Current Hypertension Reports (2021) 23: 18
https://doi.org/10.1007/s11906-021-01136-7

PEDIATRIC HYPERTENSION (C HANEVOLD, SECTION EDITOR)

Hypertension in Children and Adolescents with Turner Syndrome (TS), Neurofibromatosis 1 (NF1), and Williams Syndrome (WS)

Ramya Sivasubramanian[1] · Kevin E. Meyers[2]

Accepted: 25 February 2021 / Published online: 29 March 2021

Abstract

Purpose of Review Turner syndrome (TS), neurofibromatosis type 1(NF1), and William Syndrome (WS) are 3 genetic conditions that are all associated with a substantial increase in risk of hypertension. In this review, we focus on factors leading to hypertension and on clinical manifestations and management of hypertension in children and adolescents with these genetic conditions

Recent Findings In most instances, hypertension is secondary. There is a high prevalence of masked hypertension in TS; however, the extent to which control of the BP helps reduce the risk of aortic dissection/aneurysm in TS is not yet fully elucidated. Vasculopathies are the least emphasized but most important manifestation of NF1. Of note, routine screening for pheochromocytoma in NFI is not recommended as it is not cost-effective. Cardiovascular complications are the major cause of death in patients with WBS. ABPM identifies patients without overt aortic or renovascular narrowing. Antihypertensive agents such as ARBs that have direct vascular wall effects and agents that inhibit oxidative stress (minoxidil) should be considered, even in those who do not exhibit overt hypertension. Elevated blood pressure in children and adolescence manifests early with end-organ changes and when left untreated, increases risk for premature onset of cardiovascular disease.

Summary Vigilant monitoring of the blood pressure is recommended. Accurate early diagnosis and management of hypertension will delay or prevent target organ damage and ensure a healthier transition to adulthood among children afflicted with these conditions.

Keywords Pediatric hypertension · Turner syndrome · Neurofibromatosis 1 · Williams Syndrome

Introduction

Hypertension among children and adolescents is still underdiagnosed or missed in the clinical setting [1•]. This is especially true of high-risk children under 3 years of age and includes those children who have a genetic syndrome with a known increased risk for systemic hypertension. The reported prevalence of hypertension in childhood is 2–4% but is significantly higher in the 3 genetic syndromes that are discussed in this manuscript. There is a robust body of evidence that now clearly shows that elevated blood pressure in children and adolescence manifests with end-organ changes and that untreated hypertension in adolescents and young adults increases risk for early onset of cardiovascular disease in adulthood [2, 3•]. Children with elevated BP trajectories, even as early as 7 years of age, are more likely to have hypertension as adults when compared with children who have normal BP during childhood [4, 5].

Turner syndrome (TS), neurofibromatosis type 1 (NF1), and William Syndrome (WS) are 3 genetic conditions that are all associated with an increased risk of hypertension. The hypertension in most instances is secondary and occurs for a variety of reasons. In this review, we focus on the manifestations and causes of hypertension in children and adolescents with these three genetic conditions, namely Turner syndrome (TS), neurofibromatosis type 1 (NF1), and Williams Syndrome (WS) (Table 1).

This article is part of the Topical Collection on *Pediatric Hypertension*

✉ Kevin E. Meyers
meyersk@email.chop.edu

[1] Division of Pediatric Nephrology, Department of Pediatrics, Children's Hospital of Philadelphia, 9th Floor Beurger Building, 3405 Civic Center Boulevard, Philadelphia, PA 19104, USA

[2] Division of Pediatric Nephrology, Department of Pediatrics, Children's Hospital of Philadelphia and University of Pennsylvania, 9th Floor Beurger Building, 3405 Civic Center Boulevard, Philadelphia, PA 19104, USA

Table 1 Secondary causes of hypertension in TS, NF1, and WS

Condition	Gene affected	Secondary causes of hypertension				Prevalence of condition	Prevalence of hypertension
		Renal Vascular	Pheochromocytoma	Parenchymal kidney	Cardiac		
TS	45XO	Yes	No	Yes	Yes	1:2000	20–40%
NF1	17q11.2 AD	Yes, may also have extrinsic renal artery compression	Yes	Yes, uncommon, secondary to obstruction	No	1:3000–1:6000	16–19%
WS	7q11.23 deletion	Yes	No	Yes. Nephrocalcinosis secondary to hypercalcemia	Yes	1:10,000	32%

Discussion

Turner Syndrome

Turners syndrome (TS) occurs in about 50 in 100,000 (1/2000) newborn girls and arises from a complete or partial loss of the second X chromosome (45XO). TS is the only known monosomy that is compatible with life [6] and is associated with short stature, primary ovarian failure, congenital cardiac defects, and a 3-fold increase in age-related mortality [7]. TS may be complicated by a number of cardiovascular risk factors including diabetes, hypertension, and, particularly, problematic, aortic root dilatation and dissection [8, 9]. The frequency of HTN among girls with TS is as high as 20–40% [10] in childhood and increases to 60% in young women [11]. The causes and contributing factors to hypertension in TS are multifactorial.

Causes of Hypertension in TS

One study noted that at least 33% of girls with TS have congenital anomalies of the kidneys and urinary tract (CAKUT) and that 50% develop complications related to CAKUT including urinary tract infections, proteinuria, and hypertension [12]. However, renal function in TS is usually normal [13••].

Renal Parenchymal

Renal scarring is secondary to renal parenchymal infection (pyelonephritis), which may manifest with proteinuria and with renin-driven hypertension [14].

Anatomical

The most commonly noted anatomical renal findings in TS are horseshoe kidneys (20%), crossed-fused ectopia, pelvic ectopia, renal cystic dysplasia, hydronephrosis, and renal agenesis. Reflux, duplicated collecting systems and ureteric stricture also occur [13••, 15]. The genetic factors that increase risk of CAKUT in TS girls are as of yet unknown and are not associated with either Collectrin or HNF-1β gene mutations [16].

Renal Vascular

Multiple renal arteries may vascularize each kidney in Turner syndrome, particularly when the renal arteries are associated with renal ectopia. The renal arteries may uncommonly be stenosed, resulting in renin-mediated renovascular hypertension.

Coarctation of the Aorta

Coarctation of the aorta occurs in about 6 to 11% of TS girls. Of girls diagnosed with coarctation of the aorta at least 12.6% have karyotype-confirmed TS. Such a high frequency, combined with the known clinical benefits of an early diagnosis of TS, supports genetic screening for TS syndrome in female infants and children presenting with coarctation of the aorta [17, 18]. Even after coarctation repair hypertension may persist, often as "masked" hypertension, in up to 40% of children [19, 20]. Of note, mid-aortic syndrome does not seem to be specifically associated with TS.

Factors That May Contribute to Development of Hypertension in TS

Aortic Wall Distensability

Intrinsic abnormalities in the structure of the aorta may contribute to elevation of the BP in TS patients [9, 21, 22]. Aortic wall function in the descending aorta is impaired in TS with lower distensibility among those with coarctation of the aorta, and all TS patients have a higher Aix, and elevated central diastolic blood pressure when compared with sex- and age-matched controls [21, 23].

Sympathovagal Tone

TS women have significantly higher diastolic BP in the supine position compared to controls, and the adaptive rise in BP, when changing from a sitting to a standing position is reduced [24].

Obesity

Increased obesity risk in TS further highlights the importance of understanding the cardiometabolic risk (CMR) in TS. BMI, however, may not accurately depict body fatness and cardiometabolic risk in the setting of short stature and altered body proportions. Greater subcutaneous fat has been observed in TS compared to BMI-matched controls; given that visceral rather than somatic adiposity is related to CMR, the difference suggests BMI may not accurately capture CMR in TS. In fact, in one study in contrast to controls, no correlations were found between BMI and insulin sensitivity or lipids in TS [12]. These results highlight the importance of evaluating BMI as a screening tool to identify excess adiposity and cardiometabolic risk in TS.

Estrogen

Girls and women with TS have decreased estradiol levels. The average estradiol level among girls with TS (6.4 +/− 4.9 pmol/l estradiol equivalents) is much lower than in the normal prepubertal girls (12.7 +/− 10.8 pmol/l estradiol equivalents). Of note, carotid intimal medial thickness (CIMT) has a linear association with systolic BP that is inversely proportional to estragon levels [25, 26]. Estragon replacement use may help not only with cardiometabolic risk reduction but also with BP control in TS [27]. However, although a study utilizing 24-h ABPM was able to show a reduction in heart rate with the use of estriodiol therapy, the study was unable to show an effect on systolic and diastolic BP, which increased significantly in late adolescence into early adulthood [28].

Management of HTN in TS

Hypertension, which is still underdiagnosed, is of particular concern in TS given the increased risk of aortic root dissection and aneurysm [29]. A Swedish study in TS girls and young adults showed that the risk of aortic dissection was more than 12 times greater than in an age and sex matched control population [30]. The extent to which control of the BP helps reduce the risk of aortic dissection/aneurysm is not yet fully elucidated [31••]. Left ventricular hypertrophy (LVH) is a common cardiac occurrence in TS. Of note LVH is seen in TS with in-office BP in the normal range, making it crucial to consider masked hypertension or a loss of diurnal variation as identified by the absence of nocturnal dipping. *In-office BP measurements may miss hypertension in as many as 4 out of every 5 girls with TS*, underscoring the importance of ABPM monitoring in this group of patients [21, 32]. Indeed, ABPM has been identified as the best tool to identify masked hypertension and to predict hypertension induced left ventricular hypertrophy in TS [29].

Non-pharmacological medical management of hypertension should be aimed at weight control and regulation of sodium intake. Pharmacological management is similar to those children and young women without TS [10]. In the absence of identification of a secondary cause for the hypertension, one should consider using long-acting angiotensin receptor blockers (ATIIR inhibitors) and possibly β-blockers. The rationale for this choice of antihypertensive agents is inferred in that they are effective in slowing the rate of aortic dilatation in other genetic aortopathies such as Marfan and Ehlers-Danlos Syndromes [33, 34].

Neurofibromatosis 1

NF1 occurs in about 1/2500 to 1/3000 live births and about half of affected persons have a novel mutation. NF1 has an AD inheritance and the gene is situated on chromosome 17q11.2. Mutations in the NF1 gene result in dysregulation of the RAS/MAPK pathway. The major known function of the NF1 gene product neurofibromin is to downregulate RAS, thus acting as a tumor suppressor, explaining the occurrence of tissue overgrowth and tumor formation in NF1. Vasculopathies are the least emphasized but most important manifestation of NF1, both as a cause of morbidity and mortality in children and young adults. Neurofibromin is expressed in the vascular endothelium and in vascular smooth muscle. The loss of neurofibromin in these tissues is thought to underlie the NF1 vasculopathy [35]. Cardiovascular manifestations of NF1 that may result in systemic hypertension include renal artery stenosis, mid-aortic syndrome, and neuroendocrine tumors, namely pheochromocytoma, paraganglioma, and neuroblastoma [36]. Cerebrovascular disease is also part of the spectrum of the NF1 vasculopathy. Moya moya syndrome, cerebral aneurysm, internal carotid, and cerebral artery stenosis/occlusion have all been reported in NF1 and may occur in conjunction with the peripheral vasculopathy [37]. Of note, up to 20% of patients with NF1 may develop hypertension [38••].

Causes of Hypertension in NF1

Renal Parenchymal

Renal parenchymal changes in NF1 are unusual. Occasionally parenchymal changes present as areas of segmental hypoplasia (Ask-Upmark Kidney (AUK)) or more often are secondary to obstruction because of neurofibromas in the bladder with subsequent reflux and urogenital tract infection. AUK is characterized by a scarred segment of the kidney with primitive tubular and glomerular structures [39]. This condition is suspected when segmental hypoplasia is noted in the absence of recurrent urinary tract infections and vesicoureteral reflux or renal parenchymal ischemia. Plasma and renal vein renin

levels may be increased, and contrast-enhanced angiography (CTA) and dimercaptosuccinic acid scintigraphy (DSMA) show areas of hypoperfusion and reduced kidney size.

Obstructive Uropathy

Neurofibromas while frequent in NF1 are an infrequent cause of bladder outlet obstruction that may lead to obstruction, hypertension, and infrequently chronic kidney damage [40, 41]. The hypertension may occur as described above or may be secondary to the obstruction itself with salt and water retention.

Renal Vascular

Renal artery stenosis (RAS) occurs in over 7% of children and adolescents with NF1 and may be bilateral [36]. The imaging appearance of RAS in NFI can mimic that of FMD; however, the stenosis is more often at the renal aortic takeoff than in the middle sections of the renal arteries, whereas in FMD, RAS occurs more often in the mid and distal portions of the main renal artery [42]. RAS may also occur secondary to external compression from, for example, a plexiform neurofibroma.

Mid-aortic Syndrome

Mid-aortic syndrome (MAS) is characterized by narrowing of the abdominal aorta, often with involvement of the renal and splanchnic arterial branches. Although uncommon, accounting for 0.5 to 2% of all cases of aortic narrowing [43], MAS is an important cause of renovascular hypertension in children and adolescents with NF1. Hypertension is severe and extensive disease requires treatment with several antihypertensive medications and/or surgical repair (Fig. 1). A multidisciplinary approach with long-term monitoring is important for conservation of end-organ function and quality of life [44••].

Pheochromocytoma/Paraganglioma

Pheochromocytoma/paraganglioma is detected in about 0.7% of persons with NF1. Routine screening for pheochromocytoma in NFI is not recommended as it is not cost-effective. Work-up for pheochromocytoma should be done in those with unexplained paroxysmal palpitations, headache, dizziness, and sweating [45]. Work-up should include a 24-h urine collection for catecholamine and serum metanephrine measurements with MIBG imaging as indicated.

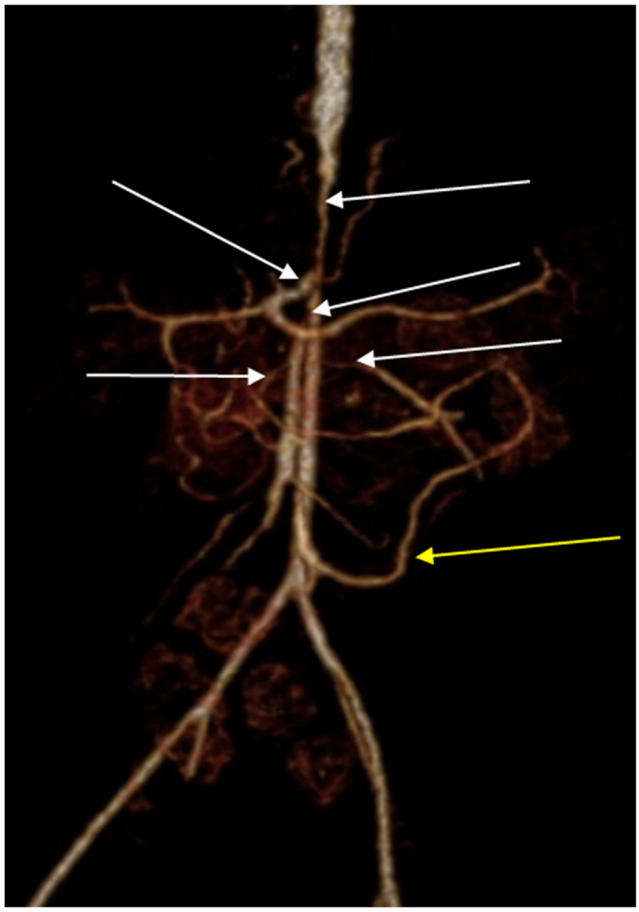

Fig. 1 This 3D reconstruction of a CTA abdomen from a 6-year-old female with NFI shows middle-abdominal aortic stenosis, celiac axis stenosis, superior mesenteric artery stenosis, and bilateral renal artery stenosis (white arrows). An arc of Riolan arising from the inferior mesenteric artery is shown (yellow arrow), indicating collateral revascularization to the foregut

Factors That May Contribute to Development of Hypertension in NF1

The pathophysiology behind the vasculopathy in NF1 can be broadly categorized into large vessel and small vessel involvement [46]. The histopathologic picture as outlined below is variable.

Large Vessels

Neurofibromatosis or ganglioneuromatous tissue around large vessels such as the aorta, carotid, and proximal renal arteries can cause intimal proliferation, thinning of media, and fragmentation of elastic tissue leading to stenosis and aneurysms. Medium-sized elastic and muscular arteries show predominance of intimal vascular smooth muscle cell proliferation with variable degrees of fibrosis and neo-angiogenesis [47]. In the renal arteries, the pathology is indistinguishable from that of FMD. Carotid artery intima-media thickness (cIMT) is increased in NF1 compared with normal controls [48••].

Small Vessels

Small vessels show mainly intimal proliferation [48••]. Endothelial function is significantly damped in NF1 subjects with reduced small vessel dilatation after ischemia and exercise when compared with controls [48••].

Management of HTN in NF1

The management of HTN in NF1 depends on the underlying cause. RAS may be treated conservatively with antihypertensive medications; ACEi and ARBs can be used after the stenosis has been shown to be unilateral [49]. Endovascular management is the preferred approach for management of most NF1-associated RAS. The lesions are amenable to renal angioplasty and respond well to cutting balloon therapy [50, 51]. Hypertension usually persists after renal angioplasty; however, the increased blood pressure is easier to control [52, 53]. Surgery is required for refractory and long-segment stenosis [54•].

Williams-Beuren Syndrome

Williams-Beuren Syndrome (WBS) is characterized by a variable microdeletion of chromosome 7q11.23 that usually occurs de novo. The WBS critical microdeletion region is associated with loss of 26–28 genes, but even in atypical patients with smaller deletions, the deletion always includes the gene that encodes for elastin (ELN). The resulting hemizygosity of ELN is responsible for the vascular abnormalities. Cardiovascular abnormalities occur in over 80% of WBS patients; most have a generalized arteriopathy [55]. Supravalvular aortic stenosis (SVAS) occurs in about two-thirds of patients. Systemic arterial abnormalities include focal or diffuse narrowing that may involve the thoracic or abdominal aorta, coronary, renal, and other visceral arteries [56]. In-office diagnosis of systemic hypertension is made in about 30% of WBS children and adolescents and is most often asymptomatic [57]. As discussed below though, the actual prevalence of systemic hypertension is at least 50%. Cardiovascular complications are the major cause of death in patients with WBS. Other major clinical features of WBS include distinctive facial features that changes with age, decreased linear growth, usually thin as children and overweight as adults, hypercalcemia, abnormal glucose metabolism, subclinical hypothyroidism, dental anomalies (small, abnormally shaped teeth, absent teeth, malocclusion), gastrointestinal dysmotility (reflux, constipation), diverticular disease, musculoskeletal anomalies (joint stiffness, scoliosis), sensorineural hearing loss, genitourinary anomalies (urinary frequency, bladder diverticuli), neurological problems (abnormal tone, hyperreflexia, and cerebellar findings), mild to moderate cognitive delay, average full-scale IQ is 55–60, range from 40 to 90, *with relative* strengths in selected language domains and a prominent weakness in the visuospatial domain, characteristic personality, and anxiety-driven emotional traits.

Causes of Hypertension in WS

Most WBS persons have hypertension related to the diffuse underlying vasculopathy that is influenced by additional syndrome-related factors [58]. Only a minority have renal artery stenosis, diffuse narrowing of the aorta, aortic coarctation, or a combination of abnormalities as causative factors for hypertension. Renal artery stenosis is usually found at the take-off from the aorta and may be unilateral or bilateral [59]. Three studies using 24-h ambulatory monitoring found hypertension in 40–70% of patients, most without overt aortic or renovascular narrowing [60–62]. Of interest, the risk of hypertension is decreased in WBS patients whose deletion includes the NCF1 gene [63].

Factors That May Contribute to Development of Hypertension in WBS

Elastin

Human and mouse studies have established that defects in the elastin gene, leading to elastin haploinsufficiency, underlies the arteriopathy seen in WBS. Abnormal elastin production results in vascular stiffness [64] with occlusive vascular abnormalities including supra-valvular aortic stenosis and stenosis of other large muscular arteries including the renal arteries [65]. Vascular wall elastin helps direct smooth muscle phenotype and function [66]. Prior studies have reported that elastin haploinsufficiency results in subendothelial migration and vascular smooth muscle cell hyperplasia causing intrusion on the vascular lumen and arterial stenoses. However, more recent work suggests that the stenoses seen in WBS arise from deficient circumferential arterial growth and is the primary determinant of aortic luminal narrowing in the setting of elastin haploinsufficiency [67].

Hypercalcemia

Hypercalcemia occurs in approximately 15% of children with the WBS [68]. It may occur at any age and monitoring of calcium homeostasis is recommended [69]. A single study found a higher incidence of hypertension in WBS diagnosed with infantile hypercalcemia.

However, no direct links between hypertension and hypercalcemia in WBS have been firmly established [60]. Hypercalcemia may be accompanied by hypercalciuria, although isolated hypercalciuria can occur predisposing to development of nephrocalcinosis and kidney injury [59, 70].

The hypercalcemia is responsive to treatment with glucocorticoids and bisphosphonates [68].

Anxiety

WBS patients conceal their anticipatory anxiety, phobias, and perseverative tendencies with a generally social and friendly demeanor. In-office blood pressure is often initially elevated and should be repeated using manual means at the end of the visit.

Impaired Glucose Metabolism

Adolescents and adults with WBS have increased fat mass, decreased lean mass, impaired glucose homeostasis, and reduced bone-mineral-density [71].

Hypothyroidism

Subclinical hypothyroidism occurs in 15 to 30% of WBS patients who may have mild thyroid hypoplasia on ultrasonography [72, 73]. Overt hypothyroidism is infrequent and antithyroid antibodies are not reported in WBS.

Management of HTN in WS

Medical control of hypertension in WBS is very important. Dietary management for weight control and limitation of sodium intake should be instituted as indicated. A secondary cause for the hypertension should be evaluated using tomographic imaging (computed tomography or MRI) to assess the aorta and renal arteries, as Doppler ultrasound provides suboptimal assessment [74•]. Digital subtraction angiography, however, remains as the gold standard for vascular assessment, particularly of the renal vessels. Medical management may require use of more than one antihypertensive agent. ACEi or ARBs can be used after bilateral RAS in ruled out. Importantly, in a study done in a heterozygous (ELNþ/_) murine model, the renal interlobar artery basal tone and myogenic response were increased, renal blood flow was lower, and there was damage to the glomerular filtration barrier at the level of the podocyte foot processes, a finding that was independent of BP. The increased vascular tone and exaggerated myogenic response was normalized after administration of candesartan, a long-acting AT1 blocker (ARB). These findings suggest that ARBs could be an attractive antihypertensive therapy for patients with WBS [75]. Calcium channel blockers (Dihydropyridine) can be used as first-line of therapy, and β-blockers can also be used and may give additional benefit with respect to prevention of arrhythmia and sudden death [76].

In order to [64], in a randomized controlled trial conducted over a 12–18-month period, minoxidil was shown to improve elastogenesis as evidenced by an increase in functional intima media thickness in children with WBS [77•]. Additional pharmacological treatments such as mammalian target of rapamycin inhibitors are being explored for treatment of the vasculopathy [78, 79••].

Conclusion

Hypertension is frequently found in children and adolescents with TS, NF1, and WS.

These children form part of the subset of genetic causes of hypertension where blood pressure should be measured at routine office visits including in those children under 3 years of age. Hypertension is most often secondary and the underlying cause should be sought and managed as clinically indicated. It is of vital importance that concomitant with diagnosis of these conditions, careful attention is paid to the cardiovascular system with vigilant screening and monitoring of the blood pressure for hypertension. Accurate early diagnosis and management of hypertension will prevent target organ damage and ensure a healthier transition to adulthood for persons afflicted with these conditions.

Compliance with Ethical Standards

Conflict of Interest None reported

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.• Moin A, Mohanty N, Tedla YG *et al.* Under-recognition of pediatric hypertension diagnosis: examination of 1 year of visits to community health centers. J Clin Hypertens (Greenwich) 2021;23(2):257–64. https://doi.org/10.1111/jch.14148. **This study highlights the proportion of missed diagnosis of hypertension and prehypertension and the lack of appropriate follow-up in pediatric patients, stratified by sex, age, race/ethnicity, and weight status.**

2.•• Urbina EM, Mendizabal B, Becker RC, et al. Association of blood pressure level with left ventricular mass in adolescents. Hypertension. 2019;74:590–6 **This study elaborates on the association of systolic BP (SBP) percentile, independent of obesity, on left ventricular mass index (LVMI), and also estimates**

which SBP percentile best predicts left ventricular hypertrophy in youth.

3.• Tran AH, Urbina EM. Hypertension in children. Curr Opin Cardiol. 2020;35:376–80. **This is a review that focuses on changes in hypertension guidelines, epidemiology, predictors of hypertension, blood pressure (BP) measurement, effects on target organs, and treatment of hypertension in children**.

4.• Aris IM, Rifas-Shiman SL, Li LJ, et al. Early-life predictors of systolic blood pressure trajectories from infancy to adolescence: findings from Project Viva. Am J Epidemiol. 2019;188:1913–22 **This study investigates the relationship between early-life factors and systolic BP (SBP) from infancy to adolescence. 13 This insightful study analyzes the frequency of renal dysfunction and congenital anomalies of the kidney-urinary tract in pediatric patients with TS.**

5. Park B, Park B, Lee HA, Lee S, Han H, Park E, et al. Association between pre-and postnatal growth and longitudinal trends in serum uric acid levels and blood pressure in children aged 3 to 7 years. BMC Pediatr. 2020;20:23.

6. Bondy CA. Congenital cardiovascular disease in Turner syndrome. Congenit Heart Dis. 2008;3:2–15.

7. Stochholm K, Hjerrild B, Mortensen KH, Juul S, Frydenberg M, Gravholt CH. Socioeconomic parameters and mortality in Turner syndrome. Eur J Endocrinol. 2012;166:1013–9.

8. Bondy CA. Aortic dissection in Turner syndrome. Curr Opin Cardiol. 2008;23:519–26.

9. Lopez L, Arheart KL, Colan SD, Stein NS, Lopez-Mitnik G, Lin AE, et al. Turner syndrome is an independent risk factor for aortic dilation in the young. Pediatrics. 2008;121:e1622–7.

10. Gravholt CH, Naeraa RW, Nyholm B, Gerdes LU, Christiansen E, Schmitz O, et al. Glucose metabolism, lipid metabolism, and cardiovascular risk factors in adult Turner's syndrome. The impact of sex hormone replacement. Diabetes Care. 1998;21:1062–70.

11. Groote K, Demulier L, De B, et al. Arterial hypertension in Turner syndrome: a review of the literature and a practical approach for diagnosis and treatment. J Hypertens. 2015;33:1342–51.

12. Landin-Wilhelmsen K, Bryman I, Wilhelmsen L. Cardiac malformations and hypertension, but not metabolic risk factors, are common in Turner syndrome. J Clin Endocrinol Metab. 2001;86:4166–70.

13.•• Izumita Y, Nishigaki S, Satoh M, et al. Retrospective study of the renal function using estimated glomerular filtration rate and congenital anomalies of the kidney-urinary tract in pediatric Turner syndrome. Congenit Anom (Kyoto). 2020;60:175–9. **This study looks at the prevalence and causes of renal dysfunction and of CAKUT in pediatric patients with TS. Most have normal renal function. CAKUT was not always present in those with reduced renal function**.

14. Je BK, Kim HK, Horn PS. Incidence and spectrum of renal complications and extrarenal diseases and syndromes in 380 children and young adults with horseshoe kidney. AJR Am J Roentgenol. 2015;205:1306–14.

15.•• Gravholt CH, Andersen NH, Conway GS, et al. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. Eur J Endocrinol. 2017;177:G1–G70 **This paper is based on an international effort to serve as a guideline in addressing recent advances that cover all specialty fields involved in the care of girls and women with TS.**

16. Pasquali L, d'Annunzio G, Gastaldi R, di Battista E, Calcaterra V, Larizza D, et al. Collectrin gene screening in Turner syndrome patients with kidney malformation. J Genet. 2009;88:105–8.

17. Donadille B, Heart C-MS. Turner syndrome. Ann Endocrinol (Paris). 2020.

18. Eckhauser A, South ST, Meyers L, Bleyl SB, Botto LD. Turner syndrome in girls presenting with coarctation of the aorta. J Pediatr. 2015;167:1062–6.

19.•• Agbas A, Gokalp S, Canpolat N, et al. Is the burden of late hypertension and cardiovascular target organ damage in children and adolescents with coarctation of the aorta after early successful repair different to healthy controls? Cardiol Young. 2020;30:1305–12 **This study assesses the frequency of late hypertension and the relationship between ambulatory hypertension and cardiovascular target organ damage in 25 children and adolescents after early and successful repair of coarctation of the aorta.**

20. Akyurek N, Atabek ME, Eklioglu BS, Alp H. Ambulatory blood pressure and subclinical cardiovascular disease in children with turner syndrome. Pediatr Cardiol. 2014;35:57–62.

21.•• Fox DA, Kang KT, Potts JE, et al. Non-invasive assessment of aortic stiffness and blood pressure in young Turner syndrome patients. J Pediatr Endocrinol Metab. 2019;32:489–98 **This detailed prospective cohort study assesses the biophysical properties of the aorta and ambulatory blood pressure (BP) in females with TS and compares these findings to those in healthy female age-matched controls.**

22. De Groote K, Devos D, Van Herck K, et al. Abnormal aortic arch morphology in Turner syndrome patients is a risk factor for hypertension. Heart Vessel. 2015;30:618–25.

23.•• Wen J, Trolle C, Viuff MH, et al. Impaired aortic distensibility and elevated central blood pressure in Turner Syndrome: a cardiovascular magnetic resonance study. J Cardiovasc Magn Reson. 2018;20:80 **This study investigates if arterial stiffening can be observed in Turner Syndrome patients and is an initial step in the development of aortic dilatation and subsequent dissection by determining aortic distensibility at three locations: ascending aorta, transverse aortic arch, and descending aorta.**

24.•• Brun S, Berglund A, Mortensen KH, et al. Blood pressure, sympathovagal tone, exercise capacity and metabolic status are linked in Turner syndrome. Clin Endocrinol. 2019;91:148–55 **This cross-sectional study investigates cardiac autonomic changes in relation to metabolic factors, body composition, and 24-h ambulatory blood pressure measurements in Turner syndrome patients without known hypertension.**

25. Andersen NH, Hjerrild BE, Sorensen K, et al. Subclinical left ventricular dysfunction in normotensive women with Turner's syndrome. Heart. 2006;92:1516–7.

26. Sozen AB, Cefle K, Kudat H, Ozturk S, Oflaz H, Akkaya V, et al. Left ventricular thickness is increased in nonhypertensive Turner's syndrome. Echocardiography. 2009;26:943–9.

27. Elsheikh M, Casadei B, Conway GS, Wass JA. Hypertension is a major risk factor for aortic root dilatation in women with Turner's syndrome. Clin Endocrinol. 2001;54:69–73.

28. Brun S, Cleemann L, Holm K, Salskov G, Erlandsen M, Berglund A, et al. Five-year randomized study demonstrates blood pressure increases in young women with turner syndrome regardless of estradiol dose. Hypertension. 2019;73:242–8.

29. Los E, Quezada E, Chen Z, Lapidus J, Silberbach M. Pilot study of blood pressure in girls with turner syndrome: an awareness gap, clinical associations, and new hypotheses. Hypertension. 2016;68:133–6.

30. De Groote K, Demulier L, De Backer J, et al. Arterial hypertension in Turner syndrome: a review of the literature and a practical approach for diagnosis and treatment. J Hypertens. 2015;33:1342–51.

31.•• Pater CM, Gutmark-Little I, Tretter JT, et al. Clinical characteristics and rate of dilatation in Turner syndrome patients treated for aortic dilatation. Am J Med Genet A. 2021;185:141–9 **This recent retrospective study describes a pre-guideline cohort of Turner syndrome patients with aortic dilatation, the rate of dilatation following diagnosis, and post -therapy dilatation rates.**

32.•• Lee YJ, Kim SM, Lee YA, et al. Relationship between systolic hypertension assessed by 24-hour ambulatory blood pressure monitoring and aortic diameters in young women with Turner syndrome. Clin Endocrinol. 2019;91:156–62 **This observational, cross-sectional study highlights the prevalence of hypertension and its risk factors and investigates the relationship between systolic hypertension and aortic diameter in young patients with TS.**

33. Mullen M, Jin XY, Child A, Stuart AG, Dodd M, Aragon-Martin JA, et al. Irbesartan in Marfan syndrome (AIMS): a double-blind, placebo-controlled randomised trial. Lancet. 2019;394:2263–70.

34. Teixido-Tura G, Forteza A, Rodriguez-Palomares J, et al. Losartan versus atenolol for prevention of aortic dilation in patients with Marfan syndrome. J Am Coll Cardiol. 2018;72:1613–8.

35. North KN, Riccardi V, Samango-Sprouse C, Ferner R, Moore B, Legius E, et al. Cognitive function and academic performance in neurofibromatosis. 1: consensus statement from the NF1 Cognitive Disorders Task Force. Neurology. 1997;48:1121–7.

36. Friedman JM, Arbiser J, Epstein JA, Gutmann DH, Huot SJ, Lin AE, et al. Cardiovascular disease in neurofibromatosis 1: report of the NF1 Cardiovascular Task Force. Genet Med. 2002;4:105–11.

37. Kaas B, Huisman TA, Tekes A, et al. Spectrum and prevalence of vasculopathy in pediatric neurofibromatosis type 1. J Child Neurol. 2013;28:561–9.

38.•• Bergqvist C, Servy A, Valeyrie-Allanore L, et al. Neurofibromatosis 1 French national guidelines based on an extensive literature review since 1966. Orphanet J Rare Dis. 2020;15:37 **This paper presents insights from critical literature review and a multidisciplinary expert consensus on NF1 and details emerging new evidence that might have therapeutic potential or a strong impact on NF1 management.**

39. Dote Y, Kibe T, Murakami T, Awazu M. Ask-Upmark kidney in a girl with neurofibromatosis type 1. CEN Case Rep. 2020;9:285–8.

40. Dogan GM, Sigirci A, Karaca L. Neurofibromas of the bladder in a child with neurofibromatosis type 1. Int Braz J Urol. 2018;44:1256–7.

41. Meesa IR, Junewick JJ. Pelvic plexiform neurofibroma involving the urinary bladder. Pediatr Radiol. 2008;38:916.

42. Srinivasan A, Krishnamurthy G, Fontalvo-Herazo L, Nijs E, Meyers K, Kaplan B, et al. Spectrum of renal findings in pediatric fibromuscular dysplasia and neurofibromatosis type 1. Pediatr Radiol. 2011;41:308–16.

43. Sethna CB, Kaplan BS, Cahill AM*, Velazquez OC, Meyers KEC* Idiopathic mid-aortic syndrome in children. Pediatr Nephrol 2008;23:1135-1142.

44.•• Kim SS, Stein DR, Ferguson MA *et al.* Surgical management of pediatric renovascular hypertension and midaortic syndrome at a single center multidisciplinary program. J Vasc Surg 2020. **This retrospective study evaluates the outcome of various surgical approaches in the treatment of renovascular hypertension and midaortic syndrome in children.**

45. Ferner RE, Huson SM, Thomas N, Moss C, Willshaw H, Evans DG, et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. J Med Genet. 2007;44:81–8.

46. Greene JF Jr, Fitzwater JE, Burgess J. Arterial lesions associated with neurofibromatosis. Am J Clin Pathol. 1974;62:481–7.

47. Lie JT. Vasculopathies of neurofibromatosis type 1 (von Recklinghausen Disease). Cardiovasc Pathol. 1998;7:97–108.

48.•• Cutruzzola A, Irace C, Frazzetto M, et al. Functional and morphological cardiovascular alterations associated with neurofibromatosis 1. Sci Rep. 2020;10:12070 **This study verifies whether subjects with NF1 have early, preclinical abnormalities of carotid artery structure, brachial artery function, and cardiac function.**

49. Meyers KE, Cahill AM, Sethna C. Interventions for pediatric renovascular hypertension. Curr Hypertens Rep. 2014;16:422.

50. Srinivasan A, Krishnamurthy G, Fontalvo-Herazo L, Nijs E, Keller MS, Meyers K, et al. Angioplasty for renal artery stenosis in pediatric patients: an 11-year retrospective experience. J Vasc Interv Radiol. 2010;21:1672–80.

51. Towbin RB, Pelchovitz DJ, Cahill AM, Baskin KM, Meyers KE, Kaplan BS, et al. Cutting balloon angioplasty in children with resistant renal artery stenosis. J Vasc Interv Radiol. 2007;18:663–9.

52.• Raborn J, McCafferty BJ, Gunn AJ, et al. Endovascular management of neurofibromatosis type i-associated vasculopathy: a case series and brief review of the literature. Vasc Endovasc Surg. 2020;54:182–90 **This paper discusses therapeutic options and highlights certain endovascular therapies in NF1.**

53. Ueda K, Awazu M, Konishi Y, Takenouchi T, Shimozato S, Kosaki K, et al. Persistent hypertension despite successful dilation of a stenotic renal artery in a boy with neurofibromatosis type 1. Am J Med Genet A. 2013;161A:1154–7.

54.• Coleman DM, Eliason JL, Beaulieu R, et al. Surgical management of pediatric renin-mediated hypertension secondary to renal artery occlusive disease and abdominal aortic coarctation. J Vasc Surg. 2020;72:2035–2046 e2031 **This important study describes the complex surgical practice for such patients with an emphasis on anatomic phenotype and contemporary outcomes after surgical management as a means of identifying those factors responsible for persistent or recurrent hypertension necessitating reoperation.**

55. Bouchireb K, Boyer O, Bonnet D, Brunelle F, Decramer S, Landthaler G, et al. Clinical features and management of arterial hypertension in children with Williams-Beuren syndrome. Nephrol Dial Transplant. 2010;25:434–8.

56. Zalzstein E, Moes CA, Musewe NN, Freedom RM. Spectrum of cardiovascular anomalies in Williams-Beuren syndrome. Pediatr Cardiol. 1991;12:219–23.

57. Furusawa EA, Esposito CSL, Honjo RS, et al. Diagnosis and management of systemic hypertension due to renovascular and aortic stenosis in patients with Williams-Beuren syndrome. Rev Assoc Med Bras (1992). 2018;64:723–8.

58. Cherniske EM, Carpenter TO, Klaiman C, et al. Multisystem study of 20 older adults with Williams syndrome. Am J Med Genet A. 2004;131:255–64.

59. Pober BR, Lacro RV, Rice C, Mandell V, Teele RL. Renal findings in 40 individuals with Williams syndrome. Am J Med Genet. 1993;46:271–4.

60. Broder K, Reinhardt E, Ahern J, Lifton R, Tamborlane W, Pober B. Elevated ambulatory blood pressure in 20 subjects with Williams syndrome. Am J Med Genet. 1999;83:356–60.

61. Radford DJ, Pohlner PG. The middle aortic syndrome: an important feature of Williams' syndrome. Cardiol Young. 2000;10:597–602.

62. Rose C, Wessel A, Pankau R, Partsch CJ, Bürsch J. Anomalies of the abdominal aorta in Williams-Beuren syndrome–another cause of arterial hypertension. Eur J Pediatr. 2001;160:655–8.

63. Del Campo M, Antonell A, Magano LF, et al. Hemizygosity at the NCF1 gene in patients with Williams-Beuren syndrome decreases their risk of hypertension. Am J Hum Genet. 2006;78:533–42.

64. Kozel BA, Danback JR, Waxler JL, Knutsen RH, de las Fuentes L, Reusz GS, et al. Williams syndrome predisposes to vascular stiffness modified by antihypertensive use and copy number changes in NCF1. Hypertension. 2014;63:74–9.

65. Pomeranz G, Pomeranz A, Osadchy A, Griton Y, Korzets Z. Supravalvular aortic and renal artery stenosis in childhood: is there a common denominator? Isr Med Assoc J. 2016;18:497–8.

66. Lannoy M, Slove S, Jacob M. The function of elastic fibers in the arteries: beyond elasticity. Pathol Biol (Paris). 2014;62:79–83.

67. Jiao Y, Li G, Korneva A, Caulk AW, Qin L, Bersi MR, et al. Deficient circumferential growth is the primary determinant of aortic obstruction attributable to partial elastin deficiency. Arterioscler Thromb Vasc Biol. 2017;37:930–41.

68. Varma TH, Sahitya DSK, Dusad S, et al. Oral prednisolone for management of persistent hypercalcemia afterhypercalcemic crisis in the Williams-Beuren syndrome. Pediatr Endocrinol Diabetes Metab. 2018;24:106–9.
69. Committee on G. American Academy of Pediatrics: health care supervision for children with Williams syndrome. Pediatrics. 2001;107:1192–204.
70. Bastug F, Nalcacioglu H, Bas VN, et al. Acute renal failure due to severe hypercalcemia and nephrocalcinosis treated with two doses of pamidronate in an infant with Williams-Beuren syndrome. Turk J Pediatr. 2018;60:210–5.
71. Shaikh S, Waxler JL, Lee H, Grinke K, Garry J, Pober BR, et al. Glucose and lipid metabolism, bone density, and body composition in individuals with Williams syndrome. Clin Endocrinol. 2018;89:596–604.
72. Cambiaso P, Orazi C, Digilio MC, Loche S, Capolino R, Tozzi A, et al. Thyroid morphology and subclinical hypothyroidism in children and adolescents with Williams syndrome. J Pediatr. 2007;150:62–5.
73. Stagi S, Manoni C, Salti R, Cecchi C, Chiarelli F. Thyroid hypoplasia as a cause of congenital hypothyroidism in Williams syndrome. Horm Res. 2008;70:316–8.
74.• Louis R, Levy-Erez D, Cahill AM, Meyers KE. Imaging studies in pediatric fibromuscular dysplasia (FMD): a single-center experience. Pediatr Nephrol. 2018;33:1593–9 **This study compares the efficacy of imaging modalities with regards to diagnosis of renal artery stenosis.**
75. Owens EA, Jie L, Reyes BAS, van Bockstaele EJ, Osei-Owusu P. Elastin insufficiency causes hypertension, structural defects and abnormal remodeling of renal vascular signaling. Kidney Int. 2017;92:1100–18.
76. Collins R. Cardiovascular disease in Williams syndrome. Circulation. 2014;127:2125–34.
77.• Kassai B, Bouye P, Gilbert-Dussardier B, et al. Minoxidil versus placebo in the treatment of arterial wall hypertrophy in children with Williams Beuren Syndrome: a randomized controlled trial. BMC Pediatr. 2019;19:170 **This study assessed the efficacy and safety of minoxidil on intima media thickness (IMT) on the right common carotid artery after twelve12-month treatment in patient with Williams-Beuren syndrome.**
78. Jiao Y, Li G, Li Q, Ali R, Qin L, Li W, et al. mTOR (Mechanistic Target of Rapamycin) Inhibition decreases mechanosignaling, collagen accumulation, and stiffening of the thoracic aorta in elastin-deficient mice. Arterioscler Thromb Vasc Biol. 2017;37:1657–66.
79.•• Kinnear C, Agrawal R, Loo C, et al. Everolimus rescues the phenotype of elastin insufficiency in patient induced pluripotent stem cell-derived vascular smooth muscle cells. Arterioscler Thromb Vasc Biol. 2020;40:1325–39. **This study evaluates restoration of SMC phenotype in elastin insufficiency patients. The mTOR inhibitor everolimus gave the most consistent improvement in SMC differentiation, proliferation and restoration of SMC function in patients with elastin insufficiency**.