

# New methods of differentiation between primary and secondary hypertension in a pediatric population: A single-center experience

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## Abstract

**Background.** Kidney diseases are the main causative factors of secondary hypertension (HTN) in children. Although primary HTN is less common in the pediatric population, its increasing prevalence, especially among teenagers, makes early diagnosis an emerging issue.

**Objectives.** To analyze the potential differences between primary HTN and HTN secondary to renal diseases, in order to tailor diagnostic procedures to pediatric patients with suspicion of HTN.

**Material and methods.** A retrospective evaluation was performed of medical records of 168 children (aged from 1 month to 18 years) diagnosed with arterial HTN in the Pediatric Nephrology Department of Wrocław Medical University (Poland). The comparative analysis concerned demographics, causes of HTN, clinical picture, laboratory tests, and parameters of ambulatory blood pressure monitoring (ABPM).

**Results.** Out of 168 children, 47% were diagnosed with primary HTN and 53% with secondary renal HTN. The patients with primary HTN were significantly older than those with HTN secondary to renal disease. Among the children with primary HTN, 26% were overweight and 42% were obese; among those with renal HTN, the proportions were 16% and 19%, respectively. The patients with primary HTN had significantly higher body mass index (BMI) percentiles and z-scores, and tended toward higher pulse pressure (PP) values. In the group with secondary HTN, ABPM parameters of diastolic blood pressure (DBP) and total cholesterol were significantly elevated. The BMI z-scores correlated positively with PP in the whole group.

**Conclusions.** As expected, HTN secondary to renal disease prevails in younger children, but primary HTN has become an emerging issue in teenagers. The diagnostics of HTN secondary to kidney disease have revealed risk factors worsening the prognosis, including higher values of cholesterol or of parameters connected with DBP. Primary HTN risk factors include obesity and a tendency towards higher PP values.

**Key words:** obesity, teenagers, ambulatory blood pressure monitoring, mean arterial pressure, pulse pressure

## Introduction

Hypertension (HTN) affects 3–5% of children.<sup>1,2</sup> Despite the increasing prevalence of primary HTN in teenagers, HTN secondary to other underlying disorders still prevails in the pediatric population.<sup>3</sup> Among causes of secondary HTN, renal diseases are predominant and responsible for faster disease progression, as well as clinically apparent complications appearing before adulthood.<sup>4</sup> Moreover, the occurrence of HTN in childhood is associated with high blood pressure (BP) in later life and early development of cardiovascular disease (CVD).<sup>5,6</sup> Thus, early diagnosis is of utmost importance in this age group.

In addition to routine procedures including demographic, laboratory and imaging data, new tools are being used to increase the efficiency of diagnostics and to establish a prognosis.

In particular, ambulatory blood pressure monitoring (ABPM) is recommended in children, as it ensures comprehensive observation during normal patient activity in both day- and nighttime periods.<sup>7,8</sup> This method ensures direct measurement of mean arterial pressure (MAP), which is reported to increase the sensitivity of mild HTN diagnoses in patients with borderline BP values.<sup>9</sup> Mean arterial pressure is also a predictor of hyperkinetic circulation, which can already be observed at the early stages of primary HTN.<sup>10</sup> Current guidelines emphasize the role of MAP in the monitoring of treatment effectiveness.<sup>2</sup> Another new tool, pulse pressure (PP), is an established predictor of target-organ damage in the course of HTN, especially in primary HTN.<sup>11</sup>

The aim of the study was to analyze the potential differences between primary HTN and HTN secondary to kidney disease, revealed in the course of diagnostic procedures including the clinical picture, laboratory test results and selected parameters assessed by ABPM.

## Material and methods

We carried out a retrospective analysis of the medical records of 168 children, aged from 1 month to 18 years, diagnosed for arterial HTN in the Department of Pediatric Nephrology at Wrocław Medical University (Poland). Basic demographic data are presented in Table 1.

Hypertension was diagnosed in children <16 years whose diastolic and/or systolic blood pressure (DBP and SBP) values, obtained during 3 independent measurements, were over the 95<sup>th</sup> percentile for their age, sex and height. In teenagers aged 16–18 years, the threshold value was  $\geq 140/90$  mm Hg.<sup>12</sup> In each child, the diagnosis of HTN was established by 3 independent oscillometric office BP measurements. Additionally, in children aged >5 years, ABPM was performed as a part of the diagnostic process.

The patients were diagnosed with primary HTN or HTN secondary to kidney disease according to the European Society of Hypertension guidelines.<sup>13</sup>

The patients were divided into 2 groups according to HTN etiology. The group diagnosed with primary HTN included 79 children, and the group with HTN secondary to renal disease comprised 89 patients. The data collected throughout the diagnostic process involved demographics, the type and cause of HTN, clinical manifestations, laboratory tests, and the results of selected ABPM measurements.

Body mass index (BMI) was assessed in both percentiles and z-scores established using the WHO AnthroPlus software (World Health Organization, Geneva, Switzerland). Patients with BMI equal to or lower than the 3<sup>rd</sup> percentile were qualified as underweight, those with BMI between the 85<sup>th</sup> and 95<sup>th</sup> as overweight, and those with BMI equal or greater than the 95<sup>th</sup> percentile were qualified as obese.

The ABPM was performed in 118 children >5 years (67 with primary and 51 with secondary HTN) using the Oscar 2 ambulatory blood pressure monitor (SunTech Medical Inc., Morrisville, USA) and interpreted in accordance with recommendations concerning ABPM in children and adolescents.<sup>12,13</sup> Each of the measurements was also divided into daytime (7:00–23:00) and nighttime (23:00–7:00) periods. When the number of measurements was insufficient (<14 in a daytime session and <7 at night), or less than 70% of the measures were interpretable, the results were excluded from the analysis. The median values of SBP and DBP, as well as their loads (percentage of measurements above the threshold) MAP and PP were assessed. If there was more than 1 ABPM examination for a single patient, the results from the time of diagnosis, before treatment introduction, was included in the analysis.

All procedures involving human treatment were performed in accordance with the Declaration of Helsinki and its further amendments. According to the rules and regulations of Wrocław Medical University, the study did not require Ethics Committee approval. However, informed consent regarding the data collection and analysis was obtained from the parents and the patients over 16 years of age.

## Statistical analysis

The results are presented as median values and interquartile ranges (IQRs) or percentages. The  $\chi^2$  test, Student's t-test and Pearson's correlation coefficient were used for normally distributed data, and non-parametric tests (Mann–Whitney U test and Spearman's correlation coefficient) were used for other variables. The p-values <0.05 were considered significant. The statistical analysis was performed with STATISTICA v. 13.0 software (StatSoft Inc., Tulsa, USA).

## Results

Out of 168 patients, 79 were diagnosed with primary HTN (47%) and 89 (53%) with HTN secondary to renal disease. Basic clinical data concerning the study groups

are shown in Table 1. The patients with primary HTN were significantly older than the children with secondary renal HTN (Table 1). However, there was no age difference between patients with primary and renal secondary HTN when only children who had undergone ABPM were analyzed. Teenagers prevailed in the primary HTN group, whereas the secondary HTN group included comparable numbers of children below and above 11 years old (Table 1). There was no gender domination in either group, and boys' and girls' age was comparable in both groups. In children under 11 years old, secondary renal HTN was diagnosed in 86.5% of the cases; in teenagers primary HTN was the main diagnosis (62%). In the group with secondary renal HTN, congenital anomalies tended to prevail in older children and glomerulopathies in younger patients, but these differences did not reach statistical significance (Table 2).

Headache, the most frequent symptom related to HTN, was present in almost 1/3 of the children, significantly more often in the primary HTN group (Table 1) and in adolescents ( $p < 0.001$ ).

Median values of BMI, BMI percentiles and BMI z-scores were significantly higher in patients with primary HTN. These patients were also more often obese (Table 1).

Serum lipid disorders showed a preponderance toward secondary HTN (Table 3), whereas serum sodium and total protein concentrations were higher in the primary HTN group than in the secondary HTN group.

The ABPM results revealed significantly higher DBP values and loads in the secondary HTN group in the 24-hour and nighttime periods, with a similar trend observed for the daytime period (Table 4).

In the whole study group, there was a relationship between BMI z-scores and median DBP values ( $R = -0.3$ ;  $p = 0.002$ ), as well as DBP loads ( $R = -0.22$ ;  $p = 0.03$ ). There was also a significant correlation between high-density lipoprotein (HDL) level and DBP values ( $R = 0.24$ ,  $p = 0.036$ ). However, in the subgroups (primary and secondary HTN), these correlations failed to reach statistical significance.

Among the children who had ABPM performed, MAP values in boys were significantly higher than in girls (60 mm Hg compared to 53 mm Hg;  $p < 0.001$ ). There was a tendency towards higher PP values in children with primary HTN, but the difference did not reach statistical significance. We also observed a significant positive correlation between BMI z-scores and PP ( $R = 0.21$ ;  $p = 0.037$ ) in the whole study group.

Table 1. Basic patient characteristics

Parameter	Primary HTN (n = 79)		Secondary HTN (n = 89)		p-value
Median age [years]	15.7		10.7		<0.001*
Age distribution	<11 years	≥11 years	<11 years	≥11 years	<0.001**
	7 (8.9%)	72 (91.1%)	45 (50.6%)	44 (49.4%)	
Gender	boys	girls	boys	girls	0.93**
	44 (55.7%)	35 (44.3%)	49 (55.1%)	40 (44.9%)	
Height [cm]	165.3		137		<0.001*
Median BMI percentile	92.3		67.3		<0.001*
Median BMI z-score	1.43		0.45		<0.001*
Overweight	25%		16%		0.19**
Obesity	43%		19%		0.002**
Headaches	43%		18%		<0.001**

HTN – hypertension; BMI – body mass index; \*Mann–Whitney U test; \*\* $\chi^2$  test.

Table 2. Specific causes of HTN secondary to renal disease (differences established with  $\chi^2$  test and optional Yates's correction)

Etiology of HTN secondary to renal disease	All patients with secondary renal HTN	Patients < 11 years	Patients ≥11 years	p-value
Congenital anomalies of kidneys and urinary tract (CAKUT)	37 (41.57%)	16 (35.56%)	21 (47.73%)	0.24
Glomerulopathies	32 (35.96%)	21 (46.67%)	13 (29.55%)	0.09
Polycystic kidney disease	11 (12.36%)	6 (13.33%)	5 (11.36%)	0.78
Hemolytic-uremic syndrome	4 (4.49%)	2 (4.44%)	2 (4.55%)	0.98
Renovascular HTN	3 (3.37%)	0 (0%)	3 (6.82%)	0.07
In total	89 (100%)	45 (100%)	44 (100%)	

HTN – hypertension.

**Table 3.** Basic laboratory test results (statistical significance assessed with Mann–Whitney U test)

Serum parameters (median value; interquartile range)	Primary HTN	Secondary HTN	p-value
Total cholesterol [mg/dL]	163.5 (143–190)	184.5 (158.5–219)	0.002
LDL cholesterol [mg/dL]	93.0 (73–113)	105.0 (84–131)	0.08
HDL cholesterol [mg/dL]	46.0 (40–54)	49.0 (44–66)	0.01
Triglycerides [mg/dL]	101.5 (76–133)	117.0 (80–195)	0.052
Creatinine [mg/dL]	0.86 (0.72–0.97)	0.83 (0.59–1.1)	0.55
Uric acid [mg/dL]	5.6 (4.5–6.5)	5.5 (4.2–6.6)	0.4
Potassium [mmol/L]	4.36 (4.1–4.6)	4.38 (4.2–4.7)	0.51
Sodium [mmol/L]	139.5 (138–141)	138.5 (136.5–140)	0.009
Total protein [g/dL]	7.4 (7.0–7.7)	6.9 (6.3–7.4)	<0.001

HTN – hypertension; LDL – low-density lipoprotein; HDL – high-density lipoprotein.

**Table 4.** Selected ABPM measurements in the 2 groups

ABPM parameter, median (IQR)	Primary HTN (n = 67)	Secondary HTN (n = 51)	p-value
24 h SBP [mm Hg]	132 (127–143)	137 (125–142)	0.57*
Daytime SBP [mm Hg]	134 (129–146)	138 (128–146)	0.62**
Nighttime SBP [mm Hg]	122 (115–132)	123 (118–131)	0.41*
24 h DBP [mm Hg]	74 (70–78)	77 (69–84)	0.02**
Daytime DBP [mm Hg]	76 (72–81)	79 (73–86)	0.06**
Nighttime DBP [mm Hg]	65 (59–70)	67.5 (64–74)	0.02**
24 h SBP load [%]	58 (35–82)	67 (42–85)	0.29**
Daytime SBP load [%]	57 (29–80)	64 (40–88)	0.23**
Nighttime SBP load [%]	63 (30–88)	67 (44.5–93.5)	0.13*
24 h DBP load [%]	32 (17–49)	48 (23–68)	0.028**
Daytime DBP load [%]	29 (13–45)	40 (16–67)	0.067**
Nighttime DBP load [%]	40 (22–63)	56 (33–82)	0.03**
24 h PP [mm Hg]	59 (53–65)	56 (50–62)	0.08**
24 h MAP [mm Hg]	94 (88–99)	96 (90–102)	0.07**

ABPM – ambulatory blood pressure monitoring; HTN – hypertension; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; PP – pulse pressure; MAP – mean arterial pressure; \*independent t-test; \*\*Mann–Whitney U test; IQR – interquartile range.

## Discussion

In our study, the majority of adolescents (11 years or older) were diagnosed with primary HTN, whereas 86.5% of the children <11 years had secondary renal HTN, which is consistent with other observations.<sup>14,15</sup> These data suggest that a renal background should be suspected first in young children with elevated BP, whereas primary HTN is the more probable diagnosis in adolescents. However, almost 38% of the adolescents in our study were diagnosed with secondary HTN. Thus, as Litwin stressed,<sup>4</sup> the role of routine screening for secondary HTN in asymptomatic teenagers should not be underestimated.

The guidelines of the Polish Society of Pediatric Nephrology also emphasize the need for differentiation between primary and secondary HTN as soon as the diagnosis is made.<sup>7</sup> These recommendations indicate that younger

age, higher BP and more intense clinical symptoms are factors suggesting secondary HTN.

The age discrepancy between primary and secondary renal HTN in our study group was most probably a consequence of the fact that 69% of the patients were teenagers. However, when the age distribution in the secondary HTN group was taken into account, teenagers still constituted a half of this group. This observation suggests that the diagnosis of HTN due to renal diseases was made rather late. Such a conclusion should evoke deep concern, especially in light of the fact that inborn anomalies are the major cause of renal HTN. Therefore, the issue of early wide screening of the pediatric population with abdominal ultrasound should be revisited. Likewise, the necessity (emphasized in the Polish Society of Pediatric Nephrology guidelines) of taking blood pressure measurements during every outpatient visit in every child over 3 years old should be kept firmly in mind.<sup>7</sup>

Headache was the only clinical symptom reported more often in patients with primary HTN than in those with secondary renal HTN. However, it was also more frequent in teenagers (38% compared to 9%), who constituted more than 90% of the patients with primary HTN. Thus, it should always be treated as an alarming sign, irrespective of the child's age.

In the study group, 68% of the children with primary HTN were overweight or obese. For secondary HTN, that percentage was significantly smaller, but still meaningful (35%). Our observation confirms the data reported by Skrzypczyk et al.<sup>16</sup> Thus, obesity may be among the most important features indicating HTN etiology. Indeed, the prevalence of obesity and its relationship with the increasing number of children diagnosed with HTN is now one of the biggest challenges in pediatrics.<sup>17–19</sup> To deal with this issue, new American BP percentile tables excluding children with overweight and obesity were introduced in 2017.<sup>20</sup>

Our analysis revealed that children with secondary HTN had higher rates of lipid profile elements, although no correlation to BP values was found. However, Garí-Llanes et al. showed a significant positive correlation between serum lipid profiles and BP values that was already present at the pre-HTN stage.<sup>21</sup> Future analyses involving a more representative group may show similar relationships.

Ambulatory blood pressure monitoring has recently emerged as a method of choice in diagnosing and monitoring HTN in the pediatric population.<sup>22</sup> The Clinical Practice Guidelines developed by the American Academy of Pediatrics emphasize the role of ABPM in confirming diagnoses, detecting and excluding masked and white-coat HTN, and assessing therapeutic results in children.<sup>23</sup> The ABPM has also been reported to be a useful tool to differentiate between primary and secondary HTN.<sup>24</sup>

In our study, among the children who underwent ABPM, DBP values and loads were significantly higher in children with secondary HTN during the 24-hour and nighttime periods. A similar trend was noticed for the daytime, but it did not reach statistical significance. These results were confirmatory of our previous analysis involving a smaller group of patients.<sup>25</sup> Flynn et al. reported similar results, although in secondary HTN greater loads were also observed in nocturnal SBP measurements.<sup>24</sup> Another study on a cohort of untreated HTN patients showed higher nighttime loads.<sup>26</sup> Undoubtedly, differences in nighttime loads may make ABPM an important tool in early suspicion of secondary HTN, as this is the reference method of monitoring BP at night.

Our patients' BMI z-scores were negatively correlated with mean DBP values and loads. Although this correlation disappeared when the subgroups of primary and secondary HTN were analyzed separately, high BMI remains an important marker suggesting primary HTN.

In our research, based on ABPM results, PP values did not differ significantly between patients with primary and secondary HTN. When PP values from office BP

records were analyzed for the whole study group, those in the primary HTN subgroup were significantly higher than in the secondary HTN subgroup ( $p < 0.02$ ). However, some patients showed significant differences between PP values calculated from office and ABPM measurements, so this method-related bias requires further verification. Pulse pressure and MAP are non-invasive BP parameters obtained from ABPM. The significance of PP has increased in recent years, as it has turned out to be a prognostic factor of HTN in currently normotensive patients, and of a target-organ damage in the course of HTN, both in children and adults.<sup>27–29</sup> Our observation is convergent with the reported role of PP as a marker of arterial stiffness in essential HTN.<sup>30</sup> Moreover, the values of PP in boys were significantly higher than those in girls, which requires confirmation on a larger group of patients. The positive correlation between BMI z-scores and PP values found in our entire HTN group was similar to results of Chandramohan et al., who revealed a statistically significant association between wide PP and high waist circumference in a large cohort of children ( $n = 4667$ ).<sup>31</sup>

The potential strength of MAP values gained from ABPM comes from the fact that the oscillometric technique measures MAP directly. MAP has been shown to be a predictor of cardiovascular mortality in adults.<sup>32</sup> In our group of patients, MAP revealed no differences in terms of the type of HTN, age or gender. However, the usefulness of this parameter in diagnosing and differentiating the type of HTN in the pediatric population remains unknown and requires further investigation.

This study confirms the worldwide tendency toward the increasing occurrence of primary HTN among teenagers, as well as its close connection with the obesity epidemic. We have also upheld the growing importance of ABPM, both due to the efficient diagnostics of nighttime BP elevation and the potential prognostic value of PP. The need for earlier diagnostics of renal HTN should be given high priority.

Our study has limitations. Apart from age-related bias, it did not take into account all the possible reasons for secondary HTN. However, it did analyze renal causes in detail. This research should be continued in order to draw more reliable conclusions, especially in the promising area of ABPM measurements.

## Conclusions

According to previous international observations, primary HTN has become an emerging issue in teenagers, whereas in younger children HTN secondary to renal disease still prevails. Primary HTN has shown a higher occurrence of obesity and a tendency towards higher values of PP, both of which may potentially facilitate diagnosis. Risk factors worsening the prognosis in HTN secondary to kidney disease include higher values of cholesterol or parameters connected with DBP.



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