Non-CKD causes of hypertension in children: Management

Dr Sriram Krishnamurthy

Professor

Department of Pediatrics,

Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER),

Pondicherry

Specific learning objectives

- To understand the management of hypertension (predominantly non-CKD causes) in children through clinical case based scenarios
- To comprehend the etiology of hypertension in children in order to enable optimal management strategies
- Choice of antihypertensive agents in various scenarios

CLINICAL PRACTICE GUIDELINE Guidance for the Clinician in Rendering Pediatric Care

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents

Joseph T. Flynn, MD, MS, FAAP,[a] David C. Kaelber, MD, PhD, MPH, FAAP, FACP, FACMI,[b] Carissa M. Baker-Smith, MD, MS, MPH, FAAP, FAHA,[c] Douglas Blowey, MD,[d] Aaron E. Carroll, MD, MS, FAAP,[e] Stephen R. Daniels, MD, PhD, FAAP,[f] Sarah D. de Ferranti, MD, MPH, FAAP,[g] Janis M. Dionne, MD, FRCPC,[h] Bonita Falkner, MD,[i] Susan K. Flinn, MA,[j] Samuel S. Gidding, MD,[k] Celeste Goodwin,[l] Michael G. Leu, MD, MS, MHS, FAAP,[m] Makia E. Powers, MD, MPH, FAAP,[n] Corinna Rea, MD, MPH, FAAP,[o] Joshua Samuels, MD, MPH, FAAP,[p] Madeline Simasek, MD, MSCP, FAAP,[q] Vidhu V. Thaker, MD, FAAP,[r] Elaine M. Urbina, MD, MS, FAAP,[s] SUBCOMMITTEE ON SCREENING AND MANAGEMENT OF HIGH BLOOD PRESSURE IN CHILDREN

Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. *Pediatrics.* 2017;140(3):e20171904

TABLE 3 Updated Definitions of BP Categories and Stages

For Children Aged 1–13 y	For Children Aged ≥13 y
Normal BP: <90th percentile	Normal BP: <120/<80 mm Hg
Elevated BP: ≥90th percentile to <95th percentile or 120/80 mm Hg to <95th percentile (whichever is lower)	Elevated BP: 120/<80 to 129/<80 mm Hg
Stage 1 HTN: ≥95th percentile to <95th percentile + 12 mmHg, or 130/80 to 139/89 mm Hg (whichever is lower)	Stage 1 HTN: 130/80 to 139/89 mm Hg
Stage 2 HTN: ≥95th percentile + 12 mm Hg, or ≥140/90 mm Hg (whichever is lower)	Stage 2 HTN: ≥140/90 mm Hg

Hypertension

- Transient/Intermittent hypertension
- Persistent hypertension

Transient hypertension in children: Causes

Renal

- **Acute post-infectious glomerulonephritis**
- Henoch-Schonlein purpura with nephritis
- Hemolytic-uremic syndrome
- Acute kidney injury
- After renal transplantation (immediately and during episodes of rejection)
- Hypervolemia
- Pyelonephritis
- Renal trauma
- Leukemic infiltration of the kidney

Drugs and Poisons

- Cocaine, Oral contraceptives, Sympathomimetic agents, Amphetamines, Phencyclidine, **Corticosteroids** and adrenocorticotropic hormone, **Cyclosporine**, sirolimus, or tacrolimus treatment after transplantation, Licorice
- Lead, mercury, cadmium, thallium
- Antihypertensive withdrawal (clonidine, methyldopa, propranolol)
- Vitamin D intoxication

Central and Autonomic Nervous System

- **Increased intracranial pressure**
- **Guillain-Barre syndrome, Transverse myelitis**
- **Porphyria**
- Familial dysautonomia
- Stevens-Johnson syndrome
- Posterior fossa lesions

Persistent Hypertension in children: Causes

Renal
Recurrent pyelonephritis/**renal scarring**
Chronic glomerulonephritis
Prematurity
Congenital dysplastic kidney
Polycystic kidney disease
Vesicoureteral reflux nephropathy
Segmental hypoplasia (Ask-Upmark kidney)
Obstructive kidney disease
Renal tumors
Renal trauma
Systemic lupus erythematosus

Vascular
Coarctation of thoracic or abdominal aorta
Renal artery lesions (stenosis, FMD, thrombosis, aneurysm)
Umbilical artery catheterization with thrombus formation
Neurofibromatosis (intrinsic or extrinsic narrowing for vascular lumen)
Renal vein thrombosis
Vasculitis (ANCA associated, polyarteritis nodosa, Takayasu arteritis)
Arteriovenous shunt
Williams-Beuren syndrome
Moya Moya disease

Endocrine
Hyperthyroidism
Congenital adrenal hyperplasia (**ll B-hydroxylase and 17-hydroxylase** defect)
Cushing syndrome
Primary hyperaldosteronism
Apparent mineralocorticoid excess
Glucocorticoid remedial aldosteronism (familial aldosteronism type 1)
Glucocorticoid resistance (Chrousos syndrome)
Pseudohypoaldosteronism type 2 (Gordon syndrome)
Pheochromocytoma
Other neural crest tumors (neuroblastoma, ganglioneuroblastoma, ganglioneuroma)
Liddle syndrome
Geller syndrome

Central Nervous System
Intracranial mass
Hemorrhage
Residual following brain injury
Quadriplegia (dysautonomia)
Sleep disordered breathing

- How do we approach a child with hypertension?
- How do we investigate/evaluate hypertension in children?

History/ Physical Examination Findings suggestive of the etiology of hypertension and/or End-organ damage

Body System	Finding, History	Possible Etiology
Vital signs	Tachycardia	Hyperthyroidism
		PCC
		Neuroblastoma
	Decreased lower extremity pulses; drop in BP from upper to lower extremities	Coarctation of the aorta
Eyes	Proptosis	Hyperthyroidism
	Retinal changes[a]	Severe HTN, more likely to be associated with secondary HTN
Ear, nose, throat	Adenotonsillar hypertrophy	SDB
	History of snoring	Sleep apnea
Height, weight	Growth retardation	Chronic renal failure
	Obesity (high BMI)	Cushing syndrome
	Truncal obesity	Insulin resistance syndrome
Head, neck	Elfin facies	Williams syndrome
	Moon facies	Cushing syndrome
	Thyromegaly, goiter	Hyperthyroidism
	Webbed neck	Turner syndrome
Skin	Pallor, flushing, diaphoresis	PCC
	Acne, hirsutism, striae	Cushing syndrome
		Anabolic steroid abuse
	Café-au-lait spots	Neurofibromatosis
	Adenoma sebaceum	Tuberous sclerosis
	Malar rash	Systemic lupus
	Acanthosis nigricans	T2DM
Hematologic	Pallor	Renal disease
	Sickle cell anemia	
Chest, cardiac	Chest pain	Heart disease
	Palpitations	
	Exertional dyspnea	
	Widely spaced nipples	Turner syndrome
	Heart murmur	Coarctation of the aorta
	Friction rub	Systemic lupus (pericarditis)
		Collagen vascular disease
	Apical heave[a]	LVH
Abdomen	Abdominal mass	Wilms tumor
		Neuroblastoma
		PCC
	Epigastric, flank bruit	RAS
	Palpable kidneys	Polycystic kidney disease
		Hydronephrosis
		Multicystic dysplastic kidney
Genitourinary	Ambiguous or virilized genitalia	Congenital adrenal hyperplasia
	Urinary tract infection	Renal disease
	Vesicoureteral reflux	
	Hematuria, edema, fatigue	
	Abdominal trauma	
Extremities	Joint swelling	Systemic lupus
		Collagen vascular disease
	Muscle weakness	Hyperaldosteronism
		Liddle syndrome
Neurologic, metabolic	Hypokalemia, headache, dizziness, polyuria, nocturia	Reninoma
	Muscle weakness, hypokalemia	Monogenic HTN (Liddle syndrome, GRA, AME)

Laboratory Tests for the Child with Hypertension

Reason to test	*Tests*	*Purpose of result*
To identify cause	Complete blood count with differential, platelets	Rule out anemia, consistent with chronic renal disease
	Electrolytes, blood urea nitrogen, creatinine, calcium, phosphorus, uric acid	Rule out renal disease, calculi; chronic pyelonephritis
	Renal ultrasound	Rule out renal scarring; congenital renal anomalies; unequal renal size
	Urinalysis, urine culture	Rule out infection; hematuria; proteinuria
To identify comorbidities	Drug screen	Identify drug-induced hypertension
	Fasting lipid panel, fasting glucose, insulin	Identify hyperlipidemias, metabolic syndrome, or diabetes
	Polysomnography	Identify sleep disorders associated with hypertension
To identify end-organ damage	Echocardiography	Identify left ventricular hypertrophy
	Retinal examination	Identify retinal vascular changes
Additional testing (as clinically indicated)	24-hour urine for protein and creatinine, creatinine clearance	Rule out chronic renal disease
	Advanced imaging: renal scan; magnetic resonance angiogram; duplex Doppler flow studies; 3-dimensional computed tomography; arteriography (classic or digital subtraction)	Rule out renovascular disease
	Ambulatory blood pressure monitoring	Rule out physician anxiety-induced ("white-coat") hypertension
	Hormone levels (thyroid, adrenal)	Rule out hyperthyroidism, adrenal dysfunction
	Plasma renin levels	Rule out mineralocorticoid-related disease
	Urine and plasma catecholamines	Rule out catecholamine-mediated hypertension

Adapted with permission from National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004;114(2 suppl 4th report):562.

Etiology of hypertension in children as per age group

Causes of Childhood Hypertension According to Age Group

Age	*Causes*
One to six years	Renal parenchymal disease; renal vascular disease; endocrine causes; coarctation of the aorta; essential hypertension
Six to 12 years	Renal parenchymal disease; essential hypertension; renal vascular disease; endocrine causes; coarctation of the aorta; iatrogenic illness
12 to 18 years	Essential hypertension; iatrogenic illness; renal parenchymal disease; renal vascular disease; endocrine causes; coarctation of the aorta

Distribution of causes of hypertension in literature

Wyszyńska T, et al. A single pediatric center experience with 1025 children with hypertension. Acta Paediatr. 1992;81(3):244.

- Between January 1982 and December 1989 1025 patients aged between one month and 18 years with increased blood pressure
- Borderline hypertension was found in 389 children;
- 636 had sustained significant hypertension.
- **Renal parenchymal diseases- 68%**
- **Renovascular-10%**
- **Endocrine- 11%**
- Of the 258 children aged less than 15 years, all but six children had known causes of hypertension
- **75% of adolescents had essential hypertension.**
- In the 389 children with borderline hypertension, 65% developed fixed hypertension over a period of 2-3 years.

Non-CKD causes of hypertension

- AKI (including IRGN, RPGN, ATN, ATIN, HUS)
- Renovascular hypertension (e.g., Vasculitis)
- Monogenic hypertension
- Coarctation of aorta
- Endocrine causes
- Drugs
- Obesity
- Raised ICP, GBS, Transverse myelitis
- Excluded: Reflux nephropathy, Cystic kidney diseases, other causes of CKD

CASE 1

A 5-year-old boy

- Breathing difficulty x 3 days
- Referred as a case of pneumonia
- At referral, BP was found to be 130/90 mm Hg (Stage 2 hypertension)
- On reviewing Mild periorbital edema and oliguria x 3 days
- Multiple Pyodermas 3 weeks ago; no cola colored urine
- Urinalysis-RBC casts, 120 RBC/HPF, 1+ proteinuria
- Up:Uc 1.1
- Urea 38 mg/dL, creatinine 0.7 mg/dL (eGFR 68)
- ASO 150 IU/L, C3 low
- Serum albumin 3.3 g/dL
- Diagnosis ? Cause of hypertension?

Diagnosis and follow up

- **IRGN (PSGN)**

- Management with IV furosemide, oral nifedipine
- Amlodipine added
- Edema subsided
- At 8 week follow up, C3 normal
- eGFR 104, BP normal
- Nil albuminuria; urine RBC 6/HPF

Post-streptococcal glomerulonephritis (PSGN)

- Features of acute nephritic syndrome
- Clinico-serological evidence of recent streptococcal infection
- Low serum C3 levels, with normalization of C3 levels on an 6 week follow up.

Vijayakumar M. Acute and crescentic glomerulonephritis. Indian J Pediatr. 2002;69:1071
Eison TM. Post-streptococcal glomerulonephritis. Pediatr Nephrol 2011

Eison TM, Ault BH, Jones DP, Chesney RW, Wyatt RJ. Post-streptococcal acute glomerulonephritis in children: clinical features and pathogenesis. Pediatr Nephrol. 2011;26:165–80.

Question 1

- Which of the following antihypertensives is not recommended in IRGN?

1. Nifedipine
2. Furosemide
3. Amlodipine
4. Enalapril

Antihypertensives in PSGN

- **Salt restriction and loop diuretics** are usually first line treatment; Thereafter treatment **with vasodilators**
- **ACEI not recommended during acute phase due to decrease in GFR and hyperkalemia**
- In hypertensive emergencies, use anti-hypertensive infusions (sodium nitroprusside, labetalol)

Eison TM. Post-streptococcal glomerulonephritis. Pediatr Nephrol 2011

CASE 2

A 14-year-old girl

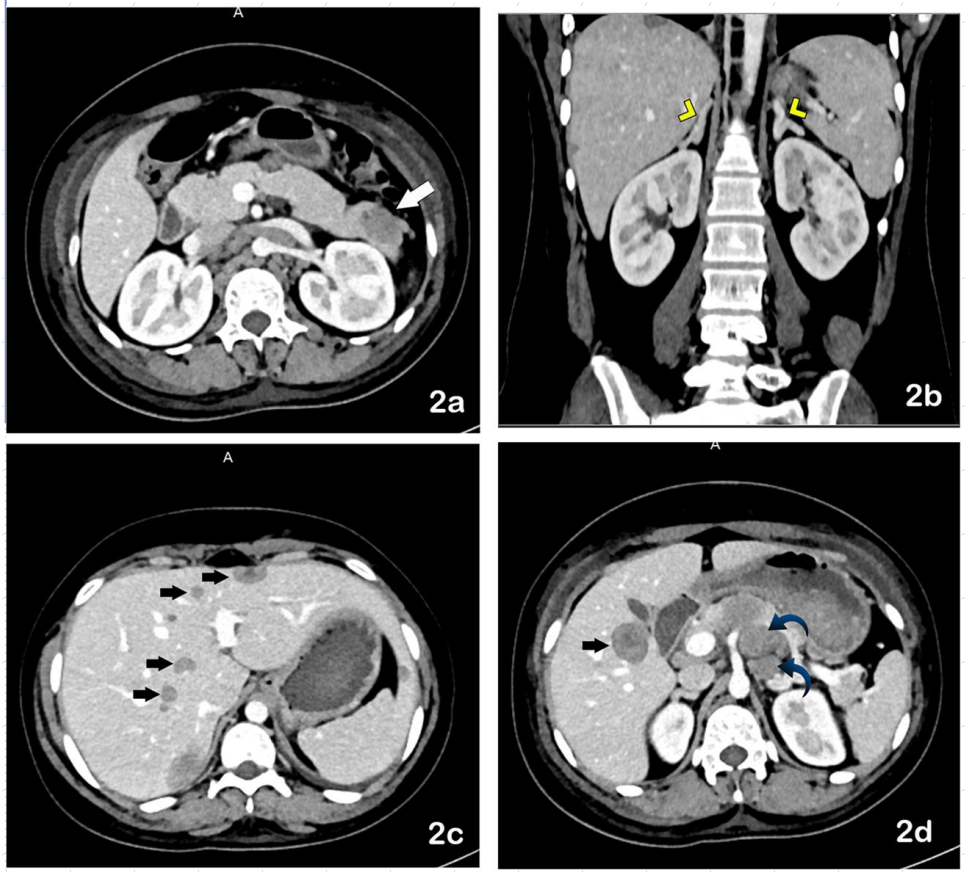
- Excessive weight gain and progressive swelling of both lower limbs for 1 month
- High BP (160/110 mmHg, stage 2 hypertension)
- She denied drugs, traditional medicines, or steroids
- Her face had a Cushingoid appearance, with extensive acneiform eruptions
- Weight and height: 50 kg (0.06 Z) and 151 cm (−1.56 Z) (Her weight was 43 kg 1 month ago
- No discrepancy in four limb BP, all pulses palpable

Further work-up

- Serum creatinine- 0.54 mg/dL, urinalysis normal
- Hypokalemic metabolic alkalosis (bicarbonate 45.7, K 2.8)
- Echocardiogram- Concentric LVH
- Plasma cortisol (at 8 am) > 75 mcg/dL (reference value 4.3–22.4 mcg/dL)
- Plasma ACTH- 363 pg/mL (reference value 10–60 pg/mL)

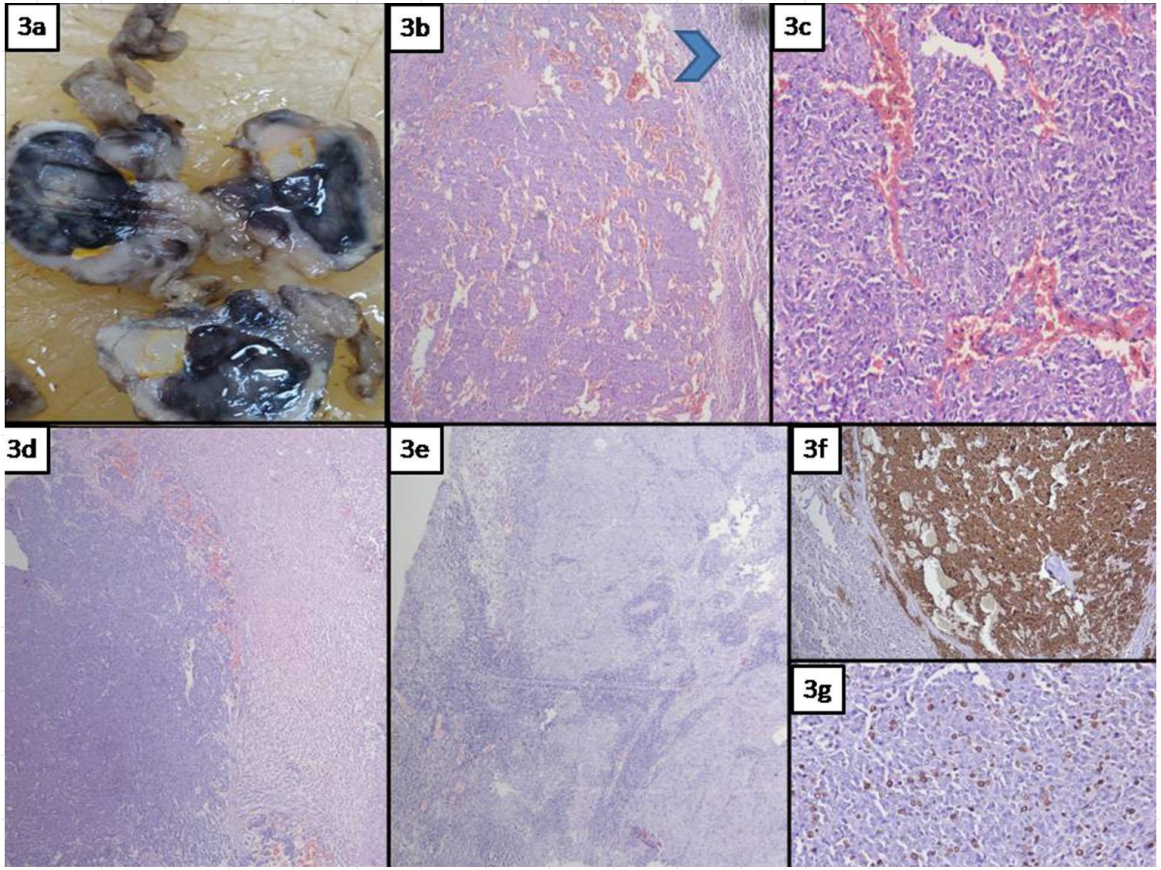
- Diagnosis: ACTH-dependent Cushing syndrome
- MRI cranium showed no evidence of pituitary or hypothalamic lesions

CECT abdomen



Contrast-enhanced computed tomography (CECT) of the abdomen showing a **hypodense poorly enhancing lesion in the tail of the pancreas** (tumor—solid white arrow). b Bilateral enlarged adrenal glands (open yellow arrows). c Multiple hypodense poorly enhancing lesions in the liver (metastases—solid black arrows). d Multiple heterogeneously enhancing retroperitoneal lymph nodes—paraaortic and celiac lymph nodes (curved blue arrows)

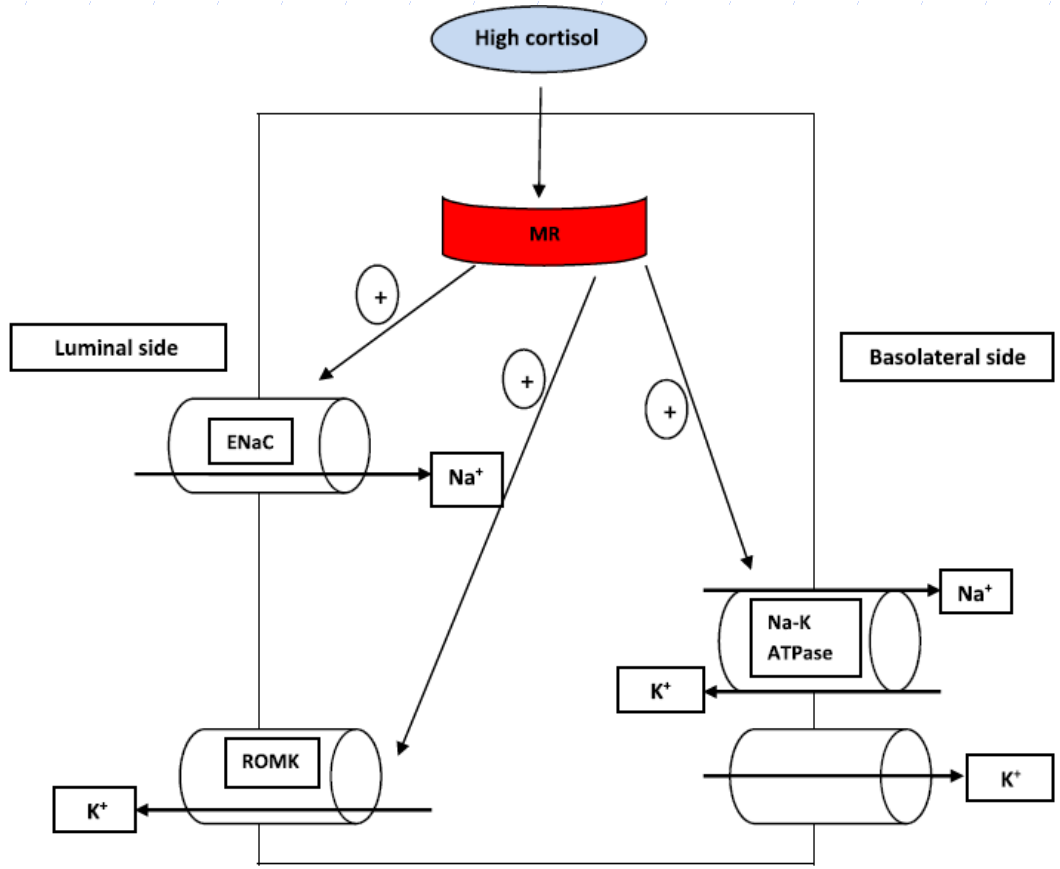
Distal pancreatectomy specimen: well-circumscribed **pancreatic neuroendocrine tumor**



Mechanism of hypertension in Endogenous Cushing syndrome

- Mineralocorticoid action exerted by supraphysiological levels of serum cortisol
- Mineralocorticoid receptor (MR) can be chiefly activated by cortisol
- However, this is kept in check by 11β-HSD
- In cortisol excess, the levels of cortisol would exceed the capacity of 11β-HSD to inactivate it to cortisone, thus making it available to bind to MR, mimicking excess aldosterone.

Hypokalemic metabolic alkalosis: Cushing syndrome



Management

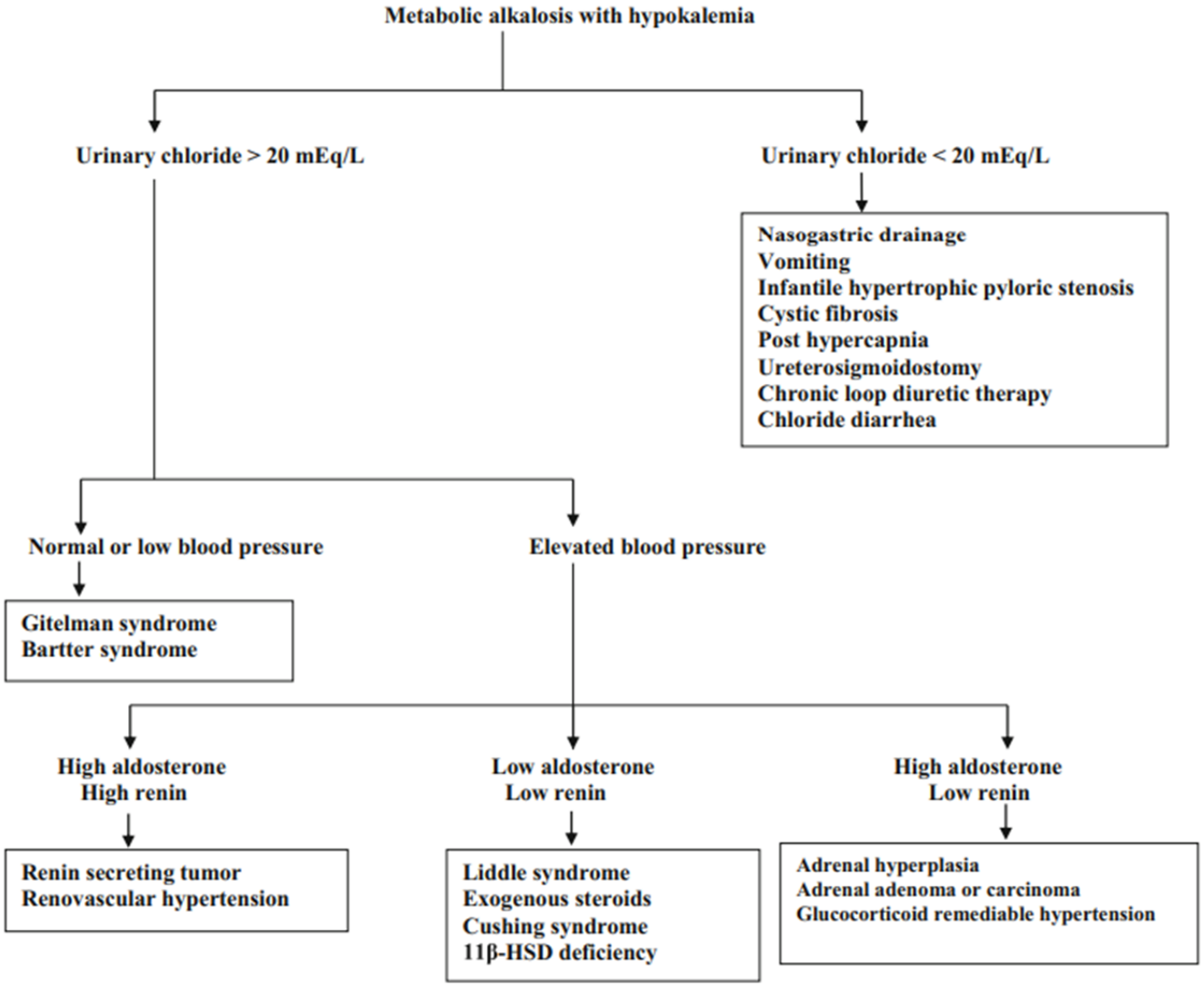
- Amlodipine, atenolol and prazosin initially
- **Later spironolactone added**
- Led to much better control of hypertension
- Pancreatectomy: hypertension resolved
- Chemotherapy

CASE 3

18 month old boy

- Presented with acute flaccid paralysis
- Referred as a case of GBS
- Failure to thrive (Weight 7 kg; -2 SD)
- BP- 132/90 (stage 2 hypertension)
- Serum K- 1.8 mEq/L, Na- 136, Cl-94, HCO3 32 mEq/L
- Serum creatinine-0.18 mg/dL
- Review of history- LBW-1.8 kg
- Hypercalciuria (Ca: Cr 1.5), no nephrocalcinosis
- Concentric LVH, Grade 2 hypertensive retinopathy

Approach to metabolic alkalosis



Further investigations

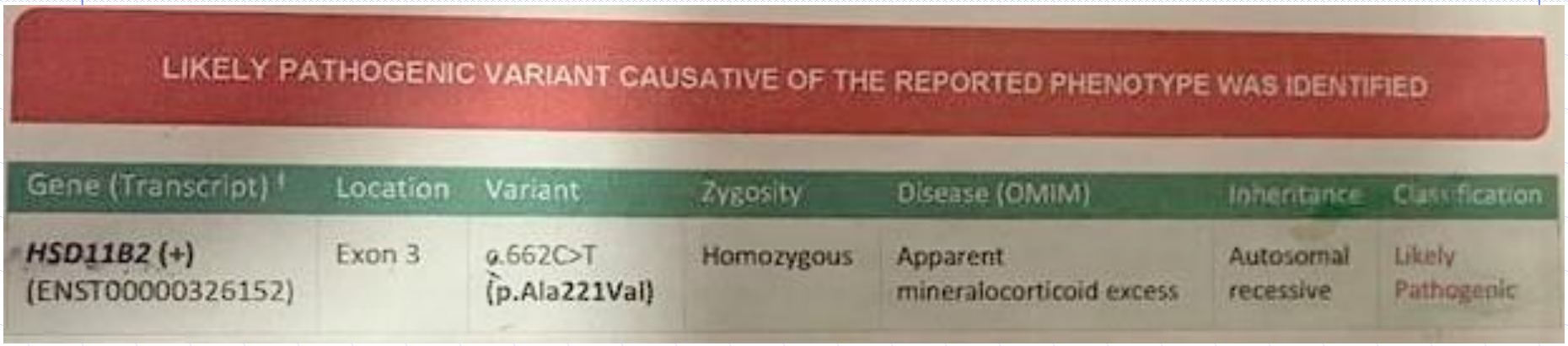
- Urine chloride- 60 mEq/L
- Plasma renin activity- 0.3 ng/mL/h (normal for age 3.0–9.0 ng/mL/h) (Low)
- Serum aldosterone- 0.5 ng/dL (1-124 ng/dL) (upright) (Low)
- Elevated 24-h urinary free cortisol-to-cortisone ratio- 4.5 (normal 0.5)

Question 2

- Which of the following is NOT a differential diagnosis in hypertension with hypokalemic metabolic alkalosis?

1. Renovascular hypertension
2. Liddle syndrome
3. 11 Beta-hydroxysteroid dehydrogenase 2 deficiency
4. Gitelman syndrome

Next Generation sequencing



LIKELY PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS IDENTIFIED

Gene (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
HSD11B2 **(+)** (ENST00000326152)	Exon 3	g.662C>T (p.Ala221Val)	Homozygous	Apparent mineralocorticoid excess	Autosomal recessive	Likely Pathogenic

HSD11B2 homozygous likely pathogenic variant detected

Diagnosis- 11 Beta hydroxysteroid dehydrogenase deficiency (Syndrome of Apparent Mineralocorticoid excess)

Management: Spironolactone and oral KCl supplements

Approach to monogenic hypertension

- Monogenic disorders of hypertension are a distinct group of diseases causing dysregulation of the renin–angiotensin–aldosterone system and are characterized by low plasma renin activity.
- (i) excessive aldosterone synthesis (familial hyperaldosteronism)
- (ii) dysregulated adrenal steroid metabolism and action (apparent mineralocorticoid excess, congenital adrenal hyperplasia, activating mineralocorticoid receptor mutation, primary glucocorticoid resistance)
- (iii) hyperactivity of sodium and chloride transporters in the distal tubule (Liddle syndrome and pseudo hypoaldosteronism type 2).
- The final common pathway is plasma volume expansion and catecholamine/sympathetic excess that causes urinary potassium wasting

Familial Hyperaldosteronism

Table 1 Clinical features, genetic defects, and management of familial hyperaldosteronism (FHA) types I to IV

FHA type	Gene	OMIM genotype, locus	Protein	Inheritance	Age of onset	Hypertension; potassium	Clinical and biochemical features	Diagnosis	Therapy
Type I	*CYP11B1/ CYP11B2*	*610613, 8q24.3	Aldosterone synthase ①	AD	Variable, infancy to young adulthood	Moderate–severe; usually normal	Intracranial aneurysms, early-onset stroke; occasional bilateral adrenal hyperplasia	High ARR, long-PCR sequencing; aldosterone <4 ng/dL following DST, high 18OHF	Low-dose steroids ± MRA or ENaC blocker
Type II	*CLCN2*	*600570, 3q27.1	Voltage-gated chloride channel-2 ②	AD	Variable, average age of 15 years[a]	Severe (incomplete penetrance reported); low in 9 patients[a]	Normal adrenals; rarely unilateral nodule or mild hyperplasia in two patients	High ARR (may be normal), genetic testing; family history ≥2 affected members differentiated from PA	MRA, other antihypertensive agents
Type III	*KCNJ5*	*600734, 11q24.3	G protein–activated inward rectifier potassium channel ③	AD	Infancy, early childhood[b]	Severe; usually very low[b]	Bilateral adrenal hyperplasia in severe forms; polyuria, metabolic alkalosis[b]	High ARR, genetic testing; high 18OHF; DST does not suppress aldosterone	MRA; bilateral adrenalectomy (severe forms)
Type IV	*CACNA1H*	*607904, 16p13.3	T-type voltage-gated calcium channel (Cav3.2) ④	AD	Variable, infancy to adulthood[c]	Severe, two normotensive; very low[c]	Unilateral nodule or adrenal hyperplasia in three patients; developmental delay or attention deficit in two patients[c]	High ARR, genetic testing; normal 18OHF; DST suppressed aldosterone in one patient	MRA

Monogenic hypertension with low PRA and low aldosterone

Table 2 Clinical, biochemical, and genetic characteristics of hypertension associated with low plasma renin activity (PRA) and low plasma aldosterone[a]

Disease	Gene	OMIM genotype, locus	Protein	Inheritance	Age of onset	Hypertension; potassium	Clinical and biochemical features	Diagnostic markers	Therapy
Apparent mineralocorticoid excess	*HSD11B2*	*614232,16q22.1	11β-Hydroxysteroid dehydrogenase-2 ⑨	AR	Infancy, early childhood (later in type 2)	Severe; markedly low (mild in type 2)	LBW, growth failure, polyuria, metabolic alkalosis, nephrocalcinosis, hypercalciuria	Urinary THF+5αTHF:THE >1 or free cortisol:cortisone >0.5	MRA, ENaC blocker; dexamethasone
Congenital adrenal hyperplasia	*CYP17A1* *CYP11B1*	*609300,10q24.32 *610613,8q24.3	17α-Hydroxylase ⑥ 11β-Hydroxylase ⑦	AR AR	*CYP17A1*: adolescence, *CYP11B1*: childhood	Variable; hypokalemia in *CYP17A1* defect	*CYP17A1*: delayed puberty, sexual infantilism *CYP11B1*: ambiguous genitalia, short stature, advanced bone age, precocious puberty	Screen: low morning cortisol *CYP17A1*: high progesterone relative to 17α-progesterone *CYP11B1*: high 11-deoxycortisol and deoxycorticosterone	Hydrocortisone replacement, MRA if required
Glucocorticoid resistance	*NR3C1*	*138040,5q31.3	Glucocorticoid receptor ⑨	AD, AR	Usually adults; 9 children aged 2–12 years reported	Severe in children, low or normal	Adrenal hyperplasia, virilization, poor growth, precocious puberty, hypoglycemia, metabolic alkalosis	High urinary free cortisol; cortisol >50 nmol/L after overnight DST	Dexamethasone, MRA if required
Activating MR mutation	*NR3C2*	*600983,4q31.23	Mineralocorticoid receptor ⑨	AD	Adolescence, adults	Severe, low	Hypertension exacerbated in pregnancy	Exacerbation of hypertension by spironolactone	Finerenone, ENaC blocker
Liddle syndrome									
Type 1	*SCNN1B*	*600760	ENaC ⑩ β subunit	AD	Late childhood, adolescence; can occur at any age	Usually severe but might be normal; low to normal	Metabolic alkalosis, family history in 90%	Low urinary aldosterone (<5 μg/day) or its metabolites	ENaC blocker
Type 2	*SCNN1G*	*600761,16p12.2	γ Subunit	AD					
Type 3	*SCNN1A*	*600228, 12p13.31	α Subunit	AD					
PHA type II									
PHA 2A	–	1q31–q42	–	AD	Adolescence, adulthood (infancy, childhood in types 2D and 2E)	Variable; hyperkalemia with rare instances of normokalemia	Variable metabolic acidosis, short stature, hypercalciuria in *WNK* mutations	Thiazide trial: normalizes blood pressure, electrolytes	Thiazide
PHA 2B	*WNK4*	*601844,17q21.2	With no lysine kinase 4 ⑪	AD					
PHA 2C	*WNK1*	*605232,12p13.33	With no lysine kinase 1 ⑪	AD					
PHA 2D	*KLHL3*	*605775,5q31.2	Kelch-like 3 ⑫	AD, AR					
PHA 2E	*CUL3*	*603136,2q36.2	Cullin 3 ⑫	AD					

Encircled numbers correspond to the abnormalities depicted in Fig. 1b

AD autosomal dominant, *AR* autosomal recessive, *DST* dexamethasone suppression test, *ENaC* epithelial sodium channel, *LBW* low birth weight, *MR* mineralocorticoid receptor, *MRA* mineralo-

Pediatric Nephrology
https://doi.org/10.1007/s00467-021-05246-x

EDUCATIONAL REVIEW

Monogenic forms of low-renin hypertension: clinical and molecular insights

Priyanka Khandelwal[1] · Jaap Deinum[2]

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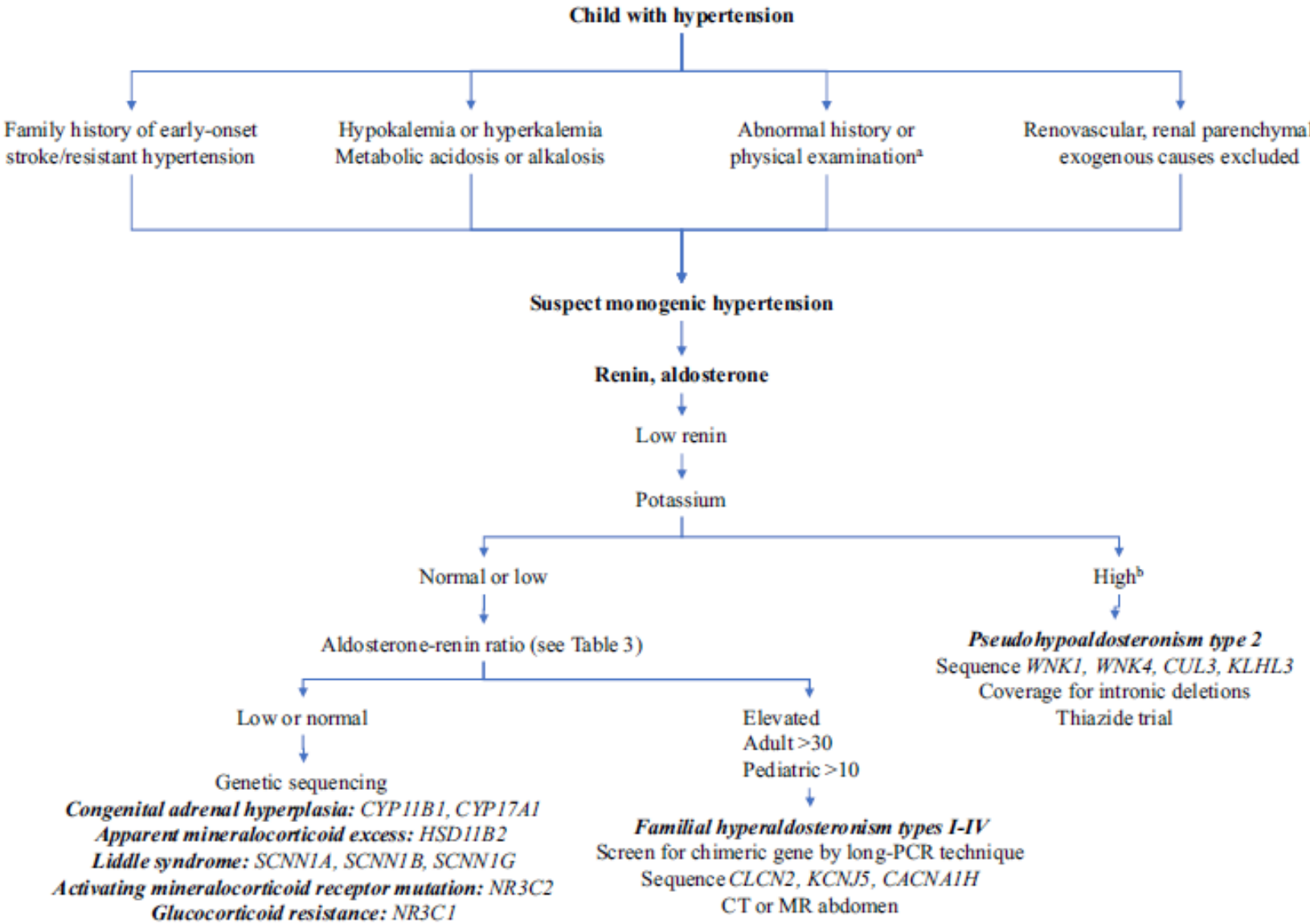
Approach to Monogenic hypertension



Monogenic hypertension might not always have hypokalemia or hyperkalemia!

A 10 year old boy with refractory hypertension with normokalaemia

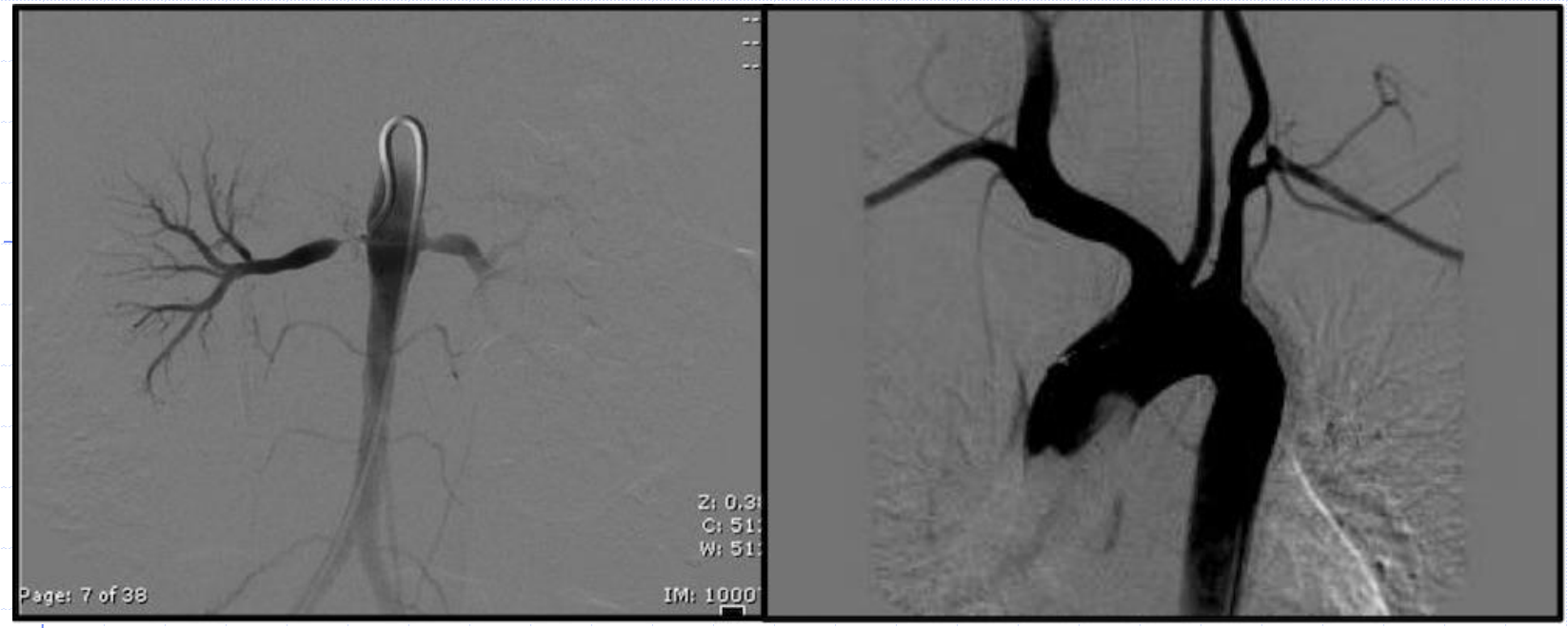
PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

Gene (Transcript) #	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
***CUL3* (-)** (ENST00000264414.9)	Exon 9	c.1329_1332del **(p.Asn443LysfsTer11)**	Heterozygous	Pseudo hypoaldosteronism type IIE	Autosomal dominant	Pathogenic

CASE 4

A 5 year old girl

- Referred for evaluation of **dilated cardiomyopathy** (after an episode of CCF)
- **BP- 180/120 mm Hg in Right upper limb**
- Physical examination findings were significant for weak left carotid, brachial, and radial pulses and bilateral carotid bruits.
- Renal ultrasonography with Doppler was performed, suggestive of **renal artery stenosis**
- Serum creatinine-0.35 mg/dL, urinalysis- normal
- ESR-80 mm/h
- CRP- 27 mg/L
- **Multiple antihypertensive agents required- Amlodipine, prazosin, hydrochlorothiazide, carvedilol, clonidine, minoxidil**



Angiography of her brain, chest, and abdominal vasculature was performed, revealing **significant narrowing of the left common, external, and internal carotids, and of the bilateral subclavian, hepatic, splenic, and renal arteries;** celiac axis narrowing; asymmetric kidney size; and diffuse thickening of the aorta from the heart through the abdomen, with a bright wall signal.

Diagnosis- Takayasu arteritis

EULAR/PRINTO/PRES classification criteria of childhood TA

- Angiographic abnormalities plus 1 of 5 following criteria (sens 100%, spec 99.9%)

1. Pulse deficit or claudication
2. Four limbs blood pressure discrepancy > 10 mmHg
3. Bruit
4. Hypertension >P95th
5. Acute phase reactant

- Angiography (conventional, CT, or MRI) of the aorta or **its main branches** and pulmonary arteries showing aneurysm/ dilatation, narrowing, occlusion or thickened arterial wall not due to fibromuscular dysplasia, or similar causes; changes usually focal or segmental

Ann Rheum Dis 2010;69:798-806.

Further Management

- Methylprednisolone pulses
- Persistent inflammatory activity
- Mycophenolate mofetil with prednisolone
- Antihypertensive drugs (Amlodipine, prazosin, hydrochlorothiazide, carvedilol, clonidine, minoxidil)
- Enalapril avoided due to B/L RAS
- Later, underwent balloon angioplasty of renal arteries
- Better control of hypertension
- Gradual tapering of steroids

Question 3

- Which of the following antihypertensives should not be used in Takayasu arteritis with bilateral renal artery stenosis?

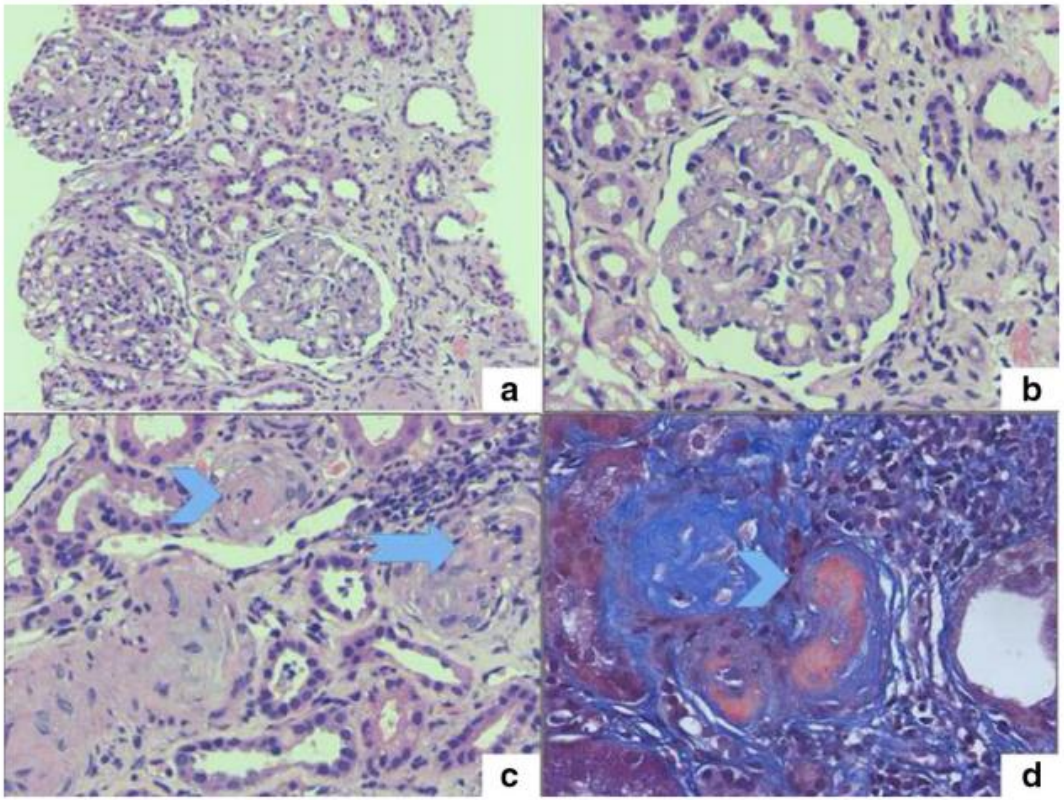
1. Enalapril
2. Hydrochlorthiazide
3. Amlodipine
4. Atenolol

CASE 5

A 7-year-old boy

- Fever 7 days ago for 2 days
- Pallor, decreased urine output x 5 days; BP- 136/90 at another hospital; Referred for High BP to our hospital
- No diarrhea, dysentery, rash, jaundice
- On examination- edema, signs of intravascular FO
- **BP-150/100 mm Hg, Stage 2 hypertension**, no HSM
- Hemoglobin 4.1 g/dL, TLC 10100, N51, L49,
- **Platelet count 1,60,000, schistocytes nil, LDH 460, Reticulocyte count 2%**
- Blood urea 210 mg/dL, serum creatinine 4.9 mg/dL, potassium 7 mEq/L, sodium 127
- Urinalysis 10 RBC/HPF, proteinuria 2+; Started on HD

Renal biopsy: TMA



a, b Histopathological sections of the kidney biopsy showing glomerular mesangiolysis (H&E × 100 and H&E × 200). c Blood vessel showing thrombi (arrowhead) and fibrin (arrow). d Masson's trichrome staining of the kidney biopsy specimen showing luminal red-colored thrombi (arrowhead) (MT × 400)

Further investigations

- Direct Coomb's test negative, CXR- no consolidation
- Coagulation profile and LFT normal
- Stool for Stx PCR negative
- Repeated evaluation for malaria negative
- HIV, HBsAg, HCV negative
- Serum C3 32 (low), ANA and dsDNA negative
- Required amlodipine, atenolol, prazosin, clonidine for BP control

- Diagnosis?
- Cause of hypertension?

aHUS (with no thrombocytopenia)

- **Factor H autoantibodies- 8500 AU/mL (n <150)**
- Plasmapheresis 17 sessions over 1 month
- Hemodialysis 10 sessions
- IV cyclophosphamide monthly pulses x 6 with prednisolone
- Maintenance MMF with prednisolone x 2 years

- **Serum creatinine 4 years later:**

  0.89 mg/dL (eGFR 79)- CKD stage 2
- **Continues to be hypertensive, amlodipine, atenolol, prazosin, has concentric LVH, no retinopathy**
- Albuminuria 2+, **Up: Uc 0.8, enalapril added.**
- Now no proteinuria. HUS activity is in remission.

CASE 6

A 9-year-old girl

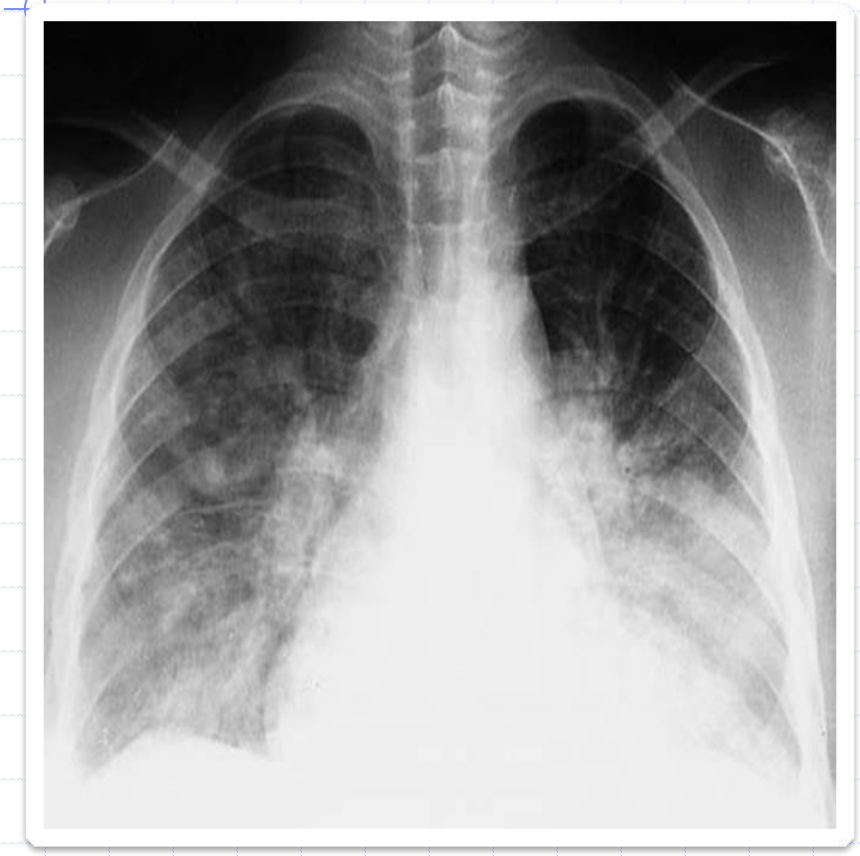
- Periorbital and pedal oedema for 1 week.
- Red urine and oliguria noticed for 4 days
- She had been growing well and was asymptomatic.
- No history of pyoderma, pharyngitis, rash or arthritis.

- **Blood pressure 140/90 mm Hg (Stage 2 hypertension)**
- Blood urea was 196 mg/dL(15-40)
- Serum creatinine 5.2 mg/dL (0.5-1)
- Urinalysis showed RBC casts and 2+ proteinuria.

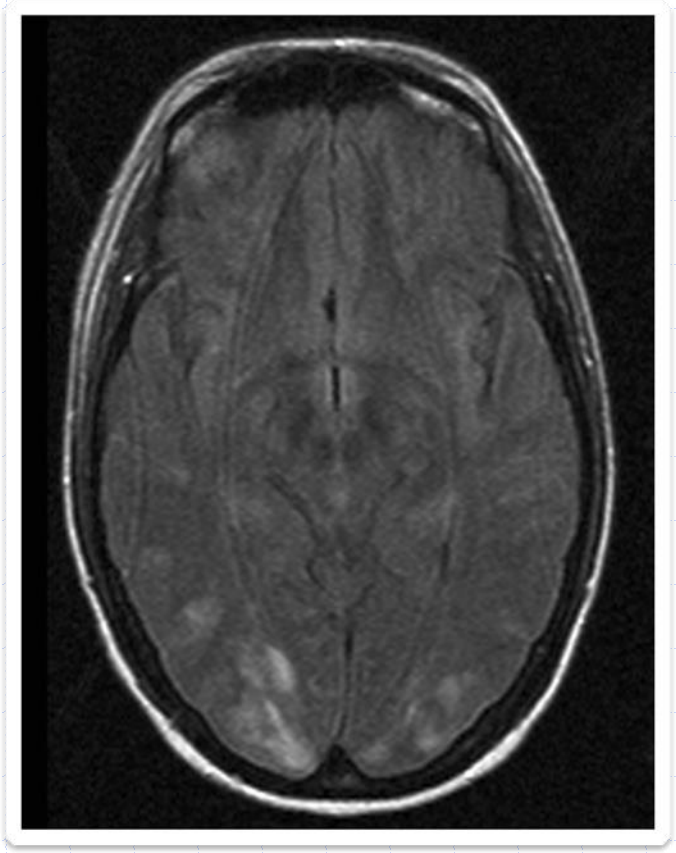
Investigations

- Serum C3 was 0.4 g/L (0.9–1.8).
- HBsAg, HIV, ANA, ANCA negative
- ECG normal.
- Fundus normal

Chest x ray



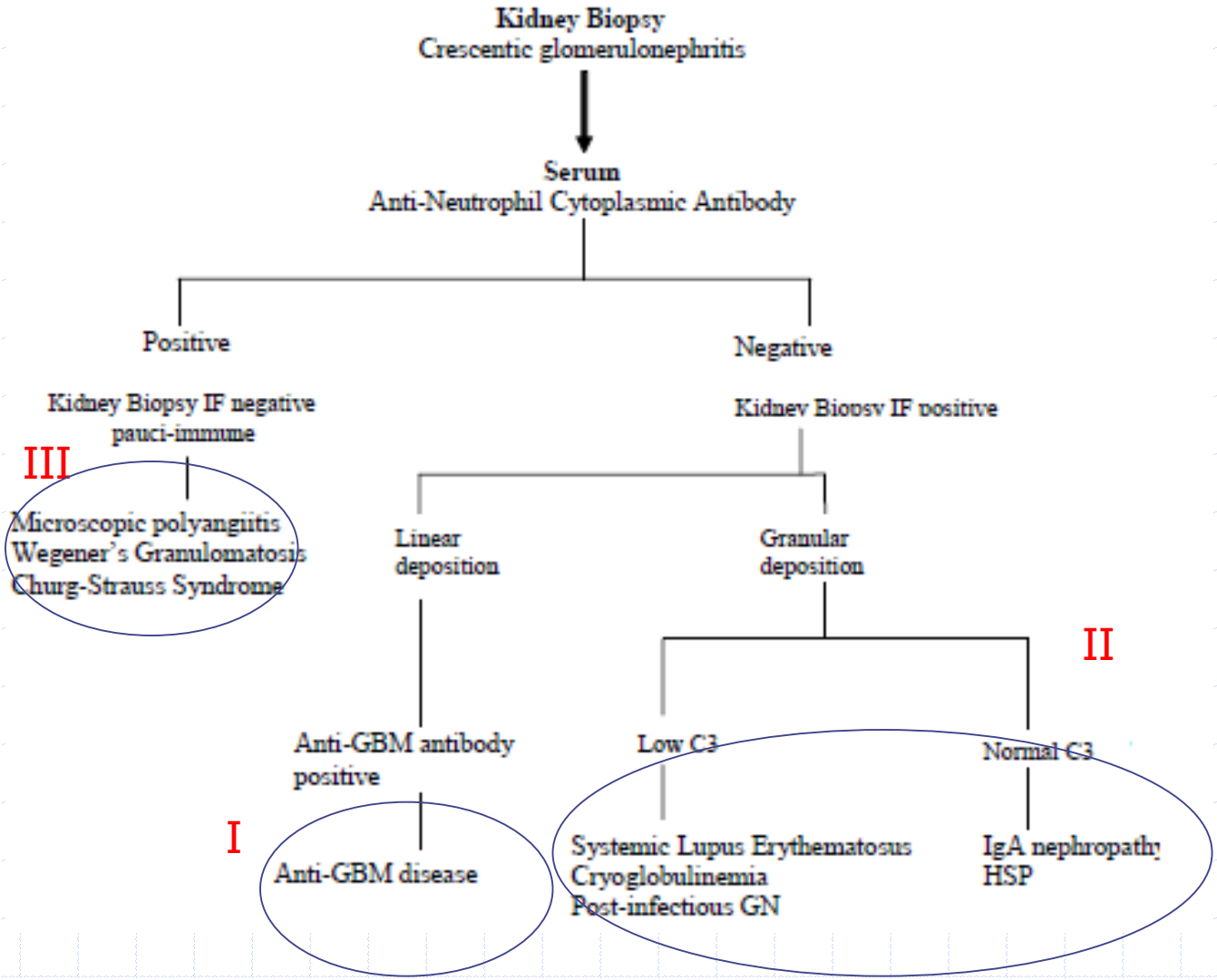
CECT Cranium



Diagnosis

- Rapidly progressive glomerulonephritis

RPGN


Kidney Biopsy
Crescentic glomerulonephritis
Serum
Anti-Neutrophil Cytoplasmic Antibody
Positive
Negative
Kidney Biopsy IF negative
pauci-immune
III
Microscopic polyangiitis
Wegener's Granulomatosis
Churg-Strauss Syndrome
Kidney Biopsy IF positive
Linear deposition
Granular deposition
II
Anti-GBM antibody positive
I
Anti-GBM disease
Low C3
Normal C3
Systemic Lupus Erythematosus
Cryoglobulinemia
Post-infectious GN
IgA nephropathy
HSP

Renal histopathological findings:C3GN

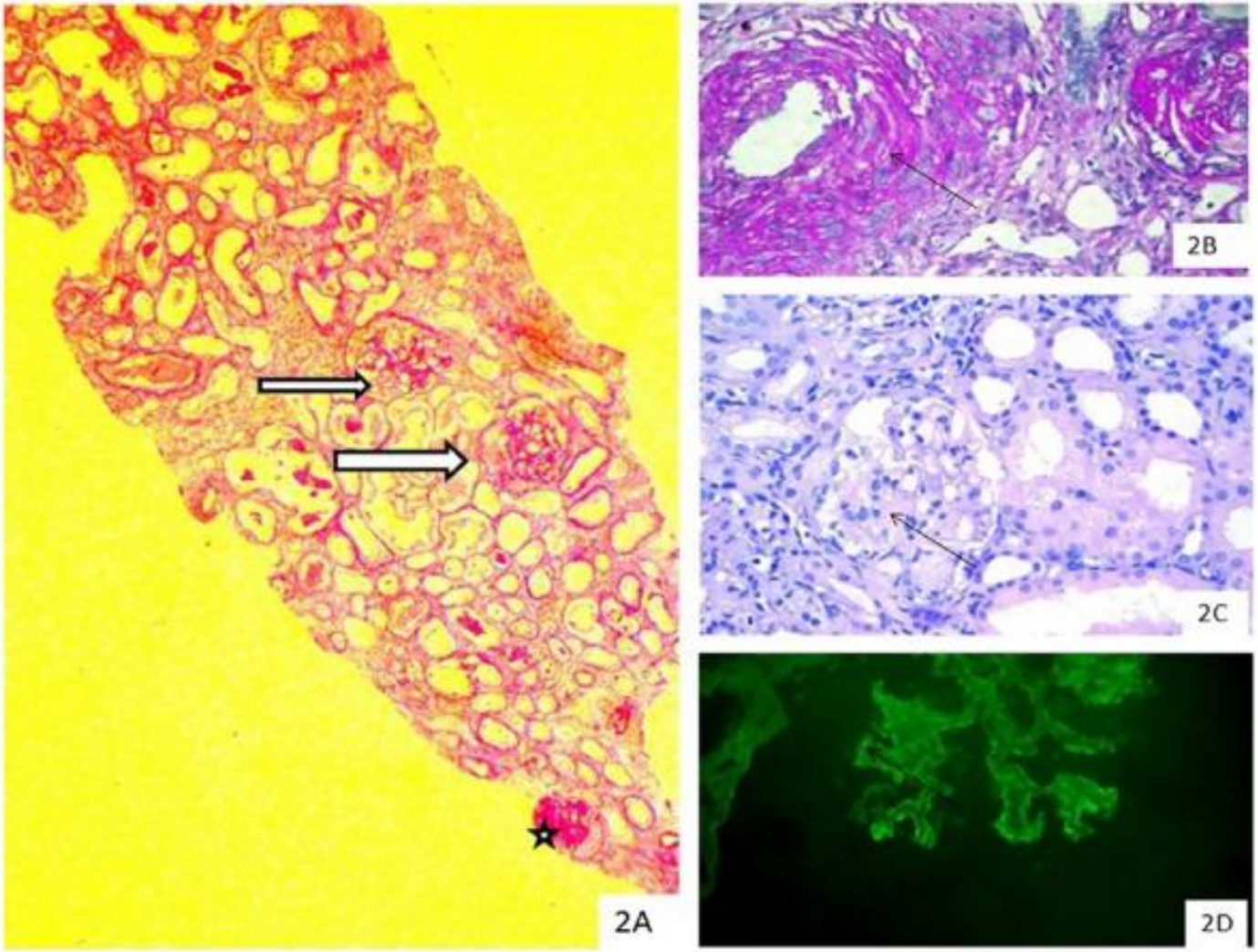


Figure 2 A. Three glomeruli, one of which shows a cellular crescent (small arrow) and the second one has a fibrocellular crescent (large arrow) and sclerosed glomeruli (open asterisk) (periodic acid Schiff stain, ×40); B. Sclerosed glomeruli with concentric hyperplastic arteriosclerosis (arrow) with >50% occlusion of the vascular lumen (periodic acid Schiff stain, ×20); C. Segmental sclerosis of glomeruli with pink hyaline deposits (arrow) (haematoxylin and eosin stain, ×40); D. Coarse granular sub-epithelial deposits of C3 the glomerular capillary wall (arrow) (FITC stain, DAKO antibodies USA, ×20)

Clinical course….

- ASO negative
- **Uncontrolled hypertension-nitroprusside infusion: (Amlodipine, prazosin, atenolol, clonidine, minoxidil)**

- Eight sessions of haemodialysis over the next 2 weeks.
- Three daily **methylprednisolone pulses** followed by 6 monthly **cyclophosphamide pulses** along with oral prednisolone (2 mg/kg/day) for 4 weeks.
- Thereafter, prednisolone was tapered

Final diagnosis

- Crescentic Glomerulonephritis (RPGN) due to C3GN

- Hypertension in this case required multiple antihypertensive drugs and hemodialysis along with treatment of RPGN with immunosuppressive drugs

Follow up

- Serum creatinine decreased to 0.72 mg/dL (eGFR 105) at the end of 3 months
- Up:Uc 0.1 at the end of 3 months
- Off antihypertensives by the 4th month
- On tapering doses of oral steroids and MMF

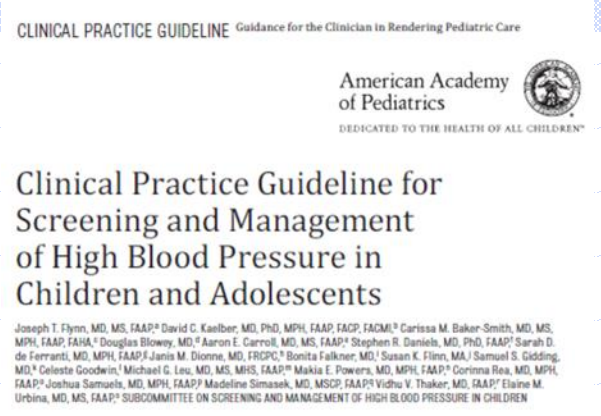
- Role of ABPM?
- Management strategies?

High risk conditions for which ABPM may be useful

Condition	Rationale
Secondary HTN	Severe ambulatory HTN or nocturnal HTN indicates higher likelihood of secondary HTN[161,167]
CKD or structural renal abnormalities	Evaluate for MH or nocturnal HTN,[168–172] better control delays progression of renal disease[173]
T1DM and T2DM	Evaluate for abnormal ABPM patterns,[174,175] better BP control delays the development of MA[176–178]
Solid-organ transplant	Evaluate for MH or nocturnal HTN, better control BP[179–188]
Obesity	Evaluate for WCH and MH[23,189–192]
OSAS	Evaluate for nondipping and accentuated morning BP surge[43,46,193,194]
Aortic coarctation (repaired)	Evaluate for sustained HTN and MH[58,112,113]
Genetic syndromes associated with HTN (neurofibromatosis, Turner syndrome, Williams syndrome, coarctation of the aorta)	HTN associated with increased arterial stiffness may only be manifest with activity during ABPM[58,195]
Treated hypertensive patients	Confirm 24-h BP control[155]
Patient born prematurely	Evaluate for nondipping[196]
Research, clinical trials	To reduce sample size[197]

Masked hypertension, white coat hypertension, adjusting drug doses in CKD

Drugs for hypertension


CLINICAL PRACTICE GUIDELINE Guidance for the Clinician in Rendering Pediatric Care

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

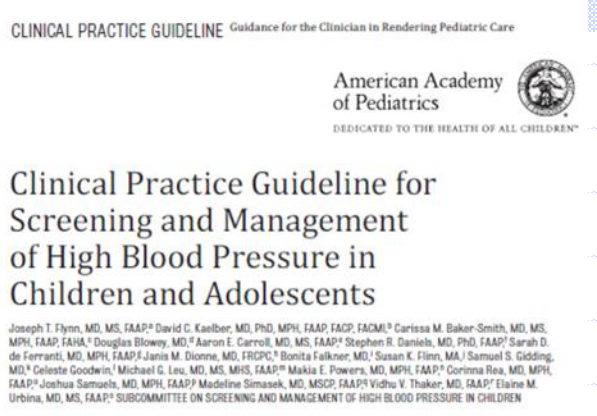
Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents

Joseph T. Flynn, MD, MS, FAAP,[a] David C. Kaelber, MD, PhD, MPH, FAAP, FACP, FACMI,[b] Carissa M. Baker-Smith, MD, MS, MPH, FAAP, FAHA,[c] Douglas Blowey, MD,[d] Aaron E. Carroll, MD, MS, FAAP,[e] Stephen R. Daniels, MD, PhD, FAAP,[f] Sarah D. de Ferranti, MD, MPH, FAAP,[g] Janis M. Dionne, MD, FRCPC,[h] Bonita Falkner, MD,[i] Susan K. Flinn, MA,[j] Samuel S. Gidding, MD,[k] Celeste Goodwin,[l] Michael G. Leu, MD, MS, MHS, FAAP,[m] Makia E. Powers, MD, MPH, FAAP,[n] Corinna Rea, MD, MPH, FAAP,[o] Joshua Samuels, MD, MPH, FAAP,[p] Madeline Simasek, MD, MSCP, FAAP,[q] Vidhu V. Thaker, MD, FAAP,[r] Elaine M. Urbina, MD, MS, FAAP,[s] SUBCOMMITTEE ON SCREENING AND MANAGEMENT OF HIGH BLOOD PRESSURE IN CHILDREN

- Children and adolescents with CKD, HTN, and proteinuria should be treated with an ACE inhibitor or ARB. [B, strong]

- In hypertensive children and adolescents who have failed lifestyle modifications (particularly those who have LV hypertrophy on echocardiography, symptomatic HTN, or stage 2 HTN without a clearly modifiable factor [eg, obesity]), clinicians should initiate pharmacologic treatment with an ACE inhibitor, ARB, long-acting calcium channel blocker, or thiazide diuretic. [B, moderate]

Treatment goals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- **In children and adolescents diagnosed with HTN**, the treatment goal with nonpharmacologic and pharmacologic therapy should be a reduction in SBP and DBP to **<90th percentile** and <130/80 mm Hg in adolescents ≥ 13 years old (grade C, moderate recommendation).

- *Children and adolescents with **CKD** should be evaluated for HTN at each medical encounter; Children or adolescents with both CKD and HTN should be treated **to lower 24-hour MAP to <50th percentile** by ABPM; and Regardless of apparent control of BP with office measures, children and adolescents with CKD and a history of HTN should have BP assessed by ABPM at least yearly to screen for MH (grade B; strong recommendation).*

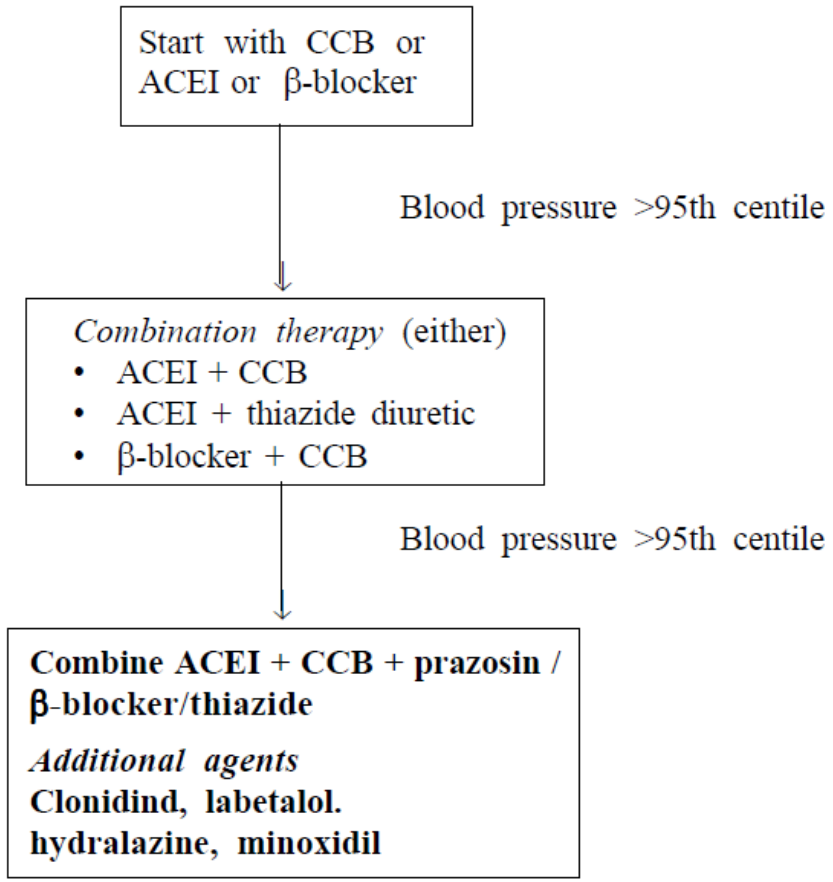
Wühl E, Trivelli A, Picca S, et al; ESCAPE Trial Group. Strict blood-pressure control and progression of renal failure in children. N Engl J Med. 2009;361(17):1639–1650

Question 4

- Which of the following antihypertensives should not be preferred in an adolescent with obesity and hypertension?

1. Amlodipine
2. Atenolol
3. Thiazides
4. ACE inhibitors

Drugs according to hypertension guidelines : ISPN 2007



In CKD, Sodium intake is restricted to between 1-1.5 g (45-65 mEq sodium, 2.6-3.8 g salt).

Essential hypertension:
ACEI/CCB, later Beta blockers
Thiazides not preferred in obesity

Acute glomerulonephritis:
Furosemide, if required…CCB

CKD stages 1-3
Enalapril (control of proteinuria)

Renal scars
Enalapril

Pheochromocytoma
Catecholamine blockade (Phentolamine, prazosin, Phenoxybenzamine, later beta blockade as adjunct)

Take home messages

- Hypertension in children is commonly of renal or renovascular origin
- Look for target organ damage in children with hypertension (Concentric LVH/ retinopathy)
- Serum creatinine, urinalysis, USG-KUB, Renal doppler, DMSA scan, CT angiogram/DSA useful in evaluation
- Treatment goals: SBP/DBP<90th centile
- Prompt and correct antihypertensive usage is essential for optimal control and good outcomes
- No substitute for a meticulous clinical examination

Thank You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