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EDITORIAL COMMENTARY

Diagnostic evaluation of the hypertensive child

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Global estimates of childhood hypertension show a prevalence of 4%, peaking in young adolescents aged 13–15 years old at 7.1–7.9% [1]. During the last decade, several scientific organizations have focused their actions on the diagnosis and management of hypertension in children and adolescents updating their previously published guidelines, including recommendations about the young in the adult guidelines, or publishing separate consensus documents [2–6]. The diagnostic evaluation of the hypertensive child, a key issue in all documents, includes screening for secondary causes of hypertension, assessment of cardiovascular risk, and hypertension mediated organ damage (HMOD). As there is absence of robust evidence to balance between proper testing and unnecessary investigations, significant variance exists among guidelines on the recommendations and/or grading for the initial diagnostic investigations after diagnosis of hypertension is established (Table 1). In the current issue of *Pediatric Nephrology*, Ding et al. provide new evidence for the utility of different diagnostic tests for the initial evaluation of hypertensive children and adolescents by retrospective data analysis in a tertiary pediatric nephrology center in Canada [7].

Etiology of pediatric hypertension

Secondary hypertension was found in about half (56.3%) of the children in the study by Ding et al. diagnosed with hypertension based on office or ambulatory blood pressure measurements [7]. Among key findings of the study is the high, top-ranged, diagnostic yield of kidney ultrasound for hypertension etiology in all children, independent of age and presence of obesity, while routinely performed laboratory investigations, including creatinine and urinalysis, did not significantly contribute to underlying etiology diagnosis.

Although primary hypertension is a growing problem in the context of the increased global incidence of pediatric obesity, secondary causes of hypertension should be considered in children and adolescents. In studies conducted at primary care clinics or school-based screening studies, the prevalence of secondary hypertension was found to be 3.7–9.0% compared to 20–44% in subspecialty referral clinics [8]. Underlying kidney etiology, parenchymal or vascular are the more prevalent causes of secondary hypertension in childhood [9, 10].

Indications for screening for secondary hypertension

Indications for further evaluation of hypertensive children and adolescents for underlying disorders and proper diagnostic evaluation are similar among different scientific organizations for children younger than 6 years. Children younger than 6 years old are at high risk for secondary hypertension and should undergo screening tests for underlying kidney disease including kidney ultrasound (Table 1). Preterm birth showed significant associations with hypertension in observational studies in childhood [11], and has been reported to be a risk factor for secondary hypertension in previous studies [12]. Higher grade of hypertension, stage 2 hypertension, is also considered a risk factor for an underlying pathology and an indication for screening for secondary hypertension in the European Society Hypertension (ESH) guidelines [2, 6]. The American Academy Pediatrics (AAP) 2017 guidelines, highlight that diastolic hypertension, rather than the severity of blood pressure elevation, is more predictive of secondary hypertension based on the results of observational studies [10, 13]. In the AAP 2017 guideline, it is recommended that obese children, older than 6 years old, having positive family history of hypertension, and no signs of underlying cause would not require extensive evaluation for secondary causes [3]. However, the study by Ding et al. showed a high prevalence (36.9%) of secondary

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Table 1 Recommendations for the initial diagnostic evaluation of children with hypertension

	ESH 2016 [2]	AAP 2017 [3]	Hypertension Canada 2020 [4]	Joint statement of HyperChildNET and EAP 2023 [5]	ESH 2023 [6]
Chemistry panel (electrolytes, BUN, serum creatinine)	All children with HTN	All children with HTN (not graded)	All children with HTN (grade D)	All children with HTN (not graded)	All children with HTN (not graded)
Urinalysis	All children with HTN	All children with HTN (not graded)	All children with HTN (grade D)	All children with HTN (not graded)	All children with HTN (not graded)
Kidney ultrasound	All children with HTN	Children < 6 years of age or those with abnormal kidney function or urinalysis (not graded)	All children with HTN (Grade D)	All children with HTN (not graded)	All children with HTN (not graded)
Lipid profile	All children with HTN	All children with HTN (not graded)	All children with HTN (grade C)	All children with HTN (not graded)	All children with HTN (not graded)
Fasting glucose	All children with HTN	At risk for diabetes (not graded)	All children with HTN	All children with HTN (not graded)	All children with HTN (not graded)
Echocardiography	All children with HTN at diagnosis	All children with HTN at initiation of pharmacological treatment (grade C, moderate recommendation)	All children with HTN (grade C)	All children with HTN at diagnosis (grade B)	All children with HTN at diagnosis (not graded)
Retinal examination	In symptomatic children, encephalopathy or malignant HTN	No recommendation	All children with HTN (grade C)	In severe HTN/HTN emergency (grade C)	In severe HTN/HTN emergency (not graded)
Proteinuria/microalbuminuria	All children with HTN	Microalbuminuria is not recommended in children with primary HTN (grade C, moderate recommendation) Proteinuria is recommended in children with CKD (grade B, strong recommendation)	All children with HTN albumin/creatinine ratio (grade C)	All children with HTN (grade D)	All children with HTN (not graded)

ESH European Society Hypertension, *AAP* American Academy Pediatrics, *EAP* European Academy Paediatrics, *HTN* hypertension

hypertension even in adolescents > 12 years old [7] and highlighted the diagnosis of secondary hypertension in half of the children with traditional risk factors, overweight, and obesity, challenging the AAP 2017 recommendations.

Diagnostic tests for secondary hypertension

History and clinical examination are recommended to guide patient-specific diagnostic evaluation beyond initial laboratory tests including creatinine, blood urea nitrogen (BUN), electrolytes, and urinalysis that should be offered to all children [2–6]. A targeted, cost-saving approach with regard to initial laboratory testing for evaluation of secondary causes of hypertension has been evaluated by different published guidelines. In this concept, the AAP 2017 guideline updated the Fourth Report recommendation for kidney ultrasound and recommended it to be performed only for children younger than 6 years old and those with abnormal creatinine levels or urinalysis [3]. However, in the study by Ding et al., neither creatinine nor urinalysis were sensitive markers of underlying kidney pathology supporting the results of previous studies [10, 14]. Kidney scars, cysts, small-sized or dysplastic kidneys, or solitary kidney may underlie the pathogenesis of secondary hypertension without any laboratory sign of abnormal kidney function [15, 16]. Moreover, in older children, kidney ultrasound may give clues for the presence of renovascular hypertension [17]. Although kidney ultrasound is subjective to operator experience and skills, its role in the detection of asymptomatic underlying kidney pathology is vital for early detection and appropriate clinical decision-making. Once chronic kidney disease (CKD) is diagnosed, preventive measures may start to slow the progression of disease and the importance of strict blood pressure control has been established by strong evidence [18]. Thus, the study by Ding et al. revisits the utility of kidney ultrasound in the initial screening of hypertensive children for underlying etiology, supporting ESH, European Academy Paediatrics (EAP) and Canadian guideline recommendations for it to be performed in all children with hypertension.

Further urine testing with urine albumin-to-creatinine ratio (ACR) and protein-to-creatinine ratio (PCR) were performed in low numbers of patients in the Ding et al. study limiting the evaluation of the diagnostic yield of these tests. Of note, a large meta-analysis shows high diagnostic value of PCR for the diagnosis of underlying kidney pathology in hypertensive children [12].

In the study by Ding et al., DMSA was performed in a subset of children showing a high diagnostic yield for secondary hypertension [7]. However, this testing indication was guided by history of recurrent urinary tract infections or dysplastic kidneys and maybe useful for the detection of kidney scars in hypertensive children with related history or in case of unexplained hypertension despite normal ultrasound [19].

Diagnostic testing in obese hypertensive children

School screening studies, as well as cross-sectional studies, showed higher prevalence of primary hypertension in obese children [20–22]. On the other hand, several studies have shown that the obesity epidemic also affects children with all CKD stages [23]. Ding et al. showed that obese children with hypertension may benefit from kidney ultrasound testing, as it presented a high diagnostic yield for underlying kidney abnormalities in obese similar to non-obese children.

Ding et al. also showed that the yield of lipid profile testing is high only in obese hypertensive children, supporting extensive cardiovascular risk assessment only in obese patients. This is line with the recent Pediatric Renal Nutrition Taskforce clinical practice recommendations focusing on obesity and metabolic syndrome in children with CKD, highlighting the role of assessment for metabolic abnormalities in case of overweight or obesity [23].

Assessment of cardiovascular risk and HMOD

Beyond obesity, family history of cardiovascular, or dyslipidemia could also guide lipid screening in all hypertensive children [24]. Nevertheless, while the evidence remains low, evolving longitudinal cohort data show the adverse role of multiple cardiovascular risk factors on atherosclerotic cardiovascular disease in early adulthood [25], favoring consensus recommendations for lipid and glucose screening for the cardiovascular risk assessment of all hypertensive children (Table 1).

Assessment for HMOD offers important information on the individual cardiovascular risk and could guide clinical decisions from diagnosis with regard to intensity of non-pharmacological treatment, time to wait for initiation of pharmacological treatment, and choice of drug [26]. Echocardiography is recommended by all published guidelines for the evaluation of left ventricular hypertrophy (LVH), which is the hallmark HMOD in childhood. It should be underlined that echocardiography is the gold standard for the diagnosis of LVH in children as, in contrast to adults, electrocardiography (ECG) has low sensitivity in children for the assessment of LVH [3]. Ding et al. confirmed that echocardiography has very high diagnostic yield for the identification of HMOD. This is in line with numerus studies and recent meta-analysis that support the close association of blood pressure elevation in childhood and indices of LVH assessed by echocardiography [27, 28]. The role of

left ventricular systolic and diastolic function parameters assessed by echocardiography needs to be established.

Conclusion and perspectives

The study by Ding et al. emphasizes the high diagnostic utility of kidney ultrasound in the initial evaluation of hypertension underlying etiology, as well as echocardiography for the assessment of HMOD, drawing attention to related controversial issues among guidelines [7]. Controversies may pose significant challenges in the implementation of recommendations into routine clinical practice and could result in low compliance of the attending physicians with the guidelines. Variations in practice will also inevitably and appropriately occur when taking into account availability or cost of a test and insurance aspects, further affecting the implementation of the recommendations. In confirmation of these concerns, recent data from the USA show that among children evaluated for hypertension in primary care only 2% had appropriate screening laboratory tests conducted, and none had a kidney ultrasound performed [29].

The study by Ding et al. may have several limitations being retrospective and performed at a tertiary nephrology center which may have resulted in a high prevalence of secondary hypertension and possibly referral bias. When blood pressure screening is performed at population level as in school-based screening studies, the prevalence of secondary hypertension is lower. Given the high rates of underrecognized pediatric hypertension, referred patients may have more pronounced symptomatology, risk factors, comorbidities, or greater parent anxiety and compliance with medical appointments [29, 30]. However, the main research question which the study is attempting to answer is what the initial testing would be in children after hypertension diagnosis. Currently, all guidelines address their recommendations to primary care physicians and subspeciality centers. Whether referring or testing at primary care, the target population for initial screening is the same, children with established hypertension identified by blood pressure measurement.

While strong recommendations on the basis of robust, high-quality data from multiple randomized controlled trials showing evidence of benefit that outweighs harm from diagnostic tests are desperately needed, efforts may focus on the implementation of diagnostic approaches with the intent of identifying and managing underlying etiology in asymptomatic hypertensive children, limiting or preventing cardiovascular or kidney complications for the best health care of children and adolescents with high blood pressure.

Declarations

Conflict of interest The authors declare no competing interests.

References

1. Song P, Zhang Y, Yu J, Zha M, Zhu Y, Rahimi K, Rudan I (2019) Global prevalence of hypertension in children: a systematic review and meta-analysis. JAMA Pediatr 173:1154–1163
2. Lurbe E, Agabiti-Rosei E, Cruickshank JK, Dominiczak A, Erdine S, Hirth A, Invitti C, Litwin M, Mancia G, Pall D, Rascher W, Redon J, Schaefer F, Seeman T, Sinha M, Stabouli S, Webb NJ, Wühl E, Zanchetti A (2016) 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J Hypertens 34:1887–1920
3. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, de Ferranti SD, Dionne JM, Falkner B, Flinn SK, Gidding SS, Goodwin C, Leu MG, Powers ME, Rea C, Samuels J, Simasek M, Thaker VV, Urbina EM, Subcommittee on screening and management of high blood pressure in children (2017) Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics 140:e20171904
4. Rabi DM, McBrien KA, Sapir-Pichhadze R, Nakhla M, Ahmed SB, Dumanski SM, Butalia S, Leung AA, Harris KC, Cloutier L, Zarnke KB, Ruzicka M, Hiremath S, Feldman RD, Tobe SW, Campbell TS, Bacon SL, Nerenberg KA, Dresser GK, Fournier A, Burgess E, Lindsay P, Rabkin SW, Prebtani APH, Grover S, Honos G, Alfonsi JE, Arcand J, Audibert F, Benoit G, Bittman J, Bolli P, Côté AM, Dionne J, Don-Wauchope A, Edwards C, Firoz T, Gabor JY, Gilbert RE, Grégoire JC, Gryn SE, Gupta M, Hannah-Shmouni F, Hegele RA, Herman RJ, Hill MD, Howlett JG, Hundemer GL, Jones C, Kaczorowski J, Khan NA, Kuyper LM, Lamarre-Cliche M, Lavoie KL, Leiter LA, Lewanczuk R, Logan AG, Magee LA, Mangat BK, McFarlane PA, McLean D, Michaud A, Milot A, Moe GW, Penner SB, Pipe A, Poppe AY, Rey E, Roerecke M, Schiffrin EL, Selby P, Sharma M, Shoamanesh A, Sivapalan P, Townsend RR, Tran K, Trudeau L, Tsuyuki RT, Vallée M, Woo V, Bell AD, Daskalopoulou SS (2020) Hypertension Canada's 2020 comprehensive guidelines for the prevention, diagnosis, risk assessment, and treatment of hypertension in adults and children. Can J Cardiol 36:596–624
5. Wühl E, Calpe J, Drożdż D, Erdine S, Fernandez-Aranda F, Hadjipanayis A, Hoyer PF, Jankauskiene A, Jiménez-Murcia S, Litwin M, Mancia G, Mazur A, Pall D, Seeman T, Sinha MD, Simonetti G, Stabouli S, Lurbe E (2023) Joint statement for assessing and managing high blood pressure in children and adolescents: Chapter 2. How to manage high blood pressure in children and adolescents. Front Pediatr 11:1140617
6. Mancia Chairperson G, Kreutz Co-Chair R, Brunström M, Burnier M, Grassi G, Januszewicz A, Muiesan ML, Tsioufis K, Agabiti-Rosei E, Algharably EAE, Azizi M, Benetos A, Borghi C, Hitij JB, Cifkova R, Coca A, Cornelissen V, Cruickshank K, Cunha PG, Danser AHJ, de Pinho RM, Delles C, Dominiczak AF, Dorobantu M, Doumas M, Fernández-Alfonso MS, Halimi JM, Járai Z, Jelaković B, Jordan J, Kuznetsova T, Laurent S, Lovic D, Lurbe E, Mahfoud F, Manolis A, Miglinas M, Narkiewicz K, Niiranen T, Palatini P, Parati G, Pathak A, Persu A, Polonia J, Redon J, Sarafidis P, Schmieder R, Spronck B, Stabouli S, Stergiou G, Taddei S, Thomopoulos C, Tomaszewski M, Van de Borne P, Wanner C, Weber T, Williams B, Zhang ZY, Kjeldsen SE, Authors/Task Force Members (2023) 2023 ESH guidelines for the management of arterial hypertension The Task Force for the management of

arterial hypertension of the European Society of Hypertension Endorsed by the European Renal Association (ERA) and the International Society of Hypertension (ISH). J Hypertens. https://doi.org/10.1097/HJH.0000000000003480
7. Ding FL, Elias I, Wright R, De Mello A, Cojocaru D, Dionne J (2023) Yield of diagnostic testing in evaluating etiology and end organ effects of pediatric hypertension. Pediatr Nephrol. https://doi.org/10.1007/s00467-023-06101-x
8. Nugent JT, Young C, Funaro MC, Jiang K, Saran I, Ghazi L, Wilson FP, Greenberg JH (2022) Prevalence of secondary hypertension in otherwise healthy youths with a new diagnosis of hypertension: a meta-analysis. J Pediatr 244:30–37.e10
9. Gupta-Malhotra M, Banker A, Shete S, Hashmi SS, Tyson JE, Barratt MS, Hecht JT, Milewicz DM, Boerwinkle E (2015) Essential hypertension vs. secondary hypertension among children. Am J Hypertens 28:73–80
10. Baracco R, Kapur G, Mattoo T, Jain A, Valentini R, Ahmed M, Thomas R (2012) Prediction of primary vs secondary hypertension in children. J Clin Hypertens (Greenwich) 14:316–321
11. Chainoglou A, Chrysaidou K, Kotsis V, Stabouli S (2022) Preterm birth, kidney function and cardiovascular disease in children and adolescents. Children (Basel) 9:1130
12. Nugent JT, Jiang K, Funaro MC, Saran I, Young C, Ghazi L, Bakhoum CY, Wilson FP, Greenberg JH (2023) Does this child with high blood pressure have secondary hypertension?: the rational clinical examination systematic review. JAMA 329:1012–1021
13. Flynn J, Zhang Y, Solar-Yohay S, Shi V (2012) Clinical and demographic characteristics of children with hypertension. Hypertension 60:1047–1054
14. Wiesen J, Adkins M, Fortune S, Horowitz J, Pincus N, Frank R, Vento S, Hoffman C, Goilav B, Trachtman H (2008) Evaluation of pediatric patients with mild-to-moderate hypertension: yield of diagnostic testing. Pediatrics 122:e988-993
15. Siomou E, Giapros V, Papadopoulou F, Pavlou M, Fotopoulos A, Siamopoulou A (2014) Growth and function in childhood of a normal solitary kidney from birth or from early infancy. Pediatr Nephrol 29:249–256
16. Toffolo A, Ammenti A, Montini G (2012) Long-term clinical consequences of urinary tract infections during childhood: a review. Acta Paediatr 101:1018–1031
17. Makhija P, Wilson C, Garimella S (2018) Utility of Doppler sonography for renal artery stenosis screening in obese children with hypertension. J Clin Hypertens (Greenwich) 20:807–813
18. Wuhl E, Trivelli A, Picca S, Litwin M, Peco-Antic A, Zurowska A, Testa S, Jankauskiene A, Emre S, Caldas-Afonso A, Anarat A, Niaudet P, Mir S, Bakkaloglu A, Enke B, Montini G, Wingen AM, Sallay P, Jeck N, Berg U, Caliskan S, Wygoda S, Hohbach-Hohenfellner K, Dusek J, Urasinski T, Arbeiter K, Neuhaus T, Gellermann J, Drozdz D, Fischbach M, Moller K, Wigger M, Peruzzi L, Mehls O, Schaefer F (2009) Strict blood-pressure control and progression of renal failure in children. N Engl J Med 361:1639–1650
19. Ahmed M, Eggleston D, Kapur G, Jain A, Valentini RP, Mattoo TK (2008) Dimercaptosuccinic acid (DMSA) renal scan in the evaluation of hypertension in children. Pediatr Nephrol 23:435–438
20. Nika T, Stabouli S, Kollios K, Papadopoulou-Legbelou K, Printza N, Antza C, Papachristou F, Kotsis V (2019) Obesity and season as determinants of high blood pressure in a school-based screening study. J Hum Hypertens 33:277–285
21. Gomes RS, Quirino IG, Pereira RM, Vitor BM, Leite AF, Oliveira EA, Simões e Silva AC (2011) Primary versus secondary hypertension in children followed up at an outpatient tertiary unit. Pediatr Nephrol 26:441–447
22. Flynn JT, Alderman MH (2005) Characteristics of children with primary hypertension seen at a referral center. Pediatr Nephrol 20:961–966
23. Stabouli S, Polderman N, Nelms CL, Paglialonga F, Oosterveld MJS, Greenbaum LA, Warady BA, Anderson C, Haffner D, Desloovere A, Qizalbash L, Renken-Terhaerdt J, Tuokkola J, Walle JV, Shaw V, Mitsnefes M, Shroff R (2022) Assessment and management of obesity and metabolic syndrome in children with CKD stages 2–5 on dialysis and after kidney transplantation-clinical practice recommendations from the Pediatric Renal Nutrition Taskforce. Pediatr Nephrol 37:1–20
24. Maliachova O, Stabouli S (2018) Familial hypercholesterolemia in children and adolescents: diagnosis and treatment. Curr Pharm Des 24:3672–3677
25. Jacobs DR Jr, Woo JG, Sinaiko AR, Daniels SR, Ikonen J, Juonala M, Kartiosuo N, Lehtimäki T, Magnussen CG, Viikari JSA, Zhang N, Bazzano LA, Burns TL, Prineas RJ, Steinberger J, Urbina EM, Venn AJ, Raitakari OT, Dwyer T (2022) Childhood cardiovascular risk factors and adult cardiovascular events. N Engl J Med 386:1877–1888
26. Lurbe E, Litwin M, Pall D, Seeman T, Stabouli S, Webb NJA, Wühl E (2018) Insights and implications of new blood pressure guidelines in children and adolescents. J Hypertens 36:1456–1459
27. Goulas I, Evripidou K, Doundoulakis I, Kollios K, Nika T, Chainoglou A, Kotsis V, Stabouli S (2023) Prevalence of masked hypertension and its association with left ventricular hypertrophy in children and young adults with chronic kidney disease: a systematic review and meta-analysis. J Hypertens 41:699–707
28. Goulas I, Farmakis I, Doundoulakis I, Antza C, Kollios K, Economou M, Kotsis V, Stabouli S (2022) Comparison of the 2017 American Academy of Pediatrics with the fourth report and the 2016 European Society of Hypertension guidelines for the diagnosis of hypertension and the detection of left ventricular hypertrophy in children and adolescents: a systematic review and meta-analysis. J Hypertens 40:197–204
29. Rea CJ, Brady TM, Bundy DG, Heo M, Faro E, Giuliano K, Goilav B, Kelly P, Orringer K, Tarini BA, Twombley K, Rinke ML (2022) Pediatrician adherence to guidelines for diagnosis and management of high blood pressure. J Pediatr 242:12-17.e11
30. Stabouli S, Sideras L, Vareta G, Eustratiadou M, Printza N, Dotis J, Kotsis V, Papachristou F (2015) Hypertension screening during healthcare pediatric visits. J Hypertens 33:1064–1068