Prediction of Primary vs Secondary Hypertension in Children

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Despite current guidelines, variability exists in the workup of hypertensive children due to physician preferences. The study evaluates primary vs secondary hypertension diagnosis from investigations routinely performed in hypertensive children. This retrospective study included children 5 to 19 years with primary and secondary hypertension. The proportions of abnormal laboratory and imaging tests were compared between primary and secondary hypertension groups. Risk factors for primary vs secondary hypertension were evaluated by logistic regression and likelihood function analysis. Patients with secondary hypertension were younger (5–12 years) and had a higher proportion of abnormal creatinine, renal ultrasound, and echocardiogram findings. There was no significant difference in abnormal results of thyroid function, urine catecholamines, plasma renin, and aldosterone. Abnormal renal ultrasound findings and age were predictors of secondary hypertension by regression and likelihood function analysis. Children aged 5 to 12 years with abnormal renal ultrasound findings and high diastolic blood pressures are at higher risk for secondary hypertension that requires detailed evaluation. *J Clin Hypertens (Greenwich).* 2012; 14:316–321. ©2012 Wiley Periodicals, Inc.

Increasing awareness of hypertension (HTN) has led to heightened focus on pediatric HTN. Most children are identified to have high blood pressures (BP) at their pediatrician's office during routine office visits. Some of these patients are then referred to pediatric subspecialists, mostly pediatric nephrologists, for the evaluation and management of HTN.

Unlike in adults, secondary HTN due to an identifiable cause (most frequently renal or renovascular) is more common in children.[1–4] However, recent studies have reported on the increasing incidence of primary HTN in children.[5–12] This changing landscape is due to the increasing incidence of obesity and associated higher BP trends in children.[8] Routine measurement of BP on well visits as recommended by the American Academy of Pediatrics[13] and longitudinal studies tracking high BPs from adolescence into adulthood have also contributed to the increased focus on pediatric HTN.[14,15] The guidelines of the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents[4] aim to stratify the workup of high BP in children based on age, obesity, and severity of HTN. The recommended routine workup for all children with elevated BP includes serum urea nitrogen (BUN), creatinine, electrolytes, urinalysis, urine culture, complete blood cell count, renal ultrasonography (USG), echocardiogram, and retinal examination. According to these recommendations, children with stage 2 HTN, very young children, and children and adolescents with clinical signs that suggest systemic conditions require more immediate and extensive evaluation than children with stage 1 HTN. The extensive evaluation may include renovascular imaging (technetium dimercaptosuccinic acid [DMSA] scan, magnetic resonance angiography, duplex Doppler flow, 3-dimensional computerized axial tomography scan, and arteriography), plasma renin activity (PRA), plasma and urine steroid levels, and plasma and urine catecholamines.

The choice of these tests varies across practicing physicians and is directed by personal preferences and institutional protocol.[6,16] This could be due to (1) normal examination in most children with HTN,[4] (2) reviews and position papers recommending additional workup based on clinical suspicion,[4,17,18] (3) no definite limit for age cutoff for identifying young children,[4,17,18] and (4) limited studies focusing on evaluation of children with HTN.[6,16]

A study of various investigations performed in hypertensive children may help practitioners to avoid tests that are usually negative, leading to a more cost-effective approach to children with elevated BP. The current study, by evaluating the results of laboratory and imaging tests done in asymptomatic children with elevated BP, aims to identify factors that suggest increased risk for primary vs secondary HTN.

METHODS

The study is a retrospective chart review of patients found to have high BP at their pediatrician's office and then referred to the pediatric nephrology clinic at Children's Hospital of Michigan from January 2002 to December 2005. The study was approved by the Human Investigation Committee at Wayne State University and Research Review Committee at the Detroit Medical Center.

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The study included children between the ages of 5 and 19 years who were diagnosed with primary or secondary HTN. We excluded patients with pre-existing renal, cardiac, neurologic, and endocrine conditions and patients taking medications associated with elevated BP (corticosteroids, β-agonists, oral contraceptives, and stimulant medications in patients with attention deficit hyperactivity disorder). There were 9 patients who were excluded because of medications, 7 patients with neurological disorders, and 2 patients with history of Takayasu arteritis.

Hypertension was defined as systolic and/or diastolic BP ≥95th percentile for age, sex, and height on ≥3 occasions.[4] The BPs were measured after the patient had been sitting quietly for at least 10 minutes, initially by automated electronic device (Dinamap 200×; General Electric Monitoring Systems, Waukesha, WI) and then confirmed by auscultation. Systolic BP was determined by the onset of the Korotkoff sounds and diastolic BP by the disappearance of the same. Stage 1 HTN was defined as per the Fourth Task Force's recommendations.[4] Staging of HTN in the patient population was performed retrospectively based on the BP reading in the pediatric nephrology clinic. Secondary HTN was defined as high BP secondary to an identifiable abnormality causing HTN such as renal artery stenosis, renal scarring, hyperthyroidism, coarctation of the aorta, or pheochromocytoma. Primary HTN was a diagnosis of exclusion, given to patients with high BP and normal investigations in the workup for secondary causes.

Evaluation of patients consisted of a complete history and physical examination. Data collected included age, sex, family history of HTN, symptoms associated with HTN, and body mass index (BMI). *z* Scores were calculated for systolic BP, diastolic BP, and BMI to estimate level of BP elevation and degree of adiposity. Family history was considered positive if at least one parent had a history of HTN. The workup for children with elevated BP included complete blood cell count, electrolytes, BUN, creatinine, PRA, serum aldosterone, thyroid function tests (TFTs) including free thyroxine and thyroid-stimulating hormone; urinalysis, and spot urine catecholamines. Spot urine catecholamines included urine vanillylmandelic acid and homovanillic acid, measured with the use of high-performance liquid chromatography. Imaging studies consisted of a renal USG, echocardiogram, and DMSA scan. Echocardiography was considered abnormal if there was left ventricular hypertrophy (LVH). USG showing single kidneys, asymmetric renal size (size difference in the 2 kidneys of ≥1.5 cm), increased echogenicity, renal or perirenal mass, congenital anomalies including cysts, duplication, or ectopia were grouped as abnormal for data analysis.

SPSS (version 18.0; SPSS, IBM, Armonk, NY) was used for statistical analysis. Chi-square test was used to compare the frequency of normal vs abnormal results of BMI; blood, urine, and imaging tests; and presence of family history and symptoms between patients with primary and secondary HTN. Mann-Whitney test was used to compare age means as well as *z* score means since the distribution was not normal (based on Kolmogorov-Smirnov test).

A binary logistic regression analysis was performed to identify independent variables associated with an increased risk for a diagnosis of primary or secondary HTN (dependent variable). Odds ratios (ORs) calculated by logistic regression analysis were analyzed and variables with ORs >1 and $P<.05$ were associated with increased risk for a diagnosis of secondary HTN. Unlike logistic regression analysis, likelihood function analysis is not affected by sample size as compared with OR obtained via binary logistic regression.[19] Therefore, this statistical analysis was also performed to evaluate the prediction of primary and secondary HTN from normal and abnormal results of the laboratory and imaging investigations. Likelihood ratios (LRs) function using statistical methods based on the Law of Likelihood, which is fundamental to the general issue of interpreting statistical data as evidence. Based on the approach referred as "The Evidential Paradigm," it provides a fundamental structure for presenting and evaluating LRs as measures of statistical evidence for one hypothesis over another. LRs were interpreted as follows: ratios between 1 and 8 = weak evidence, between 8 and 32 = moderate evidence, and >32 = strong evidence.[19]

RESULTS

There were 167 patients included in the study: 110 with primary HTN and 57 with secondary HTN. Primary HTN accounted for 55% (n=36) of the patients in the 5- to 12-year age group. Patients with secondary HTN (5–19 years; n=57) included 45 patients (78.9%) with renal scarring, 7 patients (12.3%) with renal artery stenosis, and 1 patient (1.8%) each with a single kidney, aortic coarctation, juxtaglomerular tumor, pheochromocytoma, and hyperthyroidism.

The demographics, family history, symptoms, and HTN stages for the 167 patients are shown in Table I. The majority of patients with primary HTN were male (69.1%), whereas those with secondary HTN had a slight female predominance (54.4%) ($P<.01$). Patients with primary HTN were older (13.3±3.23 years) than patients with secondary HTN (11.7±3.57 years) ($P<.01$). The overall mean age of the patients was 12.79 years (±3.43). A higher proportion of children with primary HTN had a positive family history of HTN ($P=.01$), stage 1 HTN ($P=.03$), and older age group (12–19 years) ($P=.02$) on presentation. Of note, frequency of overweight and obese children did not differ in the primary (75.5%) vs secondary (61.4%) HTN groups ($P=.73$).

Table II shows a comparison of *z* scores for systolic and diastolic BP, as well as BMI between patients with primary and secondary HTN according to age group. Patients with secondary HTN who were in the older

TABLE I. Demographics, Family History, Symptoms, and Hypertension Stages in Patients With Primary and Secondary HTN

	Primary HTN (n=110)	Secondary HTN (n=57)	*P* Value
Age, mean (SD), y	13.3 (3.23)	11.7 (3.57)	<.01
Age 5–12 y, No. (%)	36 (32.7)	30 (52.6)	.02
Age 12–19 y, No. (%)	74 (67.3)	27 (47.4)	
Male, No. (%)	76 (69.1)	26 (45.6)	<.01
Female, No. (%)	34 (30.9)	31 (54.4)	
African American, No. (%)	71 (64.5)	35 (61.4)	
Caucasian, No. (%)	32 (29.1)	19 (33.3)	
Other, No. (%)	7 (6.4)	3 (5.3)	
Positive family history of HTN, No. (%)	45 (42.1)	11 (19.6)	.01
Headache, No. (%)	35 (31.8)	21 (36.8)	.60
Vision changes, No. (%)	2 (1.8)	2 (1.8)	1.00
BMI ≥85th percentile, No. (%)	83 (75.5)	35 (61.4)	.73
HTN stage 1, No. (%)	54 (49.1)	18 (31.6)	.03
HTN stage 2, No. (%)	56 (50.9)	39 (68.4)	

Abbreviations: BMI, body mass index; HTN, hypertension; SD, standard deviation.

TABLE II. Comparison of *z* Scores of SBP, DBP, and BMI Between Patients With Primary and Secondary HTN

	Primary HTN, Mean (SD)	Secondary HTN, Mean (SD)	*P* Value
SBP			
Age 5–11.9 y	−0.41 (0.84)	−0.11 (1.06)	NS
Age 12–19 y	0.04 (0.80)	0.56 (1.33)	NS
DBP			
Age 5–11.9 y	−0.26 (0.98)	0.09 (1.23)	NS
Age 12–19 y	−0.16 (0.72)	0.67 (1.13)	.001
BMI			
Age 5–11.9 y	−0.12 (0.92)	−0.51 (0.81)	NS
Age 12–19 y	−0.28 (1.08)	−0.04 (0.84)	NS

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HTN, hypertension; NS, not significant; SBP, systolic blood pressure; SD, standard deviation.

age group had significantly higher diastolic BP *z* scores as compared with older patients with primary HTN.

As seen in Table III, abnormal creatinine (P=.01), abnormal electrolytes (P=.04), USG (P<.01), and echocardiography (P=.03) were significantly higher in children with secondary HTN, while abnormal results on other laboratory tests did not show significant differences between the primary and secondary HTN groups. Patients with primary HTN with abnormal PRA had detailed investigations such as magnetic resonance imaging/angiography, DMSA scan, or renal arteriography to rule out renovascular causes of elevated BP. The one patient in this group who had abnormal spot urine catecholamines had 24-hour urine

TABLE III. Frequency of Abnormal Results on Laboratory and Imaging Tests in Patients With Primary and Secondary Hypertension

	Primary Hypertension (n=110), No. (%)	Secondary Hypertension (n=57), No. (%)	*P* Value
Electrolytes	0 (0)	3 (5.4)	.04
Creatinine	0 (0)	4 (7.0)	.01
Thyroid function tests	0 (0)	2 (4.3)	.11
Plasma renin activity	10 (13.3)	9 (23.1)	.19
Aldosterone	0 (0)	2 (5.6)	.10
Spot urine catecholamines	1 (1.5)	2 (5.1)	.56
Urinalysis	2 (1.9)	3 (5.4)	.34
Renal ultrasonography	10 (10.2)	19 (34.5)	.001
Echocardiography	16 (17.2)	16 (34.0)	.03

for catecholamines performed, which showed normal results. The two patients with abnormal urinalysis (proteinuria) were treated as having primary HTN for the study duration. However, these patients later developed overt nephritis and were therefore excluded from regression and *z* score analysis.

Results of USG are displayed in Table IV. Some patients with primary HTN had abnormal USG findings, which included asymmetry, simple cysts, duplication of collecting system, and increased echogenicity. The patient who had renal asymmetry had a DMSA scan performed, which did not show any scarring, and arteriography, which was normal. The details of the results of renal imaging of some of the patients were not available as they were performed at other institutions.

ORs calculated by logistic regression showed an increased risk for diagnosing secondary HTN associated with young age (5–11.9 years), elevated diastolic BP in older patients, and abnormal USG. Hypertension stage, BMI, family history, echocardiography, and systolic BP did not have statistically significant risk for diagnosing secondary HTN. Similar results were seen with LR analysis. LR for abnormal USG results

TABLE IV. Renal Ultrasound Findings in Primary and Secondary Hypertension

	Primary (n=99)	Secondary (n=54)
Normal	88	36
Asymmetry	1	8
Congenital anomalies		
Simple cysts	1	1
Duplication of collecting system	4	2
Ectopia	0	1
Increased echogenicity	4	4
Single kidney	0	1
Renal or perirenal mass	0	2

TABLE V. HTN Factors Associated With Increased Risk of Secondary

	Logistic Regression		Likelihood Function Analysis
Variable	OR (95% CI)	*P* Value	LR
Abnormal RUS findings	4.89 (1.99–12.01)	.001	742.9
DBP *z* score[a]	3.33 (1.49–7.46)	.003	–
Young age (5–11.9 y)	2.22 (1.09–4.53)	.03	22.9

Abbreviations: DBP, diastolic blood pressure; OR, odds ratio (OR >1 and *P*<.05 statistically significant); LR, likelihood ratio (between 1 and 8 = weak evidence, between 8 and 32 = moderate evidence, and >32 = strong evidence); RUS, renal ultrasound. [a]For the 12- to 19-year-old age group.

(LR=742) showed strong statistical evidence (LR >32), while LR for young age (LR=22.9) showed moderate statistical evidence for diagnosing secondary HTN (Table V).

DISCUSSION

Hypertension is one of the most commonly diagnosed medical conditions in the United States.[20] Given the significant long-term complications of uncontrolled BP and tracking of BP from childhood to adults, evaluation and management of children with elevated BP has significant clinical and financial implications. This is because unlike adults, children usually undergo a more extensive workup to look for secondary causes of HTN.[21]

Our study cohort consisted of otherwise healthy children aged 5 to 19 years with elevated BP referred to a pediatric nephrology clinic for evaluation, who, after a detailed evaluation, were diagnosed with either primary or secondary HTN. These patients in the authors' opinion were representative of the growing patient population in whom health care providers need to increasingly decide about investigations to evaluate secondary causes of HTN. The study aimed at evaluating the clinically relevant information obtained from various tests (laboratory and imaging) peformed to differentiate secondary vs primary HTN in asymptomatic children with elevated BP readings. This would help in streamlining the evaluation of increasing number of children with elevated BP and avoiding tests with negative results, with resulting cost benefits in the workup of these patients.

The Fourth Task Force Report recommends stratifying evaluation of children with elevated BP, based on classification of HTN as stage 1 or 2, ''young age,'' and whether the children are overweight or not.[4] The current study reports increased risk for secondary HTN in children younger than 12 years. This adds important information to the Task Force recommendations as there is no definition for ''young age'' in the report. Furthermore, nearly 51% of the patients with primary HTN had stage 2 HTN at presentation and, based on the recommendations of the Task Force Report, would qualify for extensive evaluation with questionable relevance to clinical management.

A recent study evaluating investigations performed for workup of HTN across 4 tertiary pediatric nephrology centers reported that BUN, serum creatinine, electrolytes, and urinalysis were the most common laboratory tests performed in patients with primary HTN; other investigations such as PRA, serum aldosterone, USG, urine catecholamines, and DMSA scan varied across centers.[6] Another study, performed after the Fourth Task Force Report of 2004, surveyed general pediatricians regarding the evaluation and treatment of HTN and reported that >50% of pediatricians order chemistry panel, urinalysis, complete blood cell count, lipid panel, and TFT for evaluation of children with HTN, while <10% ordered an echocardiogram.[16] This variability in the evaluation of children with elevated BP, although reflective of the prevalent practice patterns, is also a limitation of the current study.

In keeping with the recommendations of the Fourth Task Force Report, a USG should be performed in all patients with elevated BP. However, the use of USG in evaluating children with primary HTN ranged from 25% to 95% in a multicenter study involving 4 tertiary care centers.[6] Another study also reported that a routine USG was ordered by only 20% of the pediatricians for children with elevated BP.[16] Identification of asymmetry of the kidneys (>1.5 cm difference in length), single kidney, or a renal or perirenal mass were the relevant findings identified in patients with secondary HTN (Table IV). USG, although not a good imaging modality for detecting renal scars,[22,23] can potentially identify the need for further imaging. Findings such as small kidney size or asymmetry of the kidneys should prompt further investigations such as DMSA, which is more accurate for identification of renal scarring.[24] In our group of patients with secondary HTN, renal scarring was the most common cause of HTN. Renal scarring is considered a common secondary cause of HTN in children.[23,25] In our opinion, DMSA is a useful investigation in children with HTN and should be considered in patients younger than 12 years, patients with history of urinary tract infections, and children with abnormal USG findings.

In the older age group (12–19 years old), *z* scores for diastolic BP were found to be significantly higher in patients with secondary HTN (Table II). This is consistent with previous reports that have found that children with secondary causes of HTN have higher diastolic BPs compared with children with primary HTN.[26]

In our study, the frequency of abnormal values of TFT, serum aldosterone, spot urine catecholamines, and urinalysis was low and not statistically different between patients with primary and secondary HTN. The frequency of abnormal values of these tests was compared between patients with stage 1 and stage 2

HTN and there was also no difference (data not shown). The yield of investigations such as urine catecholamines and TFT is low in otherwise healthy asymptomatic children with HTN and should be performed when there is a clinical suspicion of these conditions. Both pheochromocytoma and hyperthyroidism are more likely to present with obvious clinical signs and symptoms in addition to high BP. Spot urine catecholamines have been reported to be as effective as 24-hour urine collections for the diagnosis of neuroblastoma.[27] Pheochromocytoma, on the other hand, usually presents with other signs of disease such as episodes of palpitations, dizziness, and flushing, and, without a strong clinical suspicion, urine catecholamine testing is not useful for diagnosis.[28]

In the initial workup of asymptomatic apparently healthy children who present with HTN, we recommend checking electrolytes and renal function. Baseline values of these tests are helpful when starting antihypertensive medications such as angiotensin-converting enzyme inhibitors and thiazide diuretics, which can affect these tests. A urinalysis should also be part of the workup since proteinuria can be present in long-standing uncontrolled HTN, indicating end organ damage, and in renal scarring.

Presence of LVH on echocardiography was significantly more common in patients with secondary HTN; however, patients with LVH did not have an increased risk of secondary HTN in the binary logistic regression or likelihood function analysis.

Despite 16.7% of study patients having abnormal PRA values, the frequency of abnormal PRA did not differ significantly between primary and secondary HTN groups. Furthermore, detailed renovascular imaging including arteriogram was performed in these patients to rule out renovascular causes of HTN. Although PRA is not helpful to distinguish between primary and secondary HTN according to our results, it could be useful for tailoring antihypertensive treatment. Laragh and colleagues proposed that hypertensive patients with elevated PRA are better candidates for antihypertensive agents that target the renin angiotensin system (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers),[29,30] as opposed to patients with suppressed PRA secondary to sodium and volume excess who would respond better to diuretic therapy.

The current practice of most pediatric health care providers is to routinely order a panel of blood tests and imaging studies in the initial evaluation of a hypertensive patient based on personal preferences and institutional protocols. In keeping with the principles of the Fourth Task Force Report,[4] the current study is an attempt to stratify the workup of children with elevated BP. We agree with the recommendations of the Task Force in including electrolytes, BUN, creatinine, USG, and echocardiogram in all children with elevated BP. The Task Force makes no recommendation to the age of children who require detailed investigations[4]; however, according to our study, children aged 5 to 12 years with an initially abnormal USG finding are at high risk for secondary HTN and require a more detailed evaluation. The study reports for the first time that routine spot urine catecholamines and TFT provide little information in asymptomatic children with elevated BP, even in children presenting with stage 2 HTN, and their use should be restricted to patients with relevant clinical findings. Although limited by its retrospective nature, our study findings provide a starting framework for pediatric health care providers for children with elevated BP in the office setting. The study findings may help in providing a more cost-effective approach towards children with elevated BP, until prospective studies focusing on evaluation of asymptomatic children with elevated BP are conducted.

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