Glucocorticoid-Remediable Aldosteronism

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ABSTRACT

Glucocorticoid-remediable aldosteronism (GRA) is a monogenic form of human hypertension that predisposes to cerebral hemorrhage. As a result of a chimeric gene duplication, aldosterone is ectopically synthesized in the cortisol-secreting *zona fasciculata* of the adrenal gland under the control of adrenocorticotropin (ACTH). Hypertension frequently has its onset during childhood and is usually refractory to standard anti-hypertensives such as ACE inhibitors and α-blockers. Hypokalemia can develop in those treated with a potassium-wasting diuretic, but random potassium levels are usually normal. Diagnosis has been facilitated by the availability of a genetic test. Suppression of ACTH release with exogenous dexamethasone is a useful diagnostic and therapeutic strategy. Treatment with the mineralocorticoid receptor antagonists spironolactone and epleronone is also efficacious. The diagnosis of GRA facilitates directed therapies and screening of at-risk individuals and kindreds. **(Arq Bras Endocrinol Metab 2004;48/5:682-686)**

Keywords: Glucocorticoid-remediable aldosteronism; Dexamethasone-suppressible hyperaldosteronism; Monogeneic hypertension; Hyperaldosteronism

RESUMO

Aldosteronismo Remediável por Glicocorticóide.
Aldosteronismo remediável por glicocorticóides (GRA) é uma forma monogênica de hipertensão humana com predisposição para a hemorragia cerebral. Como resultado da duplicação de um gene quimérico, aldosterona passa a ser sintetizada ectopicamente na zona fasciculada do córtex adrenal, secretora de cortisol, sob o controle da adrenocorticotrofina (ACTH). O início da hipertensão ocorre freqüentemente durante a infância e é usualmente refratária aos anti-hipertensivos habituais, como os inibidores da ECA e α-bloqueadores. Hipocalemia pode se manifestar naqueles tratados com diuréticos espoliadores de potássio, mas os níveis basais de potássio são usualmente normais. O diagnóstico tem sido facilitado pela disponibilidade de um teste genético. A supressão da liberação de ACTH com dexametasona exógena é uma estratégia útil para o diagnóstico e a terapêutica. Tratamento com antagonistas do receptor mineralocorticóide, espironolactona e epleronona, também é eficaz. O diagnóstico de GRA facilita a terapia direcionada e o rastreamento de indivíduos e familiares de risco para a doença. **(Arq Bras Endocrinol Metab 2004;48/5:682-686)**

Descritores: Aldosteronismo remediável por glicocorticóide; Hiperaldosteronismo supressível por dexametasona; Hipertensão monogênica; Hiperaldosteronismo

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FOLLOWING SUTHERLAND'S initial description of a father and son with an autosomal dominant hypokalemic hypertensive syndrome in 1966 (1), clinicians began to report other kindreds with biochemical features of primary hyperaldosteronism (2). Though these individuals had hypertension, suppressed plasma renin activity, and hypokalemia, they differed from others with hyperaldosteronism since their hypertension and hyperaldosteronism were reversed by the administration of glucocorticoids. The disorder became known as glucocorticoid-remediable aldosteronism (GRA). GRA has now been identified across the world, and its molecular etiology is fully characterized. GRA appears to be the commonest monogenic form of human hypertension.

PATHOPHYSIOLOGY

The adrenal cortex is composed of three distinct zones responsible for producing different steroid hormones. Aldosterone is secreted by the *zona glomerulosa*, cortisol from the *zona fasciculata*, and androgens/estrogens from the *zona reticularis*. The first steps of aldosterone biosynthesis from cholesterol to progesterone are identical to those required for the biosynthesis of cortisol. Thereafter, the metabolic pathways diverge: aldosterone synthase, regulated by angiotensin II, 18-hydroxylates corticosterone in the *zona glomerulosa* (figure 1). In contrast, the synthesis of cortisol requires hydroxylation of pregnenolone by 17α-hydroxylase, which is expressed only in the *zona fasciculata* and is regulated by adrenocorticotropin (ACTH).

Aldosterone increases sodium resorption and potassium excretion in the distal tubules and cortical collecting ducts of the kidney, thereby regulating circulating potassium concentrations as well as intravascular volume (3). Hyperaldosteronism therefore results in volume expansion, hypertension and usually hypokalemia. Such volume expansion acts to suppress the renin-angiotensin system resulting in the characteristic increase in the plasma aldosterone (PA) to plasma renin activity (PRA) ratio. The majority of patients with primary hyperaldosteronism are found to have either a unilateral aldosterone-producing adrenal adenoma or bilateral idiopathic hyperplasia. In contrast, patients with GRA have hyperaldosteronism as a result of abnormal regulation of secretion by physiologic levels of ACTH.

GENETICS

The genes for aldosterone synthase and 11α-hydroxylase are located in close proximity on the long arm of

Table 1. Algorithm for GRA diagnosis and treatment.

Screening	
Recommended for hypertensive individuals who:	
- are diagnosed with primary hyperaldosteronism without demonstrable tumor - are young (especially children) and have suppressed plasma renin activity - have a family history of cerebral hemorrhage or hypertension before age 30 years - have refractory hypertension (hypertensive on 3 classes of agents including a diuretic) - are members of known GRA kindreds	
Diagnosis	
Dexamethasone suppression test	Easily performed. Dexamethasone 0.5mg every 6hrs x 2 days, normally aldosterone < 4ng/dl on day 3 at 8am
Genetic Test	Can be arranged through the international GRA registry (http://www.brighamandwomens.org/gra)
24 hour urinary 18-hydroxycortisol & 18-oxocortisol levels	Impractical since assays only available in specialized centers. Elevated > 2x upper limit of normal; a urinary level of 18-hydroxycortisol > 10nmol/l is diagnostic (5)
Treatment	
Glucocorticoids	Dexamethasone 0.125-0.25mg, or prednisolone 2.5-5mg daily, titrated to normotension.
Mineralocorticoid receptor antagonists	Eplerenone and spironolactone are effective treatment choices.
Sodium epithelial channel antagonists	Amiloride and triamterene have also been used successfully.
Non-directed anti-hypertensives	α-blockers and ACE-inhibitors are less likely to be efficacious in the setting of a suppressed renin-angiotensin system (9). Dihydropyridine calcium channel blockers can be useful adjunctive treatments to the above diuretic agents.

chromosome 8 and have identical intron-exon structures. The two genes share 95% sequence homology but are usually only expressed in their respective adrenal zones under separate regulation by angiotensin II and ACTH, respectively.

Subjects with GRA have two normal copies of genes encoding aldosterone synthase and 11α-hydroxylase, but they also have an abnormal gene duplication. This hybrid, or chimeric, gene combines the ACTH-responsive promoter sequence of the 11α-hydroxylase gene fused to the more distal aldosterone-synthase coding sequence (figure 2). This chimeric gene results from variable, and unequal, crossing-over between the two genes (4). The variability of the crossover site suggests that these mutations arose independently in each pedigree, and did not originate from a single ancestral mutation. As a result, aldosterone synthase is ectopically expressed in the cortisol-producing zone of the adrenal cortex under the regulation of ACTH. The chimerism also results in the production of the hybrid steroids 18-oxocortisol and 18-hydroxycortisol that can be used as diagnostic aides (5).

Genetic analysis of GRA kindreds has revealed that the disorder is inherited as an autosomal dominant trait (6). Celtic ancestry is frequent among the reported pedigrees, and no cases have been reported among blacks (7).

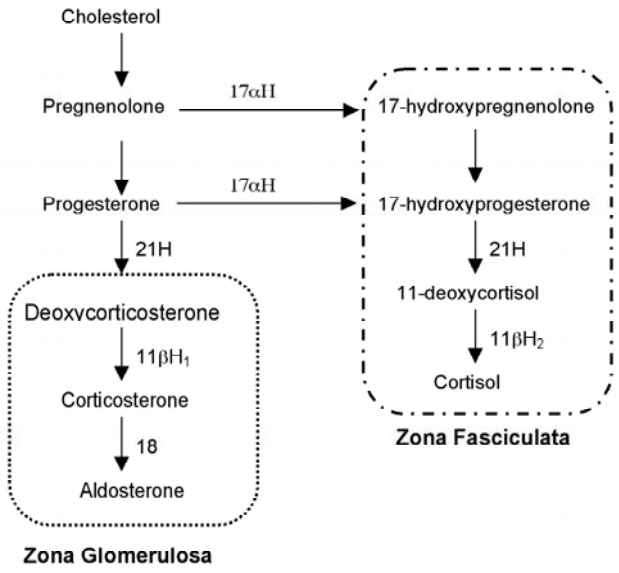

Figure 1. Normal biosynthetic pathways for cortisol and aldosterone. $11\alpha H_1$ and aldosterone synthase are present only in the *zona glomerulosa*, and are regulated by angiotensin II. $11\alpha H_2$ is present solely in the *zona fasciculata* and is regulated by ACTH. 21H= 21-hydroxylase. $11\alpha H_{1\&2}$= 11α-hydroxylase isoenzymes 1 & 2; 18 = 18-hydroxylase/aldosterone synthase. 17αH= 17α-hydroxylase.

CLINICAL FEATURES

GRA is an autosomal-dominant disorder and is the most common monogenic cause of human hypertension. GRA is usually characterized by severe hypertension, sodium retention and suppressed plasma renin activity (8). Unlike other mineralocorticoid-excess states, hypokalemia in the absence of diuretic treatment is uncommon.

Hypokalemia

Most patients with GRA have normal potassium levels (8) despite biochemical evidence for primary hyperaldosteronism. One prospective study in a large pedigree with GRA (8) revealed that normokalemia was the rule unless patients had been treated with potassium-wasting diuretics. Thus, hypokalemia lacks sensitivity as a screening test for GRA. The reason why GRA subjects have normal potassium levels is not understood, but there is not renal impairment of the actions of aldosterone.

Hypertension

GRA is usually characterized by severe hypertension with onset early in life (9). In a retrospective report, eighty percent of 20 children under the age of 18 who carried the genetic mutation had hypertension by the age of 13 years; blood pressures also correlated within sibling pairs. However, only half of the affected children had severe hypertension (blood pressure > 99th centile for age), and 4 of 20 were normotensive (9). A

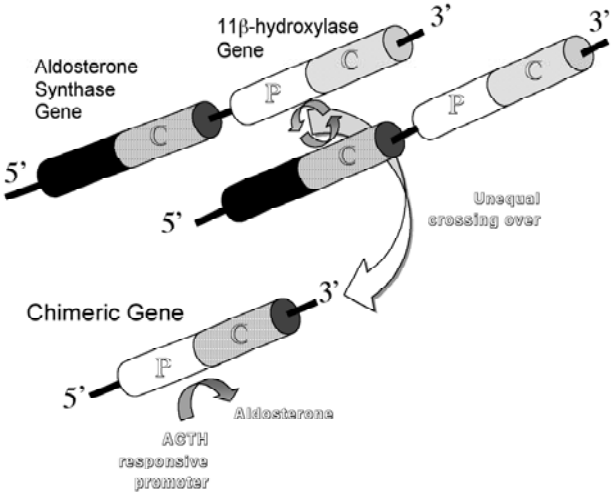

Figure 2. Chimeric gene duplication in glucocorticoid-remediable aldosteronism. P= promoter sequence. C= coding sequence.

kindred has been described where only 8 of 21 affected subjects had systolic blood pressures of greater than 140 and/or diastolic blood pressures of greater than 90mmHg (10). In other reports (11), all affected members have been hypertensive.

Possible explanations for this incomplete penetrance of hypertension include self-selected dietary salt restriction, concomitant inheritance of blood pressure-lowering genes, or decreased penetrance of the chimeric gene. Data from several GRA kindreds suggest that elevated urinary levels of the vasodilator kallikrein may serve to protect against hypertension (12). Another potential source of phenotypic variation is linkage disequilibrium with the 'a' allele of the aldosterone synthase gene (13). Individuals inheriting the mutation from their mothers were found to have significantly higher mean arterial pressures without higher aldosterone levels. The authors speculated that *in-utero* exposure to abnormal maternal mineralocorticoid concentrations (14) may up-regulate processes responsible for aldosterone responsiveness (13).

Hemorrhagic Stroke

In a retrospective study of 27 GRA pedigrees, early hemorrhagic stroke was a characteristic feature, occurring at a mean age of 32 years and associated with high mortality (61%) (15). In this report, nearly half of all GRA pedigrees and 18% of all GRA patients demonstrated early hemorrhagic strokes as a result of ruptured intra-cranial aneurysms. By contrast, there were no strokes in GRA-negative family members. Based on this report, screening with magnetic resonance imaging angiography, beginning at puberty and then every five years, has been recommended to detect asymptomatic intra-cranial aneurysms (15). A reduction in event rates as a result of such screening has not been documented.

DIAGNOSIS

GRA patients can have mild hypertension and are typically normokalemic (8); such patients are often misdiagnosed as having 'essential' hypertension. Clues pointing to a possible diagnosis of GRA include early onset of hypertension in youth, a family history of early onset hypertension or early cerebral hemorrhage, precipitation of hypokalemia when treated with potassium-wasting diuretics, and refractory hypertension to standard treatments (figure 2). Screening targeted at these features performed at one hypertension clinic discovered two index families and four further families containing 40 mutation-positive individuals in one year (16). Genetic screening of random hypertensive individuals by contrast is not efficacious (16).

The PA/PRA ratio in GRA patients is greater than 30, but this is like other etiologies of primary aldosteronism. Since hypokalemia lacks sensitivity as a screening test (8,17), the above historical clues are the most useful in pointing to a possible diagnosis of GRA.

A number of different strategies can be used to diagnose GRA including the dexamethasone suppression test, measurement of urinary 18-hydroxy/oxosteroids (5), or direct genetic analysis (figure 1).

In this disorder the cortisol-producing *zona fasciculata* ectopically produces aldosterone under the regulation of ACTH. As a result, when 0.5mg of the potent glucocorticoid dexamethasone is given every 6 hours for two days, suppression of aldosterone to undetectable levels (< 4ng/dl) is seen in GRA subjects (18). On the other hand, in one study, ten percent of sixty patients with elevated aldosterone levels and a positive dexamethasone suppression study had negative genetic testing (19).

GRA patients excrete large amounts of urinary 18-hydroxycortisol and 18-oxocortisol (5) (so-called 'hybrid' steroids) reflecting the action of aldosterone synthase on cortisol in the *zona fasciculata*. Very low levels are produced in normal subjects, but mild elevations occur with aldosterone-producing adenomas (7).

Direct screening for the chimeric gene duplication by southern blotting is preferred and is 100% sensitive and specific for diagnosing GRA and is available through the International Registry for Glucocorticoid Remediable Aldosteronism at http://www.brighamandwomens.org/gra.

TREATMENT

Non-directed anti-hypertensive therapies are often ineffective in GRA patients (9). Treatment with low dose glucocorticoids is effective (18) by providing feedback suppression of pituitary ACTH release, which suppresses the abnormal regulation of aldosterone secretion. Typical dosing in adults is 0.125-0.25mg of dexamethasone, or 2.5-5mg of prednisolone daily, usually administered at bedtime. However, iatrogenic Cushing's syndrome and impaired linear growth in children have resulted from glucocorticoid overdosing (9). The therapeutic goal should be normotension, and not normalization of biochemical markers, such as urinary 18-oxosteroid or serum aldosterone levels, since these remain elevated in the majority of patients who normalize blood pressure (20). In fact, therapy to normalize laboratory values may unnecessarily increase the risk of cushingoid side effects (20).

The type I mineralocorticoid receptor antagonists, eplerenone and spironolactone, are effective treatment alternatives. Amiloride and triamterene, sodium-epithelial channel antagonists, have also been used successfully. Both groups of agents block aldosterone action rather than reducing the production of this mineralocorticoid. Anti-hypertensives agents, such as α-blockers and ACE-inhibitors, are unlikely to be efficacious in the setting of a suppressed renin-angiotensin system (9). However, dihydropyridine calcium channel blockers can be useful adjunctive treatments to the above diuretic agents.

CONCLUSION

GRA is the commonest monogeneic form of human hypertension and often masquerades as essential hypertension. Clinicians should consider the diagnosis, particularly in hypertensive children, and those with a family history of either early-onset hypertension or early cerebral hemorrhage. A dexamethasone suppression test can be a useful screening maneuver; genetic screening and the measurement of urinary 18-oxosteroids are diagnostic. Treatment options include glucocorticoids to suppress ACTH and aldosterone levels, and mineralocorticoid receptor antagonists. Hypertension in GRA subjects can often be controlled with directed monotherapy.

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