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predominant clinical features include a young age of onset, moderate to severe blood pressure elevation, strong family history, consan- guinity (for the autosomal recessive disorders), and electrolyte abnor- malities, particularly of potassium (although this is not invariable). The disorders include (1) glucocorticoid-remediable aldoster- onism—caused by a chimeric gene where the regulatory elem- ents of the 11β-hydroxylase gene become attached to the coding region of aldosterone synthase; (2) apparent mineralocorticoid excess—due to mutations causing loss of function in the type 2 11β-hydroxysteroid dehydrogenase gene that normally inactivates cortisol in the kidney; (3) Liddle’s syndrome—caused by activating mutations in genes encoding the β-or γ-

subunits of the trimeric epi- thelial sodium channel; (4) pseudohypoaldosteronism type 2 (PHA2, Gordon’s syndrome)— caused by mutations in the WNK1 or WNK4 serine-threonine kinases genes, the Kelch-like 3 (KLHL3) gene or the cullin 3 (CUL3) gene, which regulate salt reabsorption by the Na-Cl cotransporter (SLC12A3) and the linked process of potassium secre- tion by the renal outer medullary potassium channel (ROMK). Introduction Several rare mendelian disorders where hypertension is the pre- dominant manifestation have been characterized at the molecular level (Box 16.17.4.1). These include glucocorticoid-remediable aldosteronism (or familial hyperaldosteronism type I), the syn- drome of apparent mineralocorticoid excess, Liddle’s syndrome, and Gordon’s syndrome. Hypertension and hypokalaemia are features of 11β-hydroxylase and 17β-hydroxylase deficiency—two rare recessive gene disorders of adrenal steroid-synthesizing enzymes that, among others, cause congenital adrenal hyperplasia. 11β-Hydroxylase defi- ciency usually presents in infancy or early childhood with viriliza- tion of both sexes, while presentation of 17β-hydroxylase deficiency may be delayed until adolescence or adulthood. Hypertension due to a phaeochromocytoma may be a feature of multiple endocrine neoplasia type 2 (MEN2), which when familial is inherited in an autosomal dominant pattern, Von Hippel-Lindau syndrome, or rarely to be a feature of neurofibromatosis (von Recklinghausen’s disease). Single mutations in more than 10 different genes are now recognised as the genetic defects underlying familial and sporadic pheochromocytomas and paragangliomas. Most recently, genetic causes of several types of familial hyperaldosteronism were identified including type II (CLCN2), type III (KCNJ5) and IV (CACNA1H). Glucocorticoid-remediable aldosteronism Glucocorticoid-remediable aldosteronism (GRA, OMIM 103900) is a form of mineralocorticoid hypertension that is inherited in an autosomal dominant fashion. The hypertension is accompanied by hypokalaemia (not invariably), a tendency to metabolic alkalosis, an elevated plasma aldosterone level and a suppressed renin level. Patients are usually suspected of having primary aldosteronism (Conn’s syn- drome, see Chapter 16.17.3), although the age of onset, usually in the first two decades of life, is younger than typical of primary aldoster- onism. Intracranial aneurysms are common, and the first manifest- ation may be a presentation with intracranial haemorrhage. The two hallmark features of GRA are the presence of large amounts of two abnormal steroids—18-hydroxycortisol and 18- oxocortisol—in the urine, and the lowering of blood pressure, with return of plasma aldosterone to a normal level and disappearance of the abnormal steroids, following treatment over a few days with a low daily dose of exogenous glucocorticoid, for example, 0.5–1.0 mg of dexamethasone (hence the name). Patients with GRA have a chimeric gene due to an unequal crossing- over event at meiosis between two adjacent and highly homologous genes involved in adrenocorticosteroid synthesis—aldosterone Box 16.17.4.1 Mendelian forms of blood pressure variation Hypertension • Glucocorticoid-remediable aldosteronism (GRA) • Syndrome of apparent mineralocorticoid excess (AME) • Liddle’s syndrome • Gordon’s syndrome (pseudohypoaldosteronism type II, PHA-II) • Hypertension exacerbated by pregnancy • Hypertension with brachydactyly • 11β-Hydroxylase deficiency • 17β-Hydroxylase deficiency • Familial and sporadic phaeochromocytoma/paraganglioma • Familial hyperaldosteronism Hypotension • Pseudohypoaldosteronism type 1 • Gitelman’s syndrome • Bartter syndrome • 11β-hydroxylase deficiency • Aldosterone synthase deficiency

 synthase (CYP11B2) (normally expressed only in the zona glomerulosa, involved in aldosterone synthesis, and regulated by angiotensin II) and 11β-hydroxylase (CYP11B1) (expressed in the zona fasciculata, involved in glucocorticoid synthesis, and regu- lated by ACTH). In the chimeric gene, the regulatory elements of CYP11B1

have become attached to the aldosterone synthase coding region of CYP11B2 (Fig. 16.17.4.1a). This leads to ACTH-driven production of aldosterone (and the other abnormal hormones) in the zona fasciculata, hence the clinical syndrome and its suppression by glucocorticoids. Normal (b) AME Aldosterone synthase 11β-OHase Unequal crossing over (a) 3′5′ 3′ 3′ 5′ 5′ Aldosterone synthase Chimeric gene 3′5′ 3′ 5′ 3′ 3′ 5′ 5′ 11β-HSD β α γ 11β-OHase Cortisol Cortisone Aldosterone Mineralocorticoid receptor Mineralocorticoid receptor Cortisol Defective 11β-HSD (d) (c) Na Na Na Epithelial sodium channel intracellular extracellular Cl K lumen NCCT ROMK WNK1/WNK4 KLHL3/CUL3 normal Liddle's syndrome Impaired channel internalization and degradation leads to higher surface channel density in Liddle's syndrome Fig. 16.17.4.1 Mechanisms underlying four forms of monogenetic hypertension. (a) Glucocorticoid-remediable aldosteronism (GRA). In GRA an unequal crossing event leads to a chimaeric gene where the coding region of aldosterone synthase becomes attached to the regulatory region for 11β-hydroxylase. The chimaeric gene produces excess amounts of aldosterone under the regulation of ACTH. (b) Syndrome of apparent mineralocorticoid excess (AME). The mineralocorticoid receptor in the distal renal tubule is normally protected from stimulation by cortisol by the activity of the 11β-hydroxysteroid dehydrogenase enzyme. In AME, mutations in the enzyme allow cortisol to gain access to the receptor. (c) Liddle's syndrome. The trimeric epithelial sodium channel mediates sodium reuptake in the distal renal tubule. In Liddle's syndrome, mutations in the β and γ subunits of the channel impair its intracellular biodegradation and lead to excessive channel density and activity on the surface of distal renal tubular epithelium. (d) Gordon's syndrome. WNK1 and WNK4 regulate thiazide-sensitive sodium-chloride cotransporter (NCCT) and potassium secretion via ROMK in the distal nephron. Mutations in WNK1/WNK4 or genes responsible for their intracellular degradation (KLHL3 and CUL3) lead to increased sodium reabsorption via overactive NCCT and impaired potassium secretion through ROMK.

section 16 Cardiovascular disorders 3798 The mainstay of treatment for GRA is glucocorticoids, with physiological doses (or only slightly higher, e.g. 0.125 mg of dexamethasone or 2.5 mg of prednisolone daily) sufficing. Response can be monitored by measuring the suppression of aldosterone production. Selective mineralocorticoid receptor blockers, such as spironolactone, can provide useful adjunctive treatment. Syndrome of apparent mineralocorticoid excess The syndrome of apparent mineralocorticoid excess (AME, OMIM 218030) is an autosomal recessive disorder that usually presents in childhood with hypertension, hypokalaemia, and low renin activity. Despite the clinical features of mineralocorticoid excess, levels of all known mineralocorticoid hormones are low, yet the hypertension responds to spironolactone or amiloride. Patients with the disorder cannot metabolize cortisol to its in- active metabolite cortisone normally, resulting in a prolonged half-life of cortisol and a characteristic increase in urinary cortisol (compound F) compared with cortisone (compound E) ratio. Elucidating the defect causing AME first required the solu- tion of another paradox—why cortisol, which circulates at a level several-fold greater than aldosterone, does not overwhelmingly activate the renal mineralocorticoid receptor in vivo despite the two having equal affinity in vitro. The reason relates to the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD), which has two isoforms. Type 1 11β-HSD is located in the liver, adipose tissue, muscle, pancreatic islets, and gonad and converts cortisone to cor- tisol. Type 2 11β-HSD is expressed in the mineralocorticoid target tissues—kidney, colon, and salivary gland—and inactivates cor- tisol to cortisone. In the kidney the enzyme plays the crucial role of protecting the mineralocorticoid receptor in the distal tubule from activation by cortisol. In subjects with AME a variety of loss-of-function mutations in the type 2 11β-HSD gene cause a deficiency of the enzyme, allowing cortisol

access to the mineralocorticoid re- ceptor (Fig. 16.17.4.1b). The severe form of AME, due to disabling mutations in type 2 11β-HSD, usually presents in childhood. Recently a milder form, termed AME type II, has been described, which is characterized by a later age of presentation (>30 years), a more variable degree of hypertension, and less impact on biochemical parameters. These patients have alterations in 11β-HSD2 that produce a partial ra- ther than absolute decrease in enzymatic activity, hence classifica- tion into distinct subcategories may be inappropriate, with AME best regarded as a spectrum of mineralocorticoid hypertension with severity reflecting the underlying genetic defect. The main- stay of treatment of AME is spironolactone. A low-salt diet is also important. AME resembles the syndrome observed in subjects ingesting large amounts of liquorice or taking the now redundant antiulcer drug carbenoxolone, both of which contain glycyrrhetinic acid, an inhibitor of type 2 11β-HSD, thus explaining the hypertension and hypokalaemia observed with these compounds. Spillover access of cortisol to the mineralocorticoid receptor may also, at least partly, explain the hypertension accompanying some forms of Cushing's syndrome and glucocorticoid resistance. Liddle's syndrome Liddle described a family in which the siblings were affected by early-onset hypertension and hypokalaemia, but with low renin and aldosterone levels (OMIM 177200). The clue to the nature of the mo- lecular defect underlying this autosomal dominant disorder came from the observation that the hypertension does not respond to spironolactone, the mineralocorticoid receptor antagonist, but does respond to direct inhibitors (such as amiloride or triamterene) of the trimeric epithelial sodium channel—a key channel responsible for sodium reabsorption in the distal nephron. Subsequent work re- vealed activating mutations in genes (SCNN1B, SCNN1G) encoding the β-or γ-subunits of the channel (Fig. 16.17.4.1c), All mutations so far identified cause an alteration or deletion of a proline-rich (PY) motif in the C-terminal cytoplasmic tails of the subunits that is ne- cessary for regulatory proteins such as Nedd4 to bind and intern- alize the channel. When this mechanism is impaired, the number of channels located in the apical membrane is increased, leading to over-reabsorption of sodium and water. Pseudohypoaldosteronism type 2 (Gordon's syndrome) Pseudohypoaldosteronism type 2 (PHA2, OMIM 145260), also known as Gordon's syndrome, is an autosomal dominant disorder that causes elevated blood pressure accompanied by hyperkalaemia, despite normal renal glomerular filtration. Mild hyperchloraemia, metabolic acidosis, and suppressed plasma renin activity are common associated findings. Hypercalciuria can also be a feature, leading to osteopenia, osteoporosis, and kidney stone disease. The hypertension and biochemical abnormalities are corrected by thiazide diuretics. Mutations in at least four genes are recognized causes of PHA2. Initially some cases of PHA2 were linked to mutations in two genes, WNK1 and WNK4, members of the WNK family of serine/threo- nine kinases. The genetic defects in both WNK1 and WNK4, by increasing their expression/activity in the distal nephron, lead to enhanced phosphorylation of two other enzymes, STE20/SPS1-related proline-alanine-rich protein kinase (SPAK) and oxida- tive stress-responsive kinase-1 (OSR1). Both SPAK and OSR1 are key regulators of the Na-Cl cotransporter, NCCT (encoded by the SLC12A3 gene), which is responsible for sodium reabsorption in the distal convoluted tubule and the linked process of potassium se- cretion by the renal outer medullary potassium channel (ROMK). Na-Cl cotransporter overactivity is the chief biochemical abnor- mality of the syndrome and the primary driver of enhanced sodium reabsorption, volume expansion, inhibition of renin secretion, and hypertension. Decreased potassium excretion leading to hyperkalaemia in PHA2 results from two processes. Firstly, increased Na-Cl cotransporter activity, by increasing sodium reabsorption in the distal convoluted tubule, leads to reduced sodium delivery to the connecting tubule, which results in a drop in electrochemical gradient necessary to maintain activity of ROMK

channels that transfer K+ from blood to urine across the distal tubule epithelium. Secondly, enhanced in- ternalization of ROMK channels in PHA2 leads to their decreased expression/activity on the surface of tubular epithelium.

16.17.4 Mendelian disorders causing hypertension 3799 More recently, mutations in two novel genes, Kelch-like 3 (KLHL3) and Cullin 3 (CUL3), were reported to account for a majority (≈80%) of causal genetic defects in patients with PHA2. The mutations are inherited in either autosomal dominant (KLHL3 and CUL3) or re- cessive (KLHL3) manner. The products of both genes are a part of ubiquitin ligase complex responsible for intracellular degradation of more than 50 proteins, including WNKs. The most likely molecular mechanism by which genetic defects in these genes lead to PHA2 is disruption of WNKs intracellular degradation and accumulation of WNK4/WNK1 and subsequent changes in the activity of Na-Cl cotransporter/ROMK channel. The Na-Cl transporter is the target for thiazide diuretics, which explains the specific clinical response of PHA2 to this class of drugs. Defects in the Na-Cl cotransporter lead to the salt-losing Gitelman's syndrome, which as described next is the mirror image of PHA2. Other monogenetic forms of hypertension A missense mutation in the ligand-binding domain of the mineralo- corticoid receptor has been found to cause an autosomal dominant form of hypertension that is markedly accelerated in pregnancy. The mutation, MR S810L, causes partial, aldosterone-independent activa- tion of the receptor, causing carriers to develop hypertension before age 20. Compounds such as progesterone that normally bind to but do not activate the mineralocorticoid receptor are all potent agonists of the mutant receptor, hence MR S810L carriers have dramatic accel- eration of hypertension during pregnancy stimulated by the 100-fold rise in progesterone. Although the MR S810L mutation is extremely rare, the finding does raise the question of whether related mechan- isms may underlie other forms of hypertension in pregnancy. Most recently, several missense mutations in PDE3A (a gene that encodes phosphodiesterase 3A) were identified in families with a syndrome of hypertension and brachydactyly. The syndrome is characterised by severe salt-independent hypertension, abnormalities of rostral- ventrolateral medulla and high degree of stroke-related mortality. Genetic defects causing hypotension Certain mendelian syndromes where hypotension is a feature have recently been characterized at the molecular level (Table 16.17.4.1). Many are mirror images of the genetic abnormalities causing the mendelian forms of hypertension described earlier. Pseudohypoaldosteronism type 1 (PHA1) occurs in two forms, autosomal recessive and autosomal dominant. Both are charac- terized by life-threatening dehydration in the neonatal period, hypotension, salt wasting, hyperkalaemia, metabolic acidosis, and marked elevation of renin and aldosterone. The autosomal reces- sive form (OMIM 264350) is due to inactivating mutations (com- pare with Liddle's syndrome) in one of the genes SCNN1A, SCCN1B, or SCNN1G, encoding (respectively) the α, β, and γ subunits of the epithelial sodium channel, while the autosomal dominant form (OMIM 177735) is due to loss-of-function mutations in the gene NR3C2, encoding the mineralocorticoid receptor. Gitelman's syndrome (OMIM 263800) is an autosomal recessive disorder characterized by hypotension, neuromuscular abnormalities, hypokalaemia, hypomagnesaemia, hypocalciuria, metabolic alkalosis, and an activated renin–angiotensin system. It arises due to inactivating mutations in the gene encoding the renal thiazide-sensitive Na-Cl cotransporter (SLC12A3), and typically presents in adolescence or early adulthood with neuromuscular signs and symptoms. Bartter's syndrome is caused by mutations in one or more of the genes that encode regulators of chloride transport within the thick as- cending limb of nephron. There are several types of Bartter's syndrome. The gene defects responsible are in genes encoding bumetanide- sensitive sodium-(potassium)-chloride cotransporter 2 (SLC12A1) (type 1, OMIM 601678), ATP-regulated potassium channel ROMK (KCNJ1) (type 2, OMIM 241200), chloride channel

Kb (CLCNKB) (type 3, OMIM 607364), barttin (BSDN) (type 4a, OMIM 602522), and both CLCNKA and CLCNKB genes (type 4b, OMIM 613090). The manifestation of these autosomal recessive disorders is het- erogeneous, but the most typical clinical presentations include early onset (infancy or childhood), hypovolaemia and polyuria, low or normal blood pressure, elevated prostaglandin levels, and nephrocalcinosis. The recently identified Bartter-like syndrome occurring in subjects with mutations in the CASR gene (which en- codes extracellular basolateral calcium sensing receptor) manifests as hypocalcaemic hypercalciuria. Does my patient have a recognized form of monogenetic hypertension? Identification that a patient has GRA, AME, Liddle's syndrome, or Gordon's syndrome has important consequences for treatment (Table 16.17.4.1) and family screening. Phenotypic expression is highly variable, but all of the syndromes are extremely rare and suspicion will usually go unrewarded. Features that may suggest a diagnosis of mendelian hypertension include a young age of onset, moderate to severe hypertension, strong family history, consan- guinity (for the autosomal recessive disorders), and electrolyte abnormalities, particularly of potassium (although this is not in- variable). A good starting point, as described in Chapter 16.17.3, is Table 16.17.4.1 Biochemical and therapeutic characteristics of glucocorticoid-remediable aldosteronism (GRA), syndrome of apparent mineralocorticoid excess (AME), Liddle's syndrome, and Gordon's syndrome GRA AME Liddle's Gordon's Plasma electrolytes ↑Na ↓K ↑Na ↓K ↑Na ↓K ↑Na ↑K Plasma aldosterone ↑ ↓ ↓ ↑↓ Plasma renin ↓ ↓ ↓ ↓ Specific treatment Dexamethasone Spironolactone Amiloride Thiazide Note that while the biochemical changes are characteristic, they are not invariably present.

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