

## CURRENT TOPIC

## Investigation of hypertension and the recognition of monogenic hypertension

David V Milford

Hypertension in childhood is rare and is more likely to be secondary to a medical disorder in the very young and in those with severe hypertension. Essential hypertension is rarely diagnosed in children less than 5 years of age but is diagnosed with increasing frequency from the age of 10 years. These observations justify the aggressive investigation of preschool children with persistent hypertension (blood pressure > 97th centile for height<sup>1</sup>) and school aged children with severe hypertension, because of the high probability of making a diagnosis.

The assessment of a child with hypertension should begin with a careful medical history, family medical history, and a thorough physical examination, which might provide clues to the diagnosis. When the aetiology is not evident, investigations should be directed to a renal or cardiac cause. Appropriate investigations include a full blood count, plasma electrolytes and creatinine, urine analysis, and the measurement of urinary protein excretion, which is most conveniently undertaken by measuring the ratio of urinary protein to creatinine in an early morning urine sample.<sup>2</sup> Because renal disease results in the release of renin and angiotensin II with vasoconstriction and aldosterone mediated retention of salt and water, plasma renin and aldosterone should be measured. To avoid the effects of posture it is necessary to sample after recumbency for two hours, although interpretation is difficult because of limited data to define the normal range. Renal imaging by ultrasound and DMSA (dimercaptosuccinic acid) scan is essential, whereas renal angiography and renal vein sampling for renin measurement is indicated if there is discrepant renal size or if renal artery stenosis is suggested by captopril renography. Echocardiography should be undertaken at an early stage in any child with severe hypertension to exclude coarctation and to assess left ventricular mass.

There are a very small number of families in whom salt and water overload develops not from primary renal disease but because of dysfunction of a single gene, resulting in severe hypertension. The finding of abnormal potassium levels (low or high), alkalosis, suppressed renin, and low aldosterone should prompt consideration of one of these rarer causes of hypertension (table 1). A family history of severe hypertension, especially with onset in adoles-

cence or early adulthood, is suggestive of one of the dominantly inherited conditions, whereas consanguinity predisposes to the recessive types. Because plasma aldosterone concentrations are not always suppressed, blood should be taken for angiotensin II measurement at the time of sampling for renin. In the face of an equivocal or slightly raised aldosterone concentration, salt and water overload can be confirmed by documenting suppression of angiotensin II. In considering these diagnoses it is helpful to discriminate between those in whom the salt and water overload are secondary to a mineralocorticoid effect and those in which mineralocorticoids do not play a role.

### Hypertension induced by a mineralocorticoid effect

#### SYNDROME OF APPARENT MINERALOCORTICOID EXCESS (AME)

This is an autosomal recessive condition in which affected individuals may present with failure to thrive, paroxysmal hypertension, hypokalaemia, and alkalosis.<sup>3</sup> Hypercalcaemia, osteopenia, and nephrocalcinosis also occur,<sup>4,5</sup> but their aetiology is more difficult to explain. The salt and water overload is accompanied by a suppression of renin and aldosterone concentrations.

Dexamethasone is effective in correcting the hypokalaemia by suppressing endogenous cortisol production but is variably successful in restoring blood pressure control; this lack of a more consistent antihypertensive effect is difficult to explain. Large doses of spironolactone have been used successfully to treat the hypertension, hypokalaemia, and osteopenia,<sup>4</sup> and amiloride has also proved to be effective.

It is now known that AME occurs because cortisol is allowed access to the mineralocorticoid receptor in affected individuals,<sup>6</sup> with a resultant increase in the activity of the epithelial sodium channel. Because plasma cortisol concentrations are several orders of magnitude higher than aldosterone and the mineralocorticoid receptor binds aldosterone and cortisol equally, a mechanism exists to protect the mineralocorticoid receptor by metabolising cortisol to cortisone in mineralocorticoid target tissues. The enzyme responsible is 11 $\beta$ -hydroxysteroid dehydrogenase (11 $\beta$ -HSD), which exists in two isoforms (table 2),<sup>7</sup> abnormalities in type 2 being found in cases of

Department of  
Nephrology,  
Birmingham  
Children's Hospital,  
Steelhouse Lane,  
Birmingham B4 6NH,  
UK  
D V Milford

Correspondence to:  
Dr Milford.  
email: david.milford@  
bhamchildrens.wmids.nhs.uk

Table 1 Findings in the syndromes with monogenic causes of hypertension

	Renin	Aldosterone	K <sup>+</sup>	HCO <sub>3</sub>	Fe <sub>Na</sub>	Diagnostic indicators
AME	↓	↓	↓	↑	↓	Prolonged cortisol half life Urinary cortisol metabolites increased
GRA	↓	↑	↓	↑	↓	Urinary cortisone metabolites decreased Urinary 18-oxotetrahydrocortisol and 18-hydroxycortisol:tetrahydroaldosterone ratio increased
CAH	↓	↓	↓	↑	↓	Angiotensin II decreased Ambiguous genitalia/amenorrhoea Virilisation/precocious puberty
Liddle syndrome	↓	↓	↓	↑	↓	Family history, clinical and laboratory findings
Gordon syndrome	↓	↑	↑	↓	↓	Family history, clinical and laboratory findings

AME, syndrome of apparent mineralocorticoid excess; CAH, congenital adrenal hyperplasia; Fe<sub>Na</sub>, fractional excretion of sodium; GRA, glucocorticoid remediable aldosteronism.

AME.<sup>8</sup> The diagnosis is made by demonstrating an increase in the half life of cortisol and by an increase in the concentration of urinary cortisol metabolites and a decrease in urinary cortisone metabolites. Interestingly, this enzyme can also be inhibited by glycyrrhizic acid,<sup>9</sup> a component of liquorice, explaining the sodium retaining properties of this root.

Although AME is rare, it is interesting to note that several groups have found subtle abnormalities of 11β-HSD activity in adults with essential hypertension.<sup>10</sup> Furthermore, recent data suggest that low birth weight might be associated with the development of hypertension in adulthood and, because placental 11β-HSD enzyme activity correlates positively with birth weight,<sup>11</sup> variations in activity could have important effects on fetal growth and later risks for hypertension.

#### GLUCOCORTICOID REMEDIABLE ALDOSTERONISM

Affected individuals present with an autosomal dominant trait characterised by moderate to severe hypertension from an early age onwards, and a family history of severe hypertension and death from cerebrovascular accidents. However, the degree of hypertension and hypokalaemia can be very variable.<sup>12</sup> Affected individuals have mildly raised aldosterone and suppressed plasma renin activity. However, hypokalaemia and alkalosis are not severe<sup>13</sup> because of a blunted aldosterone response to potassium ingestion<sup>14</sup> and the adrenocorticotrophic hormone (ACTH) mediated diurnal decline in aldosterone. Consequently, there is a milder degree of hyperaldosteronism compared with other forms of primary aldosteronism, with volume expansion but minimal potassium wasting. The diagnosis is made by finding increased production of the 18-oxygenated cortisol compounds, 18-oxotetrahydrocortisol and 18-hydroxycortisol, and an increased ratio of urinary 18-oxotetrahydrocortisol to urinary tetra-

rahydroaldosterone. Treatment is by the administration of exogenous steroids that act to reduce ACTH mediated aldosterone production.

The molecular biology of this condition has now been elucidated,<sup>15</sup> as a result of linkage studies in affected families that identified a segment of chromosome 8q21 known to contain the genes for aldosterone synthase and 11β-hydroxylase. These genes have remarkable similarity both in DNA sequence and intron-exon organisation; affected individuals have a novel gene containing the regulatory sequences of 11β-hydroxylase (responsible for cortisol synthesis) and the coding sequences of aldosterone synthase.<sup>16</sup> The product of this chimeric gene is an enzyme with aldosterone synthase activity, which is expressed in the zona fasciculata instead of the glomerulosa, but which is regulated by ACTH rather than angiotensin II.

Glucocorticoid remediable aldosteronism might be more common in the hypertensive population than previously thought because many affected individuals are clinically indistinguishable from patients with essential hypertension.<sup>17</sup> Genetic testing of subsets of the essential hypertensive population (for example, young patients who have low plasma renin activity) might allow the identification of those with glucocorticoid remediable aldosteronism who could then be treated with physiological doses of steroids to suppress ACTH secretion and so normalise blood pressure, reducing their subsequent morbidity and mortality.

#### CONGENITAL ADRENAL HYPERPLASIA (CAH)

This disease is associated with several enzyme defects resulting in reduced cortisol production and ACTH mediated adrenal stimulation. Hypertension is a feature of type IV (11β-hydroxylase deficiency) and type V (17α-hydroxylase deficiency) CAH, both of which are rare and have a variable presentation. In type IV CAH, the enzyme block results in an increase in sex hormone precursors with androgenic action, causing virilisation in girls and precocious puberty in boys. In type V CAH, the inability to synthesise cortisol and the early block in sex hormone synthesis results in primary amenorrhoea and delayed sexual development in girls, whereas boys have ambiguous genitalia. In both forms, aldosterone synthesis is greatly reduced, but excessive synthesis of steroid precursors with a mineralocorticoid effect results in hypokalaemia, alkalo-

Table 2 Characteristics of the two isoforms of 11β-hydroxysteroid dehydrogenase

Type 1 isoform	Type 2 isoform
Found in liver, lung, gonads, cerebellum, and pituitary (glucocorticoid targets)	Found in placenta, renal cortex and medulla, colon, and salivary gland (mineralocorticoid targets)
NADP dependent	NAD dependent
Low affinity	High affinity
Dehydrogenase/oxoreductase (cortisol ⇒ cortisone)	Dehydrogenase (cortisol → cortisone)
Normal in AME	Gene mutations in AME
Encoded on chromosome 1	Encoded on chromosome 16q22

AME, syndrome of apparent mineralocorticoid excess.

sis, and hypertension. The finding of large amounts of androgenic precursors in the urine of children with type IV CAH serves to distinguish them from those with type V disease. Treatment is with steroid supplementation in type IV and both steroid and sex hormone supplementation in type V disease. These forms of CAH can now be regarded as autosomal recessive examples of monogenic hypertension, the gene locus for type IV CAH having been identified as 8q21<sup>18</sup> and that for type V disease as 10q24.3.<sup>19</sup>

### Hypertension induced by excessive sodium uptake independent of mineralocorticoid action

#### LIDDLE SYNDROME

This is an autosomal dominant condition in which there is early onset hypertension with hypokalaemia, alkalosis, and variable hypercalcaemia.<sup>20</sup> The clinical abnormalities are corrected by a low salt diet and amiloride, an inhibitor of the epithelial sodium channel found in the distal renal tubule and the distal colon (sites of mineralocorticoid action). This channel is now known to be composed of three subunits of similar structure, each with an extracellular domain, two transmembrane domains, and an intracytoplasmic N-terminus and C-terminus. The  $\alpha$  subunit allows sodium influx by itself and the  $\beta$  and  $\gamma$  subunits, although non-conducting, greatly augment sodium influx when expressed together with the  $\alpha$  subunit. The  $\beta$  and  $\gamma$  subunits are encoded on chromosome 16 and the  $\alpha$  subunit on chromosome 12. Linkage studies have demonstrated mutations in the genes encoding the  $\beta$ <sup>21</sup> and  $\gamma$ <sup>22</sup> subunits, resulting in deletions or substitutions in a short proline rich segment of the intracytoplasmic C-terminus. The consequence is an inability to bind a protein that removes the epithelial sodium channel from the cell surface, with a resultant overexpression of sodium channels and increased sodium absorption. A kindred study has shown that heterozygotes might have hypertension and hypokalaemia,<sup>23</sup> suggesting that this condition might be underdiagnosed in those thought to have essential hypertension.

It is of note that, in contrast to these gain of function mutations found in Liddle syndrome, mutations affecting other parts of the subunits comprising the epithelial sodium channel have been found in kindreds with pseudohypoaldosteronism type I, in which there is a profound loss of function, with resultant salt and water wasting and consequent hyperaldosteronism.

#### GORDON SYNDROME

##### (PSEUDOHYPOALDOSTERONISM TYPE II)

This condition comprises short stature, hyperkalaemia with normal renal function, hypertension, hyperchloraemic metabolic acidosis, low fractional excretion of sodium, and hypercalcaemia.<sup>24</sup> Despite the volume overload, aldosterone is not always suppressed because hyperkalaemia can induce its secretion, although this rise is modest compared with the degree of hyperkalaemia. Case reports document the onset of hypertension in adolescence

### Key messages

- Aggressive investigation of preschool children with persistent hypertension, and school aged children with severe hypertension is justified because of the high probability of making a diagnosis
- When the aetiology is not evident from the history or examination, investigations should be directed to a renal or cardiac cause
- The finding of abnormal potassium concentrations (low or high), alkalosis, suppressed renin, and low aldosterone should prompt the consideration of one of the rarer causes of hypertension
- A better understanding of the physiological mechanisms operating in monogenic hypertension might provide a clue to the cause of essential hypertension and aid in the identification of individuals at risk of developing hypertension in later life

or early adulthood, but hyperkalaemia is often present at an earlier age. Treatment is either a low salt diet or thiazide diuretics.

The precise nature of the lesion responsible for the syndrome is not known. Excessive uptake of chloride in the cortical connecting segment, with sodium and water accompanying its movement, has been suggested as the underlying mechanism. A consequence of increased chloride reabsorption is a reduction in luminal electronegativity, which favours potassium retention through a reduction in the voltage gradient. Potassium retention is exacerbated by the reduction in distal delivery of sodium that is required for exchange with potassium. Infusion of sodium without chloride (for example, sodium sulphate) results in a kaluresis, supporting the concept of increased chloride uptake as the underlying mechanism.

The clinical features of Gordon syndrome have been observed previously to be the opposite of Gitelman syndrome,<sup>25</sup> the molecular basis of which has been characterised to abnormalities in the thiazide sensitive sodium chloride cotransporter, encoded on chromosome 16. In some respects this presents an analogous situation to Liddle syndrome (excessive uptake of sodium) and pseudohypoaldosteronism type I (excessive sodium loss) in which the molecular abnormality produces either a gain or loss of function in the same electrolyte channel. However, studies undertaken to date in Gordon syndrome have not identified abnormalities in the thiazide sensitive sodium chloride cotransporter but linkages to 1q31–42 and 17p11–q21 have been identified recently,<sup>26</sup> although a candidate gene is yet to be found at these loci.

### Susceptibility genes

The prevalence of essential hypertension and its associated morbidity has led to considerable interest in the identification of susceptibility genes, which are neither necessary nor sufficient to cause hypertension, but can increase the risk

of hypertension in a given environment. These are not considered to be monogenic causes of hypertension but, nonetheless, they deserve a mention because they are good examples of genetic influences in the development of hypertension. For example, a methionine to threonine mutation (M235T) in exon 2 of the angiotensinogen gene has been identified as being more prevalent in some hypertensive populations.<sup>27</sup> This mutation is thought to act by increasing plasma angiotensinogen concentrations (the substrate cleaved by renin to produce angiotensin I), with a subsequent increase in concentrations of the powerful vasoconstrictor angiotensin II. In some studies of hypertensive populations, a deletion polymorphism of the angiotensin converting enzyme gene has also been found to be more prevalent and, in particular, has been associated with development of diabetic nephropathy. Other susceptibility genes identified include insertion/deletion polymorphisms of the insulin receptor gene, the renin gene, the angiotensin II type I receptor gene, and the kallikrein gene. However, for every study demonstrating the validity of these associations there are others refuting the value of these genetic markers. Therefore, the role of susceptibility genes is presently unclear.

### Conclusion

Hypertension in children can develop as a result of renin-angiotensin system activation secondary to renal disease, but occasionally is because of salt and water overload as a consequence of abnormal electrolyte transport. A better understanding of the physiological mechanisms operating in families with monogenic hypertension might provide a clue to the cause of essential hypertension and aid in the identification of individuals at risk of developing hypertension in later life.

I am grateful to Dr M Hocking for helpful advice in the preparation of this article.

- 1 Andre JL, Deschamps JP, Gueguen R. La tension arterielle chez l'enfant et l'adolescent: valeurs rapportees a l'age et a la taille chez 17, 067 sùjets. *Arch Fr Pediatr* 1980;37:477-82.
- 2 Elises JS, Griffiths PD, Hocking MD, Taylor CM, White RHR. Simplified quantification of urinary protein excretion in children. *Clin Nephrol* 1988;30:225-9.
- 3 Honour JW, Dillon MJ, Levin M, Shah V. Fatal, low renin hypertension associated with a disturbance of cortisol metabolism. *Arch Dis Child* 1983;58:1018-20.
- 4 Batista MC, Mendonca BB, Kater CE, et al. Spironolactone-reversible rickets associated with 11 $\beta$ -hydroxysteroid dehydrogenase deficiency syndrome. *J Pediatr* 1986;109:989-93.
- 5 Milford DV, Shackleton CHL, Stewart PM. Mineralocorticoid hypertension and congenital deficiency of 11 $\beta$ -hydroxysteroid dehydrogenase in a family with the syndrome of "apparent" mineralocorticoid excess. *Clin Endocrinol* 1994;43:241-6.
- 6 Stewart PM, Corrie JET, Shackleton CHL, Edwards CRW. Syndrome of apparent mineralocorticoid excess: a defect in the cortisol-cortisone shuttle. *J Clin Invest* 1988;82:340-9.

- 7 Stewart PM, Murray BA, Mason JI. Human kidney 11 $\beta$ -hydroxysteroid dehydrogenase is a high affinity nicotinamide adenine dinucleotide-dependant enzyme and differs from the cloned type I isoform. *J Clin Endocrinol Metab* 1994;79:480-4.
- 8 Mune T, Rogerson FM, Nikkila H, Agarwal AK, White PC. Human hypertension caused by mutations in the kidney isozyme of 11 $\beta$ -hydroxysteroid dehydrogenase. *Nat Genet* 1995;10:393-9.
- 9 Stewart PM, Edwards CRW. The cortisol-cortisone shuttle and hypertension. *J Steroid Biochem Mol Biol* 1991;40:501-9.
- 10 Walker BR, Stewart PM, Shackleton CHL, Padfield PL, Edwards CRW. Deficient inactivation of cortisol by 11 $\beta$ -hydroxysteroid dehydrogenase in essential hypertension. *Clin Endocrinol* 1993;39:221-7.
- 11 Stewart PM, Rogerson FM, Mason JI. Type 2 11 $\beta$ -hydroxysteroid dehydrogenase messenger ribonucleic acid and activity in human placenta and fetal membranes: its relationship to birth weight and putative role in fetal adrenal steroidogenesis. *J Clin Endocrinol Metab* 1995;80:885-90.
- 12 Rich GM, Ulick S, Cook S, Wang JZ, Lifton RP, Dluhy RG. Glucocorticoid-remediable aldosteronism in a large kindred: clinical spectrum and diagnosis using a characteristic biochemical phenotype. *Ann Intern Med* 1992;116:813-20.
- 13 Dluhy RG, Lifton RP. Glucocorticoid-remediable aldosteronism (GRA): diagnosis, variability of phenotype and regulation of potassium homeostasis. *Steroids* 1995;60:48-51.
- 14 Litchfield WR, Coolidge C, Silva P, et al. Impaired potassium-stimulated aldosterone production: a possible explanation for normokalemic glucocorticoid-remediable aldosteronism. *J Clin Endocrinol Metab* 1997;82:1507-10.
- 15 Lifton RP, Dluhy RG, Powers M, et al. A chimaeric 11 beta-hydroxylase/aldosterone synthase gene causes glucocorticoid-remediable aldosteronism and human hypertension. *Nature* 1992;355:262-5.
- 16 Lifton RP, Dluhy RG, Powers M, et al. Hereditary hypertension caused by chimaeric gene duplications and ectopic expression of aldosterone synthase. *Nat Genet* 1992;2:66-74.
- 17 Gates LJ, MacConnachie AA, Lifton RP, Haites NE, Benjamin N. Variation of phenotype in patients with glucocorticoid remediable aldosteronism. *J Med Genet* 1996;33:25-8.
- 18 Chua SC, Szabo P, Vitek A, Grzeschik KH, John M, White PC. Cloning of cDNA encoding steroid 11-beta-hydroxylase (P450C11). *Proc Natl Acad Sci USA* 1987;84:7193-7.
- 19 Fan YS, Sasi R, Lee C, Winter JSD, Waterman MR, Lin CC. Localisation of the human CYP17 gene (cytochrome P450-17-alpha) to 10q24.3 by fluorescence in situ hybridization and simultaneous chromosome banding. *Genomics* 1992;14:1110-11.
- 20 Liddle GW, Bledsoe T, Coppage WS. A familial renal disorder simulating primary aldosteronism but with negligible aldosterone secretion. *Trans Assoc Am Phys* 1963;76:199-213.
- 21 Shimkets RA, Warnock DG, Bositis CM, et al. Liddle's syndrome: heritable human hypertension caused by mutations in the beta subunit of the epithelial sodium channel. *Cell* 1994;79:407-14.
- 22 Hansson JH, Nelson-Williams C, Suzuki H, et al. Hypertension caused by a truncated epithelial sodium channel gamma subunit: genetic heterogeneity of Liddle syndrome. *Nat Genet* 1995;11:76-82.
- 23 Findling JW, Raff H, Hansson JH, Lifton RP. Liddle's syndrome: prospective genetic screening and suppressed aldosterone secretion in an extended kindred. *J Clin Endocrinol Metab* 1997;82:1071-4.
- 24 Gordon RD, Geddes RA, Pawsey GK, O'Halloran MW. Hypertension and severe hyperkalemia associated with suppression of renin and aldosterone and completely reversed by dietary sodium restriction. *Australian Annals of Medicine* 1970;4:287-94.
- 25 Rodriguez-Soriano J, Vallo A. Renal tubular hyperkalemia in childhood. *Pediatr Nephrol* 1988;2:498-509.
- 26 Mansfield TA, Simon DB, Farfel Z, et al. Multilocus linkage of familial hyperkalemia and hypertension, pseudohypoaldosteronism type II, to chromosomes 1q31-42 and 17p11-q21. *Nat Genet* 1997;16:202-5.
- 27 Jeunemaitre X, Soubrier F, Kotelevtsev YV, et al. Molecular basis of human hypertension: role of angiotensinogen. *Cell* 1992;71:169-80.