Review Article

Pediatric endocrine hypertension

Nisha Bhavani

Department of Endocrinology and Diabetes, Amrita Institute of Medical Sciences, Cochin, Kerala, India

ABSTRACT

Endocrine causes of hypertension are rare in children and screening for endocrine hypertension in children should be carried out only after ruling out renal and renovascular causes. Excess levels and/or action of mineralocorticoids associated with low renin levels lead to childhood hypertension and this can be caused by various conditions which are discussed in detail in the article. Childhood pheochromocytomas are being increasingly diagnosed because of the improved application of genetic testing for familial syndromes associated with pheochromocytomas. Adolescents with polycystic ovarian syndrome (PCOS) can also have hypertension associated with their obese phenotype.

Key words: Pediatric endocrine hypertension, essential hypertension, adrenal, aldosterone

Introduction

Hypertension (HT) in children is defined as blood pressure consistently above the 95th percentile for age and height of the child.[1] Blood pressure in children should be measured with an appropriate sized pediatric BP cuff, with the child supine or sitting down. Adolescents may acquire essential or primary HT, but HT in younger children is almost always secondary unless otherwise proved. Renal and vascular causes are the commonest causes of HT in children. Screening for endocrine HT in children should be done only after ruling out renal and renovascular diseases. Endocrine HT *per se* is often asymptomatic in children, but signs of the underlying diseases may be evident, like features of Cushing's syndrome, growth failure, pubertal abnormalities, etc. Sustained severe HT in children can present with headache, seizures, epistaxis, visual disturbances, unexplained cardiac failure and renal failure.

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.86980

Causes of Endocrine HT in Children

Low renin HT /Mineralocorticoid HT

Adrenal steroid synthetic defects
11-beta hydroxylase deficiency
17-alpha hydroxylase deficiency
Glucocorticoid remediable hyperaldosteronism (GRA)
Apparent mineralocorticoid excess (AME)
Gordon syndrome
Liddle syndrome
Generalized glucocorticoid resistance
Cushing's syndrome

Adrenocortical tumors – adenoma, carcinoma

Adrenomedullary tumors
Pheochromocytoma
Neuroblastoma

Rare causes

Hyperthyroidism
Hyperparathyroidism
Hypervitaminosis D

Endocrine disease associated with primary HT

Polycystic ovarian syndrome (PCOS)

Drugs

Glucocorticoids
Oral contraceptive Pills OCP

Corresponding Author: Dr. Nisha Bhavani, Department of Endocrinology and Diabetes, Amrita Institute of Medical Sciences, Cochin – 682 041, Kerala, India. E-mail: nishab@aims.amrita.edu

Low renin HT

Low renin HT is a common variant of HT seen in children and may be due to various genetic causes which ultimately lead to excess levels and/or action of mineralocorticoids.[2-4]

11-beta hydroxylase deficiency

11-beta hydroxylase deficiency is the second most common form of congenital adrenal hyperplasia (CAH) contributing to 11% of all cases of CAH, with 21-hydroxylase deficiency being the most common form. It is caused by the mutations of *Cyp11B1* gene in chromosome 8q22 which normally converts deoxycorticosterone (DOC) to corticosterone and deoxycortisol to cortisol. When the enzyme is deficient, cortisol production is decreased, which feed backs on the pituitary to increase the adrenocorticotropic hormone (ACTH) that causes precursors proximal to the block to accumulate. So, DOC and deoxycortisol accumulate and the proximal precursors are channeled to form adrenal androgens. DOC acts as a mineralocorticoid and causes sodium retention, HT, potassium excretion, volume expansion, and renin suppression with consequent decreased aldosterone production. The disease can occur in classic and nonclassic forms depending on the amount of enzyme activity present. In the classic form, the female fetus develops ambiguous genitalia because of exposure to excess adrenal androgens, and will have HT, hyperpigmentation and hypokalemia. The nonclassic forms may be born with only minimal ambiguity and most often present postnatally with hyperandrogenic features like hirsuitism, acne, irregular menses, infertility, polycystic ovaries and HT. Hypokalemia is not frequently observed in nonclassic cases. Males usually present with precocious puberty, HT and hypokalemia.[5-7]

Laboratory evaluation will show an elevated deoxycortisol, DOC, modest elevations of 17-hydroxyprogesterone, androstenedione and testosterone and a suppressed renin concentration. ACTH stimulation may yield elevated deoxycortisol and DOC values. Treatment is with glucocorticoids at a dose of 15 mg/m^2 of hydrocortisone. The glucocorticoids suppress the ACTH levels, which in turn suppress the DOC secretion and normalize the renin concentration, hypokalemia and HT.[7]

17-alpha hydroxylase deficiency

17-alpha hydroxylase deficiency contributes to less than 1% of all cases of CAH. The gene for this enzyme has been mapped to chromosome 10 and mutations are common in Dutch Mennonites. 17-alpha hydroxylase is the enzyme which converts pregnenolone and progesterone to 17-hydroxy pregnenolone and 17-hydroxy progesterone, respectively. When this enzyme is deficient, 17-desoxy steroids are produced in excess leading to increased serum concentrations of DOC and corticosterone which have mineralocorticoid activity. So, renin is suppressed and aldosterone levels are decreased and patients have HT and hypokalemia. But since the precursors cannot enter the androgenetic pathway as well, the males with 46 XY chromosome have undervirilization *in utero*, leading to genital ambiguity; at puberty, they develop gynecomastia due to unknown reasons. Females with 46 XX constitution have no ambiguity, but have sexual infantilism at puberty.[8-10] Elevated levels of 17-deoxy steroids such as progesterone, pregnenolone, DOC and corticosterone in the plasma establish the diagnosis. Treatment is with glucocorticoid replacement which normalizes the DOC levels, plasma renin levels and the HT. Both males and females require sex steroid replacement at puberty, in addition.

Apparent Mineralocorticoid Excess

Apparent mineralocorticoid excess (AME) is an autosomal recessive disorder caused by deficiency of 11 beta hydroxysteroid dehydrogenase 2 (11-beta HSD 2) enzyme which is encoded by a gene in chromosome 16q22. This enzyme is normally found in the distal convoluted tubules of the kidneys, where it inactivates the circulating cortisol to cortisone and prevents it form acting on the mineralocorticoid receptor (MR). Hence, the MR is normally activated only by the microamounts of aldosterone secreted by the adrenal glands. When the 11-beta HSD 2 is deficient, inactivation of cortisol does not take place and all the cortisol secreted in macroamounts acts on the MR, causing HT and hypokalemia which in turn causes renin suppression and subsequent decrease in aldosterone from the zona glomerulosa. The increased levels of circulating bioactive cortisol causes a feedback effect on the pituitary and suppresses ACTH levels, leading to decreased secretion of all hormones from the zona fasciculata. Thus, the classic features of AME include low renin HT and hypokalemia aggravated by ACTH and glucocorticoids, low levels of cortisol and capacity to survive stress without glucocorticoid replacement in spite of low steroid level. Children with AME usually present in the neonatal period with failure to thrive, HT and persistent polyurea and polydypsia and can die form hypertensive stroke and cardiac arrest. In addition, rickets due to calcium phosphorous abnormalities with nephrocalcinosis can occur. Acquired causes of AME include excess consumption of licorice and carbenoxolone which inhibits the 11-beta HSD 2 enzyme.

Treatment is difficult; the most effective drug is aldosterone antagonist spironolactone, though other diuretics also have some action, especially thiazide diuretics in the presence of nephrocalcinosis. Dietary sodium restriction and potassium

supplementation also helps. Renal transplantation has been tried in some cases with success.[11-13]

Familial hyperaldosteronism Type 1 or glucocorticoid remediable hyperaldosteronism

GRA is an autosomal dominant condition caused by inheritance of a chimeric gene for aldosterone synthase in which the regulatory sequences are derived from *Cyp11B1* gene which encodes 11-beta hydroxylase enzyme and is under the control of ACTH, whereas the coding sequence is derived form *Cyp11B2* gene which encodes the aldosterone synthase and is under the control of angiotensin II. This happens because of unequal crossing over of highly homologous *Cyp11B1* and *Cyp11B2*. This hybrid gene is expressed in all the layers of the adrenal cortex; in the zona fasciculata, aldosterone is thus produced ectopically under the influence of ACTH, independent of control by angiotensin II. Hybrid gene products, 18-hydroxycortisol and 18-oxocortisol produced under the influence of 18-hydroxylase and 18-oxidase activities, are also markedly elevated in GRA. High aldosterone levels cause volume expansion and suppression of renin.[14]

Clinically, GRA presents with early onset HT, with the mean age of onset being 13 years. HT is moderate to severe in most cases but can be mild or normal depending on the hereditary factors controlling HT and dietary salt intake. Hence, a positive family history is always not forthcoming. Patients with GRA are more prone to develop cerebrovascular accidents, especially fatal cerebral hemorrhage from rupture of intracranial aneurysms. Left ventricular wall changes are also common, indicating excess of aldosterone in the blood and may be independent of the degree of HT. Growth is typically not affected in children with GRA unlike AME and CAH. Though hypokalemia is typically associated with hyperaldosteronism, it may not be always seen and may be precipitated only by treatment with potassium losing diuretics. Treatment with glucocorticoids, which suppress ACTH, decreases aldosterone levels and subsequent clinical and biochemical features.[15]

Diagnosis is suspected in patients with early onset HT with family history of young hemorrhagic strokes. Confirmatory tests are done in those with primary hyperaldosteronism with onset below the age of 20 years or family history of early hemorrhagic stroke or family history of primary hyperaldosteronism. For establishing the diagnosis, genetic testing for the chimeric gene is done with either Southern blotting or polymerase chain reaction (PCR) based technology. Levels of 18-oxocortiosl and 18-hydroxycortisol are markedly elevated in GRA. Suppressibility of plasma aldosterone to levels <4 ng/dl after 4 days of dexamethasone 0.5 mg every 6 hours had been used in the past to diagnose GRA but lacks specificity.

Complete suppression of ACTH with a longacting steroid like dexamethasone or prednisolone at a dose of 0.125 and 2.5 mg, respectively, daily given at bedtime controls the HT and hypokalemia if present. Dose should be kept at minimum to avoid the growth-suppressing effects of steroids in children. If HT is not controlled with glucocorticoids, the addition of aldosterone antagonists will suffice. Spironolactone is relatively cheap and easily available, but has antiandrogenic properties which may interfere with puberty in children. Eplerenone is a more specific MR antagonist in use but is more expensive. Other alternatives are potassium sparing diuretics like amiloride and triamterene. Care should be taken to avoid the use of potassium losing diuretics which can precipitate dangerous hypokalemia.[16]

Some cases of familial hyperaldosteronism are described which can present in childhood with severe HT and bilateral enlarged adrenals which respond poorly to aldosterone antagonists and may require bilateral adrenalectomy.[16]

Gordon syndrome

Gordon syndrome is an autosomally dominant inherited syndrome characterized by hyperkalemia in all and varying degrees of hyperchloremic acidosis, HT, short stature, mental subnormality and muscle weakness in the presence of normal renal glomerular function. This was first described by Gordon in 1960s, but the pathophysiology still remains unclear. Some proposed mechanisms are a defect in WNK kinases and their targets in the renal tubule, which causes sodium retention and volume expansion and HT. This in turn leads to suppressed renin concentration which prevents the kaliuretic action of aldosterone, leading to hyperkalemia. Low levels of atrial natriuretic hormone (ANH) and/or reduced responsiveness to ANH, impaired cell membrane transport and impaired prostaglandin metabolism have all been proposed as pathogenetic mechanisms in Gordon syndrome. The biochemical features are exactly opposite to that of Bartter's syndrome which is caused by loss of function mutation of Na Cl cotransporter in the renal tubules.[17-19]

HT in Gordon syndrome is usually severe and is seen more frequently in males. It may not manifest in childhood in all cases, but is seen commonly in young adulthood. Hence, the diagnosis is often missed and it masquerades as essential HT unless hyperkalemia is detected. The HT is extremely sensitive to salt intake and restriction of dietary salt leads to reversal of HT and hyperkalemia. HT usually ameliorates during pregnancy but the hyperkalemia persists, and such babies tolerate hyperkalemia better and do not usually

develop cardiac arrhythmias. Hypercalciurea and low bone mass are also seen as characteristic features in most families. Patients not responding to dietary salt restriction need thiazide diuretics which are usually started at 50% of the age- and weight-adjusted dosage because of the extreme sensitivity of the HT to thiazide diuretics. Growth rate may also normalize with thaizide diuretics.[19]

Liddle syndrome

This rare autosomal dominant syndrome is due to mutations of the beta and gamma subunits of the amiloride-sensitive epithelial sodium channel of the renal tubule, leading to sodium retention, HT, kaliuresis, hypokalemia and suppressed renin angiotensin aldosterone axis. Because of the low levels of aldosterone, it was previously called pseudoaldosteronism. The HT and hypokalemia respond to amiloride and triamterene, but not to spironolactone.[20-22]

Generalized glucocorticoid resistance

This is yet another rare familial syndrome caused by resistance to the action of cortisol due to mutation in glucocorticoid receptor leading to high ACTH levels and subsequent high cortisol levels. Patients do not have features of Cushing's syndrome, but have HT due to the high cortisol overwhelming the 11-beta HSD 2 enzyme and acting on the MR and the high ACTH driving the production of DOC which has mineralocorticoid action. In addition to HT, the patients have hypokalemia and alkalosis and signs of androgen excess. Treatment of HT is with a MR antagonist or suppression of ACTH by small doses of dexamethasone.[23,24]

Cushing's syndrome

The pathogenesis of HT in Cushing's syndrome is multifactorial; the proposed mechanisms include salt and water retention, permissive effect of cortisol on catecholamine action, role of vasopressors like angiotensin II, arginine vasopressin (AVP), endothelins, reduction in vasodilator nitrous oxide, increased oxidative stress due to oxygen free radicals, etc.[25] The systolic blood pressure is markedly elevated with moderate elevation of diastolic blood pressure. HT due to Cushing's syndrome is usually seen in older children with Cushing.[26] In addition to HT, they have truncal obesity, acne, hirsuitism, delayed puberty and behavioral abnormalities like obsessive compulsive neurosis and psychosis. Younger children present with growth retardation and weight gain. Signs of protein catabolism like thin skin, broad violaceous striae, proximal myopathy, easy bruisability and low bone mass, though characteristic of Cushing, may not be evident in children if the Cushing is associated with androgenisation androgenization as in cases of adrenal carcinoma because of the anabolic properties of androgens.[27] Exogenous steroid administration is the commonest cause of Cushing in children. Etiology of endogenous Cushing in children includes ACTH-dependent and -independent causes. ACTH secreting pituitary adenoma is common in postpubertal children, whereas ectopic Cushing is rare. ACTH-independent causes are the commonest cause of Cushing in younger kids and include adrenal tumors (both adenoma and carcinoma), ACTH-independent bilateral adrenal hyperplasia, pigmented nodular hyperplasia and Mc Cune Albright syndrome. Adrenal carcinoma usually presents with signs of hyperandrogenism in addition to hypercortisolism; these include precocious puberty in boys and virilisation in girls. Pigmented nodular hyperplasia is usually seen associated with Carney's complex which includes multiple lentigenes, atrial and cutaneous myxomas, testicular tumors, pituitary adenomas, and pigmented schwannomas. Both the adrenals are replaced by pigmented micronodules which may be visible only under the microscope. Mc Cune Albright syndrome due to Gs alpha activating mutation can involve ACTH receptor in the adrenal, leading to Cushing's syndrome, and may be associated with other features like café au lait spots, polyostotic fibrous dysplasia and endocrinopathies like precocious puberty, hypophosphatemic rickets and gigantism. HT is more common in ACTH-independent causes of Cushing in children. Diagnosis is established by demonstrating hypercortisolism as indicated by loss of normal diurnal variation of cortisol secretion, raised 24-hour urinary free cortisol concentration, raised salivary cortisol and unsuppressed serum cortisol after dexamethasone suppression. Treatment is often surgical resection of the pituitary or adrenal lesion. Pituitary adenomas may require radiotherapy in addition. Bilateral adrenalectomy is indicated in ACTH-independent bilateral adrenal hyperplasia, pigmented nodular hyperplasia and Mc Cune Albright syndrome. Children with Cushing are at risk for residual HT despite a significant improvement after surgical cure.

Pheochromocytoma

Previously, pheochromocytoma was known as the 10% tumor, as 10% of pheochromocytomas were bilateral, 10% were found in children, 10% were extra-adrenal and 10% were malignant. But presently, with the advancement of molecular genetics, this scenario has changed. Now around 25% are found to be familial pheochromocytomas, hence many more children are diagnosed with pheochromocytoma. Children have a 30% incidence of bilateral, extra-adrenal and malignant pheochromocytoma. Children mostly present between ages of 6 and 14 years with sustained HT; only around

10–20% of the children have paroxysmal HT and a similar percentage are normotensive. Orthostatic hypotension is also common in children with pheochromocytoma, and headache, sweating, nausea and vomiting are the other common complaints. Pheochromocytoma may also masquerade as acute abdomen, seizures, encephalopathy, cardiac failure and pyrexia of unknown origin(PUO). Because of the hypercatabolic state, children have growth retardation and failure to thrive in spite of having a good appetite. Diagnosis is established as in adults with measurements of 24-hour urine fractionated metanephrines or plasma metanephrines or catecholamines, followed by anatomic imaging by computed tomography (CT)/ magnetic resonance imaging (MRI) and functional imaging by metaiodobenzylguanidine (MIBG) scanning. Genetic analysis for familial syndromes like RET protooncogene for multiple endocrine neoplasia type 2 (MEN 2), VHL mutation for VHL(Von Hippel Lindeau) and succinate dehydrogenase (SDH) mutations need to be looked for in all children with pheochromocytoma.[28,29]

Preoperative preparation is with alpha blockers, phenoxybenzamine at a dose of 0.5–1 mg/kg/12 hours or parzocin at a dose of 0.1–0.4 mg/kg/day in four divided doses, and beta blockers to control the tachycardia after adequate alpha blockade is achieved. Preoperative volume expansion with salt loading and saline infusion is recommended to avoid postoperative hypotension. Both laparoscopic and open adrenalectomy are used in children with pheochromocytoma. Postoperatively, the child should be kept under long-term close follow–up, especially because recurrence and malignant potential are more in children with pheochromocytoma.

Neuroblastomas arising form adrenal glands occur in very young children and can be associated with HT.

Polycystic ovarian disease

Adolescents with PCOD are more prone to develop HT; whether this is independent of the risk of HT contributed by obesity is controversial. Other factors contributing to HT in PCOD are hyperinsulinemia, hyperandrogenism and increased sympathetic activity. Adolescents with PCOD need regular monitoring of their blood pressure; treatment of HT and prehypertension may potentially reduce their cardiovascular risk.

References

1. 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 adolescents and children. Pediatrics 2004;114 Suppl 2:555-76.
2. Hassan-Smith Z, Stewart PM. Inherited forms of mineralocorticoid hypertension. Curr Opin Endocrinol Diabetes Obes 2011;18:177-85.
3. Wranock DJ. Aldosterone related genetic effects in hypertension. Curr Hypertens Rep 2000;2:295-301.
4. Rolim AL, Lindsey SC, Kunii IS, Fujikawa AM, Soares FA, Chiamolera MI, *et al*. Ion channelopathies in endocrinology: Recent genetic findings and pathophysiological insights. Arq Bras Endocrinol Metabol 2010;54:673-81.
5. White PC. Steroid 11 beta hydroxylase deficiency and related disorders. Endocrinol Metab Clin North Am 2001;30:61-79.
6. Bhangoo A, Wilson R, New MI, Ten S. Donor splice mutation in the 11 beta hydroxylase (Cyp11B1) gene resulting in sex reversal: A case report and review of the literature. J Pediatr Endocrinol Metab 2006;19:1267-82.
7. Ahmed SF, Rodie M. Investigation and initial management of ambiguous genitalia. Best Pract Res Clin Endocrinol Metab 2010;24:197-218.
8. Anchus RJ. The genetics, pathophysiology, and management of human deficiencies of P450c17. Endocrinol Metab Clin North Am 2001;30:101-19.
9. Miller WL. Steroid 17 alpha hydroxylase deficiency–Not rare everywhere. J Clin Endocrinol Metab 2004;89:40-2.
10. Aydin Z, Ozturk S, Gursu M, Uzun S, Karadag S, Kazancioglu R. Male pseudohermaphroditism as a cause of secondary hypertension. A case report. Endocrine 2010;38:100-3.
11. Morineau G, Sulmont V, Salomon R, Fiquet-Kempf B, Jeunemaître X, Nicod J, *et al*. Apparent mineralacorticoid excess: Report of six new cases and extensive personal experience. J Am Soc Nephrol 2006;17:3176-84.
12. Stewart PM, Shackleton CH, Edwards CR. The cortisol cortisone shuttle and the genesis of hypertension. In: Mantero F, Vecse P, editors. Corticostreoids and peptide hormones in hypertension. New York: Raven Press; 1987. p. 163.
13. Stewart PM, Corrie JE, Shackleton CH, Edwards CR. Syndrome of apparent mineralocorticoid excess: A defect in cortisol cortisone shuttle. J Clin Invest 1988;82:340-9.
14. Dluhy RG, Anderson B, Harlin B, Ingelfinger J, Lifton R. Glucocorticoid remediable aldosteronism is associated with severe hypertension in early childhood. J Pedaitr 2001;138:715-20.
15. Lieberman E. Pediatric hypertension: Clinical perspective. Mayo Clin Proc 1994;69:1089-97.
16. Halperin F, Dluhy RG. Glucocorticoid remediable aldosteronism. Endocrinol Metab Clin North Am 2011;40:333-41, 8.
17. Klemn SA, Gordon RD, Tunny TJ, Thompson RE. The syndrome of hypertension and hyperkalemia with normal GFR (Gordon syndrome): Is there increased proximal sodium reabsorption? Clin Invest Med 1991;14:551-8.
18. Wilson FH, Disse-Nicodème S, Choate KA, Ishikawa K, Nelson-Williams C, Desitter I, *et al*. Human hypertension caused by mutations in WNK kinases. Science 2001;293:1107-12.
19. Stowasser M, Pimenta E, Gordon RD. Familial or genetic primary aldosteronism and Gordon Syndrome. Endocrinol Metab Clin North Am 2011;40:343-68, 8.
20. Liddle GW, Blesdoe T, Coppage WS Jr. A familial renal disorder simulating primary aldosteronism but with negligible aldosterone secretions. Trans Assoc Am Physicians 1963;76:199-213.
21. Hansson JH, Nelson-Williams C, Suzuki H, Schild L, Shimkets R, Lu Y, *et al*. Hypertension caused by truncated epithelial sodium channel subunit: Genetic hetrogenity of Lddle syndrome. Nat Genet 1995;11:76-82.
22. Warnock DJ. Liddle syndrome: Genetics and mechanisms of Na+ channel defects. Am J Med Sci 2001;332:302-7.

23. Mantero F, Boscardo M. Glucocorticoid Dependent Hypertension. J Steroid Biochem Mol Biol 1992;43:409-13.
24. Stratakis C, Karl M, Shulte H, Chrousos GP. Glucocorticoid resistance in humans: Elucidation of the molecular mechanisms and implications for pathophysiology. Ann N Y Acad Sci 1994;746:362-74; discussion 374-6.
25. Goodwin JE, Zhang J, Gonzalez D, Albinsson S, Geller DS. Knockout of vascular endothelial glucocorticoid receptor abrogates dexamethasone induced hypertension. J Hypertens 2011;29: 1347-56.
26. Lodish MB, Sinaii N, Patronas N, Batista DL, Keil M, Samuel J, *et al*. Blood pressure in Pediatric patients with Cushing syndrome. J Clin Endocrinol Metab 2009;94:2002-8.
27. Savage MO, Lienhardt A, Lebrethon MC, Johnston LB, Huebner A, Grossman AB, *et al*. Cushing's disease in childhood: Presentation, investigation, treatment and long-term outcome. Horm Res 2001;55 Suppl 1:24-30.
28. Zuber SM, Kantorovich V, Pacak K. Hypertension in pheochromocytoma. Characteristics and treatment. Endocrinol Metab Clin North Am 2011;40:295-311, 7.
29. Pacak K, Linehan WM, Eisenhofer G, Walther MM, Goldstein DS. Recent advances in genetics, diagnosis, localization and treatment of pheochromocytoma. Ann Intern Med 2001;134:315-29.

Cite this article as: Bhavani N. Pediatric endocrine hypertension. Indian J Endocr Metab 2011;15:361-6.

Source of Support: Nil, **Conflict of Interest:** None declared.