis (2%). 16 patients (64%) had more than one neurologic, cardiac, or autonomic system involvement. Based on their symptoms and the response of blood pressure or heart rate to the standing test, 24 children with NCS (53%) had orthostatic pathology. 10 (22%) children with NCS had orthostatic hypertension, 9 (20%) had postural hypotension with tachycardia syndrome (PoTS), 7 (15%) had orthostatic intolerance, and 5 (11%) had orthostatic hypotension. Orthostatic hypotension/hypertension and PoTS were both present in 7 (15%) patients.

Table II Urine analysis and Autonomic System Evaluation of Children with NCS (*n* = 45)

Urinalysis	
Orthostatic proteinuria	19 (42)
Hematuria (microscopic/macroscopic)	13 (28)
Normal	7 (15)
Mixed (proteinuria, hematuria)	6 (13)
Elevated systolic blood pressure	3 (6.6)
Orthostatic symptoms	25 (55)
More than two symptoms	16 (35)
Orthostatic pathology	24 (53)
Orthostatic hypertension	10 (22)
PoTS	9 (20)
Orthostatic intolerance	7 (15)
Orthostatic hypotension	5 (11)
Retroaortic left vein	2 (4.4)
Doppler findings	
Superior mesenteric artery angle (degrees)[a]	11.2 (3.2)
LRV renal hilum diameter/aortomesenteric ratio[b]	8.1 (7.3, 11.3)
LRV peak velocity (m/s)[b]	13.3 (9.6, 16.5)
Aortomesenteric/renal hilum peak velocity[b]	7.3 (5.7, 10.4)

PoTS Postural orthostatic tachycardia syndrome, LRV left renal vein
Values expressed as [a]mean (SD), [b]median (25th centile, 75th centile)

The resting heart rates and blood pressures were not significantly different between both groups; however, the NCS group showed a significant increase in heart rate after 5 min of standing ($P = 0.020$) (**Table III**). Of the 24 NCS patients who underwent holter monitoring, there was no statistically significant difference in the mean and minimum heart rates. However, the maximum heart rate was significantly greater in the NCS group ($P = 0.015$) than in the control group. The SDNN and rMSSD (time-domain parameters of the HRV) were significantly lower in the NCS group than in the control group ($P = 0.039$ and $P = 0.015$, respectively).

DISCUSSION

Based on the findings of this study, it may be suggested that children with NCS may exhibit autonomic dysfunction and orthostatic symptoms. Approximately half of the children exhibited orthostatic symptoms. Additionally, half of them revealed an abnormal response during the active standing test. Orthostatic hypertension was the most frequently observed pathology in the active

Table III Autonomic System Evaluation of Study Participants

	Children with NCS (n = 45)	*Controls (n = 47)*	*P value*
Baseline (supine)			
HR	84.6 (14.3)	82.6 (10.6)	0.435
SBP	108 (11.5)	105.4 (8.6)	0.227
DBP	65.4 (7.6)	68.2 (8.2)	0.96
5 min standing			
HR	96.4 (16.9)	89.2 (12)	0.020
SBP	108.2 (10.6)	106.5 (8.4)	0.412
DBP	66.8 (9)	69.6 (7.8)	0.115
Holter parameters	*(n = 24)*	*(n = 47)*	
SDNN	135.5 (42.3)	155.9 (35.2)	0.039
SDNNi	68.4 (23)	76.1 (21.9)	0.183
SDANN	120.8 (40.5)	133.7 (34.4)	0.177
rMSDD	46.2 (19.7)	61.3 (26.6)	0.020
pNN50	21.0 (13.1)	24.8 (11.3)	0.222
HR	86.4 (14.1)	83.3 (8.3)	0.260
Min HR	51.7 (9.4)	52.8 (7.5)	0.598
Max HR	172.3 (28.4)	159.4 (14.6)	0.015

Values expressed as mean (SD)
DBP Diastolic blood pressure, HR Heart rate, Max Maximum, Min Minimum, pNN50 Percentage of successive RR intervals that differ by more than 50 ms, rMSSD root mean square of successive R-wave peak to R-wave peak (RR) interval differences, SBP Systolic blood pressure, SDNN Standard deviation of the normal-to-normal (NN) intervals, SDANN SD of the average NN intervals, SDNNi Mean of the SDs of all of the NN intervals for each 5 min segment of a 24-h heart rate variability recording

standing test, followed by PoTS and orthostatic intolerance. Children diagnosed with NCS had higher maximal heart rate and lower SDNN and rMSDD values when analyzed with a 24-h holter monitoring. In addition, children with NCS exhibited orthostatic proteinuria and reduced levels of creatinine.

Children with NCS commonly display a skinny body type and a reduced proportion of adipose tissue as was also seen in our study. Low BMI can lead to NCS by reducing the angle of superior mesenteric artery [2,3]. Surprisingly, this study found that the levels of creatinine were significantly low, a finding that has not been previously documented in the NCS. This may be attributed to their low muscle mass ratio, a factor associated with a low BMI [10,11]. The previous reports on NCS have shown that microhematuria was more prevalent presentation [1,12]. However, the analysis herein reported a higher incidence of orthostatic proteinuria in children with NCS which may be due to a higher proportion of adolescents in the study [13].

Dizziness, fatigue, and syncope have previously been previously documented as orthostatic symptoms in children with NCS [14]. Inflammation, increased cytokines, and disturbances in the levels of norepinephrine, epinephrine, cortisol, or renin in the aldosterone system may contribute to symptoms and autonomic disturbances due to alterations of arteriolar resistance, exaggeration of the physiologic response, and disturbances in left renal blood flow [2,3,15,16]. More than half of the NCS patients displayed symptoms and pathologies related to orthostatic conditions. This suggests that evaluating the occurrence and frequency of orthostatic symptoms in children with NCS may be an important aspect in deciding what course of action to take during the disease's follow-up.

Standing is known to cause a decrease in parasympathetic activity and increase in sympathetic activity (heart rate increase of 10-20 bpm and diastolic blood pressure increase of 5 mmHg) [17]. Herein, the heart rate response to the standing test was greater in the NCS group. Furthermore, more than half the patients showed orthostatic disturbances during the active standing test. Of these conditions, orthostatic hypertension was the most common, followed by PoTS, orthostatic intolerance, and orthostatic hypotension. Based on the holter result, the reduction in SDNN and rMSSD values indicates a decrease in parasympathetic activity and suggests an increase in sympathetic nervous system activity in NCS children. All of these findings point to the possibility that NCS may have a negative effect on the autonomic nervous system.

Nevertheless, these findings absolutely need to be interpreted with great caution, and a few limitations need to be taken into consideration. Given the rarity of NCS, a small group patient was included, and our population may not to be fully representative. Patients' self-reported symptoms were analyzed, and it is possible that it contains selective memory, exaggeration, and recall bias. Future studies may have the potential to yield more accurate and verifiable fata by utilizing autonomic symptom scales. There is a lack of prior research evaluating the autonomic nervous system in children with NCS. This study applied the active standing test and HRV time domain parameters to assess the orthostatic response. For future research, it may be encouraged performing additional tests to assess the autonomic nervous system, such as skin conductance analysis, neuro hormonal profile and pupillary reflex testing, to enhance the accuracy of the study.

Based on our study we conclude that although the urinary signs and symptoms in children with NCS generally improve with somatic growth, they must be evaluated for associated autonomic dysfunction.

WHAT THIS STUDY ADDS?

- Children with NCS may experience orthostatic symptoms.
- Orthostatic parameters (such as active standing test and HRV) were compromised and should be monitored for orthostatic disorders in children with NCS.

Ethics clearance: Van Training and Research Hospital Non-Interventional Clinical Research Ethics Committee, Ref number: 2023/10-01; dated May 10, 2023.

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Contributors: YND: Writing, methodology, and investigation; AYK: Conceptualization and visualization; DB: Supervision and investigation; DG: Editing; SE: Review, editing, and statically analysis. All authors approved the final version of manuscript.

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