Renal Hypertension and Cardiovascular Disorder in Children with Chronic Kidney Disease

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SUMMARY
Renal hypertension is one of the earliest and the most prevalent complications of pediatric chronic kidney disease (CKD). Among renal patients, hypertension is frequently underdiagnosed and undertreated. For casual blood pressure measurement, the best method is auscultatory, while for ambulatory blood pressure measurement, oscillometric method is the most commonly used. Both casual and ambulatory blood pressure measurement provide more powerful means of diagnosing hypertension. Masked hypertension is a condition in which casual blood pressure is normal but ambulatory blood pressure is elevated. The risk of cardiovascular morbidity and mortality is higher with masked hypertension as compared to the controls. Children and adolescents with CKD are at high risk of cardiovascular disease that has been established as the leading cause of death in patients with end stage renal disease. Left ventricular hypertrophy remains the most thoroughly documented form of end-organ damage caused by hypertension in children and adolescents with CKD. Based on clear evidence on the correlation between blood pressure and cardiovascular morbidity, mortality, and renal function, renal hypertension must be aggressively treated. Target blood pressure for patients with renal hypertension should be at low normal values: <75 percentile for patients without proteinuria and <50 percentile for patients with proteinuria. Renin-angiotensin system antagonists are considered the first choice pharmacological option in hypertensive CKD 2-4 patients while the management of volume overload is the most important in dialysis patients. Successful transplantation can eliminate or significantly improve uremia-related cardiovascular risk factors and increase predicted life expectancy.

Keywords: chronic renal failure; cardiovascular disorders; left ventricular hypertrophy; children

INTRODUCTION
In contrast to adults, secondary forms of arterial hypertension predominate in infancy and childhood but, as adolescence approaches, there is a higher incidence of essential hypertension [1]. Renal hypertension is the most common (approximately 85%) identifiable secondary hypertension in children. It is one of the earliest and most prevalent complications of pediatric chronic kidney disease (CKD). Over a half of all children have hypertension even in early CKD, increasing up to 50-75% in CKD stage 5, and 50-78% in transplanted patients [2]. Long-standing and uncontrolled hypertension is associated with progression of CKD and development of early cardiomyopathy and vascular damage and re-modeling [3]. Aggressive treatment of hypertension is necessary not just to prevent the development of cardiovascular disorder (CVD), but also to improve renal survival in CKD patients. The current review focuses on the early identification and management of hypertensive disease in renal patients during childhood.

UNDERLYING DISEASE
Renal parenchymal disease
Renal hypertension occurs most frequently in renal parenchymal disease; chronic glomerulopathy and renal scarring with or without vesi-coureteral reflux and/or obstruction are predominant. In the ESCAPE trial, the prevalence of hypertension was 88% in patients with the acquired glomerulopathies, 38% in children with hypo/dysplastic kidney disorders, and 57% in other congenital or hereditary renal diseases [4]. Renal scarring of reflux nephropathy or obstructive uropathy also significantly contributes to the prevalence of pediatric renal hypertension. Approximately 10% of children with reflux nephropathy will develop hypertension, and by late adolescence, the prevalence will account for 18-20%; in long-term follow between 30% and 40% of subjects will be hypertensive [5, 6]. Other causes, such as the polycystic kidney disease, damaged kidney because of the acute kidney injury (as in patients recovering from severe HUS) and renal tumors are important but less common.

Renovascular hypertension
Renovascular disease (RVD) occurs in approximately 10% of patients with hypertension in tertiary reference center [7]. Fibromuscular dysplasia, neurofibromatosis type 1, tuberous sclerosis, Takayasu’s arteritis, middle aortic syndrome, and Williams syndrome are some of the conditions that result in renal arterial stenosis and renal ischemia [7]. It is important to diag-
nose RVD early, as it is potentially curable with interventional treatment. Recent technological advances including Doppler renal ultrasound, radioisotope renogram with ACE inhibitors, high-resolution computed tomographic (CT) angiography, and magnetic resonance (MR) angiography have improved non-invasive investigations, but renal angiography is still a gold standard for diagnosis of RVD [8]. The treatment of children with RVD should be managed by a multidisciplinary team and should be based on a combination of antihypertensive drugs, angioplasty, and surgery.

HYPERTENSION IN PATIENTS WITH THE CHRONIC RENAL FAILURE

The prevalence of hypertension increases directly with the prevalence of concomitant renal failure; by the time CKD reaches stage 5, the majority of affected children have hypertension [2]. Recent ESPN/ERA-EDTA registry [9] found hypertension in over two-thirds of patients on renal replacement therapy (RRT). Hypertension was more prevalent in patients under 3 years compared to 13-17 year old, during the first compared to over 5 years of RRT, and in patients on hemodialysis compared to transplant recipients or those on peritoneal dialysis. Over time, mean blood pressure (BP) decreased in both hemodialysis and transplant recipients patients, but not in patients on peritoneal dialysis [9]. Similar results were obtained in a cross-sectional study sample of patients on chronic dialysis aged 1-21 years enrolled in the North American Pediatric Renal Trials and Collaborative Studies registry from 1992-2008 [10]. At 6 months after dialysis was initiated, 67.9% of 3447 patients (65.7% on peritoneal dialysis and 34.3% on hemodialysis) had uncontrolled or untreated hypertension, and 57.8% were prescribed antihypertensive medications. More recent year of dialysis initiation was associated with higher use of antihypertensive medication and lower systolic BP and diastolic BP Z-scores measured over time from 6 months to 3 years after dialysis initiation. Other factors associated with higher BP included black race, glomerular disease, younger age, hemodialysis (systolic BP only), and antihypertensive use. There were significant differences in BP control by dialysis modality and disease etiology, with patients on hemodialysis or those with glomerular diseases having the highest percentage of uncontrolled hypertension [10]. In another cross-sectional study that included 624 pediatric patients on chronic hemodialysis, 79% of patients had hypertension [11]. Hypertension was uncontrolled in 74% of treated patients, and untreated in 21% of hypertensive patients. Control of BP after kidney transplantation remains also sub-optimal; over 25% of patients remain hypertensive 5 years following the transplantation [12].

EVALUATION OF RENAL HYPERTENSION

The same definition of hypertension is used for children with renal disease as for healthy ones [13]. Currently, using casual BP measurements and according to the criteria of the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents, hypertension is defined as average systolic and diastolic BP >95th percentile for age, gender, and height measured on at least three separate occasions [14]. Defining hypertension in the neonate is based on published norms for gestational and post-natal age [15, 16].

Casual BP should be measured when the patient is calm using validated, periodically checked and calibrated BP devices with the appropriately sized cuff [17]. In hemodialysis patients the cuff should be applied to the non-fistula arm. Casual BP recordings obtained by oscillometric devices have to be regularly checked by auscultatory methods (ideally with a mercury manometer) because, compared with auscultation, the oscillometric device significantly overestimates both systolic and diastolic BP, leading to frequent misclassification of BP status [18]. However, oscillometric method is preferred for non-invasive BP measurement in infants, as the Korotkoff sounds are often difficult to hear [19]. In addition, oscillometric method is preferred method for home BP monitoring. In children with the chronic renal failure, home BP monitoring was found to be superior to clinic BP measurement in predicting ambulatory BP (ABPM), but neither clinic nor home BP monitoring detected hypertension with enough sensitivity to replace ABPM [20].

ABPM has become the method of choice for diagnosis and therapeutic monitoring of arterial hypertension in pediatric and adult renal patients [21, 22]. It is without observer bias and “white coat” effect. ABPM provides more representative observation of BP throughout day and night in non-medical environment. It allows quantifying the circadian and ultradian BP variability [23]. ABPM is especially helpful in hemodialysis patients because it enables better recognition of intra- and post-dialytic (particularly nocturnal) BP changes when continued over 24 or 48 h [24, 25]. Furthermore, ABPM is superior to casual BP concerning better correlation with target-organ damage such as the left ventricular hypertrophy and the ability to diagnose masked hypertension (i.e., normal casual BP but increased ambulatory daytime BP) in children with CKD stage 5 and after renal transplantation [26, 27]. Finally, the results of ABPM are more closely related to renal function in transplanted patients than the results of casual BP [28]. Therefore, ABPM should be performed regularly in all patients on RRT, at least every 6–12 months, regardless of casual BP values.

Together casual and ambulatory BP measurements provide more powerful means of diagnosing hypertension [17, 29]. True hypertension and true normotension are conditions in which casual and ABPM agree. Alternatively, white coat hypertension is a condition in which casual measurements are consistently elevated while ambulatory measurements are normal, and masked hypertension is the inverse condition in which casual measurements are normal but ambulatory measurements are elevated [27]. BP load is defined as the percentage of valid ambulatory BP measures above the set threshold value, such as the 95th percentile of BP for gender and height [30], while normal
nocturnal BP dipping is generally defined as nocturnal decline of mean systolic and diastolic ABPM level by at least 10%. In growth retarded CKD patients, normative data for casual BP should be taken for the 5th–95th height percentile and normative data for ABPM for the patient's height regardless of the patient's age.

CARDIOVASCULAR DISORDERS IN CHILDREN WITH RENAL HYPERTENSION

The cardiovascular disorder (CVD) is the main risk factor of morbidity and mortality in CKD patients, especially of those on RRT [31]. Despite decades of improvements in care for children with the end-stage renal disease, recent epidemiological studies have demonstrated highly increased risk of cardiovascular mortality as the patients survive to adulthood [32, 33, 34]. The risk is sufficiently high as to place children with CKD in the highest American Heart Association cardiovascular risk category, on par with type 1 diabetes and familial hypercholesterolemia [35].

Four main structural abnormalities of the heart have been described in CKD patients: (1) left ventricle (LV) hypertrophy (LVH); (2) expansion of the nonvascular cardiac interstitium leading to intracardial fibrosis; (3) changes of the vascular architecture (thickening of intramyocardial arteries and reduction of capillary length density); and (4) myocardial calcification [36]. LVH is the most relevant cardiac abnormality in children with CKD5. Two forms of LVH may be distinguished [37]. Concentric (or symmetric) LVH, caused by the pressure overload, leads to disproportionate overgrowth of cardiomyocytes with thickening of both interventricular septum and left ventricular posterior wall. Eccentric (or asymmetric) LVH, caused mainly by volume overload, results primarily in dilatation of the LV chamber, and increased wall thickness sufficient to counterbalance the dilatation with predominant thickening of the interventricular septum. In CKD5, both forms of LVH may be present and have been described in dialyzed children in 70–80% of cases [38]. Concentric left ventricle remodeling may be also present in patients without LVH. Although LVH is an adaptive response to chronic pressure and volume overload (allowing maintenance of systolic function), its persistence may become detrimental because it impairs diastolic compliance and reduces coronary perfusion reserve. Reduced diastolic filling is closely associated with LVH and increased stiffness of the LV chamber owing to collagen accumulation.

In parallel with cardiac abnormalities, hypertension induces alterations in the structure and function of the arterial tree manifested as coronary calcifications and wall thickening of the carotid arteries. It can be in the form of Mönckeberg sclerosis that is a particular type of arterial medial calcification; in addition, patients with CKD can develop atherosclerotic vascular disease – a form of intimal calcification [39]. The key CVD-related risk factors include "traditional" ones (hypertension, dyslipidemia, insulin resistance, increased lipoprotein (a), obesity as well as malnutrition) and uremia-related factors of which the most common in children are deregulation of the calcium, phosphors-parathormone (Ca-P-PTH) and vitamin D axis [39]. Once vascular damage and calcification begin, they progress inexorably in uremic patients and may be only partially reversed after successful renal transplantation. Given the known prognostic significance of cardiovascular lesions and hypertensive end organ damage, early and regularly monitoring cardiac function and geometry (echocardiography) is required even in the absence of any clinical signs of CVD. Additional methods to identify increased intravascular volume include bioimpedance, sonography of the inferior vena cava diameter and determination of the ANP in plasma, as well as monitoring of hematocrit. Until data from longitudinal follow-up studies become available, serial carotid artery intima media thickness, pulse wave velocity and multi-slice CT for coronary artery calcification would be useful only for research purpose or in CKD patients at high risk for CVD.

TREATMENT OF RENAL HYPERTENSION

Therapeutic management of hypertension reduces mortality and sequels of life-threatening conditions. It reduces left ventricular hypertrophy and also the rate of progression to end-stage renal disease [40]. The results of ESCAPE trial showed that low normal BP (<75 percentile in CKD patients without proteinuria and <50 percentile in those with proteinuria) improved renal survival and contributed to regression of CVD [41].

If an identified treatable cause of hypertension was detected (such as renal artery stenosis, vasculitis, glomerulonephritis), the primary disease, leading to BP elevation, should be treated [42, 43]. Otherwise, adequate pharmacotherapy along with strict volume control and other lifestyle modifications should be helpful in BP normalization. RAS antagonists are considered the first choice pharmacological option in patients with hypertensive and/or proteinuric CKD. However, the use of more than one drug with different mechanism of action is often required for effective lowering of blood pressure. In an individualized approach, the initial antihypertensive drug is chosen on the basis of presumed mechanism and severity of hypertension; concomitant diseases and therapies; availability of appropriate formulations (e.g., suspension and dosage choices); and, when available, pediatric safety, pharmacokinetics, and efficacy data. The choice of additional antihypertensive drugs in children with CKD is largely arbitrary [41]. Diuretics or calcium channel blockers have no antiproteinuric effect and may actually promote proteinuria and more rapid CKD progression, while non-diuretics or calcium channel blockers (diltiazem and verapamil) are antiproteinuric and therefore potentially renoprotective, but have weaker effect on blood pressure. The use of β-receptor blockers seems rational in view of the sympathetic over-activation in CKD. Newer β-blockers, e.g., carvedilol, have significantly higher antiproteinuric effect than atenolol in comparable blood pressure reduction.
Once blood pressure is controlled for 6–12 months and target-organ damage has regressed or resolved, an attempt to decrease the dosage or number of antihypertensive medications should be considered.

Having in mind that hypervolemia is the main contributing risk factor of hypertension in uremic patients, an appropriate initial management of hypertension in a dialyzed child will be gradual fluid extraction to control BP and achieve an ideal “dry weight,” i.e., the weight at which most of the excess fluid has been extracted. Antihypertensive drugs should be used in dialyzed children only if BP remained elevated, despite seemingly adequate volume and sodium control. The target “dry weight” has to be periodically reassessed and adjusted according to the child’s growth and changes in muscle or fat mass. The dialysis prescription often has to be modified for better control of BP, e.g., switching to longer, more frequent (e.g., daily) or nocturnal hemodialysis sessions or by minimizing the sodium content in food and dialysate fluid. Nevertheless, long dialysis vintage has been implicated in all studies as a significant and independent risk factor of CVD.

CONCLUSION

Hypertension is one of the most common cardiovascular risk factors in children with CKD, but it is also often underdiagnosed and undertreated. A careful measurement of blood pressure should result in early detection of hypertension in patients with CKD. The choice of antihypertensive treatment should be tailored to the main contributing risk factor of hypertension.

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Ренална хипертензија и кардиоваскуларна болест код деце с хроничним обољењем бубрега

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КРАТАК САДРАЖ
Ренална хипертензија је једна од најважнијих и највећих компликација хроничне болести бубрега (ХББ) код деце, али често остаје непрепозната и нелечена. За класично, интермитентно мерење крвног притиска могуће је усклапати и терапију, а за амбулаторно мерење највеће примењује осцилометријска метода. За деце с ХББ, уметаност могуће се двојно прецизно и класично измерити крвни притиск. Ризик од кардиоваскуларног морбидитета и морбитета је већи код маскираних хипертензије. Деца и адопцени са ХББ су у високом ризику за кардиоваскуларне болести, које су главни узрок смрти у терминалном стадијуму ХББ. Хипертрофија левог срца је најбоље доказано хипертензија и аритмида у ХББ. На основу јасних доказа за корелацију хипертензије с кардиоваскуларним запастилима, морбитетом и функцијом бубрега, реналну хипертензију треба леча агресивним методама. Њен крвни притисак код деце с ХББ је на нивоу ниских нормалних вредности: <75 процентил код деце без протеинурије, односно <50 процентил код болесника с протеинуријом. Како код обољених од ХББ стадијума 2–4, избора за хипертензију са ангиотензин аминониме системе ренин-ангиотензин-абактропион, а код болесника у терминалном стадијуму главна терапијска мера је отклањање хипертензије. Успешна трансплантација бубрега отказа или побољшање умрежене факторе ризика за кардиоваскуларне обољења, чиме се побољшава преживљавање болесника.

Кључне речи: инсуфицијенција бубрега; кардиоваскуларне болести; хипертрофиса левог срца; деца

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