High Blood Press Cardiovasc Prev (2016) 23:231–235
DOI 10.1007/s40292-016-0160-5

REVIEW ARTICLE

Syndromes that Mimic an Excess of Mineralocorticoids

Chiara Sabbadin[1] · **Decio Armanini**[1]

Received: 3 February 2016 / Accepted: 13 May 2016 / Published online: 1 June 2016

Abstract Pseudohyperaldosteronism is characterized by a clinical picture of hyperaldosteronism with suppression of renin and aldosterone. It can be due to endogenous or exogenous substances that mimic the effector mechanisms of aldosterone, leading not only to alterations of electrolytes and hypertension, but also to an increased inflammatory reaction in several tissues. Enzymatic defects of adrenal steroidogenesis (deficiency of 17α-hydroxylase and 11β-hydroxylase), mutations of mineralocorticoid receptor (MR) and alterations of expression or saturation of 11-hydroxysteroid dehydrogenase type 2 (apparent mineralocorticoid excess syndrome, Cushing's syndrome, excessive intake of licorice, grapefruits or carbenoxolone) are the main causes of pseudohyperaldosteronism. In these cases treatment with dexamethasone and/or MR-blockers is useful not only to normalize blood pressure and electrolytes, but also to prevent the deleterious effects of prolonged over-activation of MR in epithelial and non-epithelial tissues. Genetic alterations of the sodium channel (Liddle's syndrome) or of the sodium-chloride co-transporter (Gordon's syndrome) cause abnormal sodium and water reabsorption in the distal renal tubules and hypertension. Treatment with amiloride and thiazide diuretics can respectively reverse the clinical picture and the renin aldosterone system. Finally, many other more common situations can lead to an acquired pseudohyperaldosteronism, like the expansion of volume due to exaggerated water and/or sodium intake, and the use of drugs, as contraceptives, corticosteroids, β-adrenergic agonists and FANS. In conclusion, syndromes or situations that mimic aldosterone excess are not rare and an accurate personal and pharmacological history is mandatory for a correct diagnosis and avoiding unnecessary tests and mistreatments.

Keywords Pseudohyperaldosteronism · Aldosterone · Mineralocorticoid receptor · Hypertension · 11 Hydroxysteroid dehydrogenase type 2 · Apparent mineralocorticoid excess syndrome · Deoxycorticosterone · Licorice

1 Introduction

Aldosterone is the main mineralocorticoid, whose action is regulated by the renin angiotensin system, by 11-hydroxysteroid dehydrogenase type 2 (HSD2) and by the mineralocorticoid receptor (MR). The epithelial effects of aldosterone are involved in the regulation of electrolyte and water balance and consequently of blood pressure. Several studies have also stressed the non-epithelial effects of aldosterone, playing a central role in the inflammatory processes. These effects are mediated not only by genomic mechanisms, involving the MR and 11-HSD2 (for example in hippocampus, heart, vessels and mononuclear leucocytes) [1], but also by non-genomic pathways through not yet clarified mechanisms [2].

All the substances that mimic aldosterone action can induce a pseudohyperaldosteronism, leading not only to alterations of electrolytes and hypertension, but also to an increased inflammatory reaction in several tissues. These clinical situations are linked to endogenous or exogenous factors [3], as reported in Table 1.

✉ Decio Armanini
decio.armanini@unipd.it

[1] Department of Medicine (DIMED), Endocrinology, University of Padua, Via Ospedale 105, 35128 Padua, Italy

Table 1 Causes of pseudohyperaldosteronism

Endogenous causes
Deficiency of 17α-hydroxylase and 11β-hydroxylase
Apparent mineralocorticoid excess syndrome (AME)
Liddle's syndrome
Cushing's syndrome
Insensitivity to glucocorticoids (Chrousos syndrome)
Aldosterone-secreting adrenocortical carcinoma
Geller's syndrome
Gordon's syndrome
Exogenous causes
Corticosteroids with mineralocorticoid activity
Hypersodic diets
Water intossications
Licorice, grapefruit
Carbenoxolone
Contraceptives
Some progestins
Particular causes of hypertension
Sclerosis of juxtaglomerular apparatus (diabetic microangiopathy and/or of the elderly)
FANS
B-Adrenergic agonists
Aging
Low-renin essential hypertension
Autonomic dysfunction
Partial/total nephrectomy or removal of renal tissue

2 Endogenous Causes of Pseudohyperaldosteronism

2.1 Deficiency of 17α-Hydroxylase and of 11β-Hydroxylase

The prevalence of these rare forms of congenital adrenal hyperplasia is about 1/1,000,000.

The deficiency of 17α-hydroxylase (OMIM 202110) is characterized by severe hypertension at birth, hypokalemia, glucocorticoid deficiency, pseudohermaphroditism in male and the lack of development of puberty in both sexes. The enzyme defect blocks the synthesis of cortisol and androgens in the adrenal fasciculata and reticularis and the synthesis of sex steroids in the gonads (Fig. 1). The consequent hypocortisolism stimulates ACTH, inducing secretion of deoxycorticosterone (DOC) by glomerulosa. Increased DOC acts like a mineralocorticoid, binding MR and causing plasma volume expansion, hypertension, suppression of renin and aldosterone. It is worth of note that 17α-hydroxylase is not involved in the synthesis of aldosterone, but ACTH mediated increase of DOC suppresses renin and aldosterone synthesis [4].

The deficiency of 11β-hydroxylase (OMIM 202010) is characterized by a clinical picture of pseudohyperaldosteronism, masculinization in female and precocious puberty in both sexes [5]. The synthesis of aldosterone and cortisol is blocked, resulting in an excessive pro-

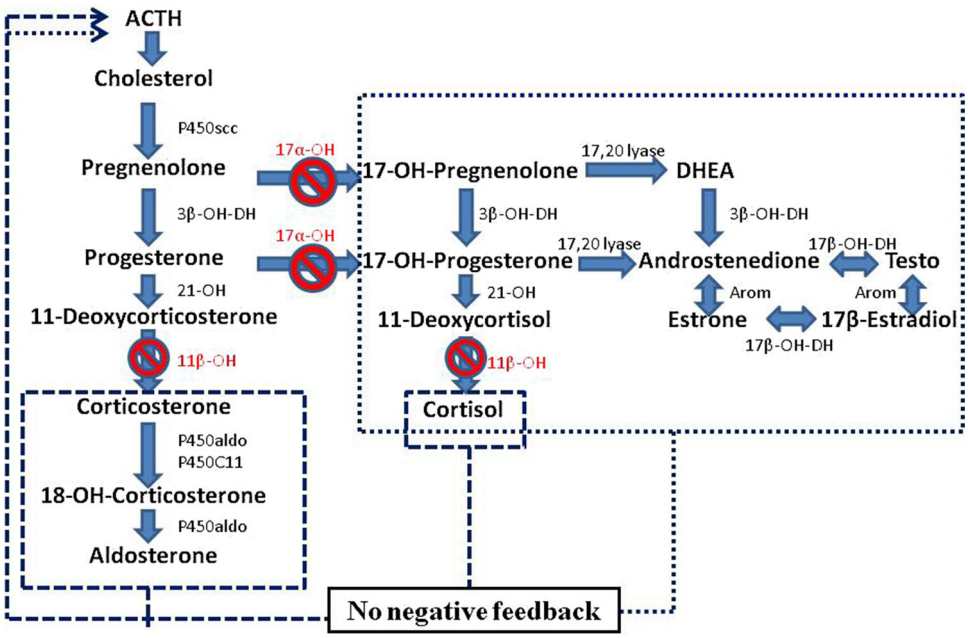

Fig. 1 Alterations of steroidogenesis in 17α-hydroxylase and 11β-hydroxylase deficiency. *17α-OH* 17α-hydroxylase, *3β-OH-DH* 3β-hydroxysteroid dehydrogenase, *21-OH* 21-hydroxylase, *11β-OH* 11β-hydroxylase, *17β-OH-DH* 17β-hydroxysteroid dehydrogenase, *Aro* aromatase

duction of DOC and adrenal androgens, stimulated by increased ACTH levels (Fig. 1).

In both diseases the treatment with glucocorticoids alone or associated with MR-receptor blockers normalizes the secretion of ACTH and DOC, and reactivates the renin aldosterone system. Other medical and/or surgical treatment should be established according to the deficiency or the excess of sex steroids.

2.2 Apparent Mineralocorticoid Excess Syndrome (AME)

A genetic or acquired defect of 11-HSD2 impairs the inactivation of cortisol to cortisone at the level of renal tubular cells and other classical target tissues. Consequently, cortisol can bind MR, producing a sodium and water reabsorption, hypokalemia and suppression of renin and aldosterone synthesis. Moreover, MR also being expressed in mononuclear leucocytes and vascular cells, its prolonged activation can induce systemic inflammation, endothelial dysfunction and increased cerebro- cardio-vascular risk [1, 6, 7]. Among congenital forms, about 50 mutations of the 11-HSD2 gene site have been identified and associated to different phenotypes of the disease and different therapeutic responses; recently epigenetic mechanisms have also been proposed to modulate the enzyme activity, influencing hypertension incidence [8].

Treatment with dexamethasone and/or MR-blockers is useful also in this syndrome.

2.3 Liddle's Syndrome

This rare disease (OMIM 177200) is related to a mutation of the epithelial sodium channels (ENaC) gene in the distal renal tubules. The mutations affect the beta and gamma subunits of the sodium channel, interfering with the ubiquitylation and degradation of channel by the ubiquitin-ligase Nedd4. This alteration leads to the constitutive expression and impaired degradation of ENaC channels, producing sodium and water reabsorption, volume expansion, hypertension, hypokalemia and suppression of renin and aldosterone [9]. The prevalence of the syndrome is unknown and its transmission is autosomal dominant.

Treatment with amiloride or triamterene can reverse the clinical picture reactivating the renin aldosterone system.

2.4 Cushing's Syndrome

Cushing's syndrome is frequently associated with hypertension, which may be caused by many mechanisms, as for example activation of renin angiotensin system, increased peripheral and renovascular resistance, reduced activity of the nitric oxide pathway and increased cardiac output [10]. The main pathogenetic mechanism is linked to the excess of cortisol which saturates 11-HSD2 activity, allowing cortisol to bind MR. A similar picture is also related to over secretion of cortisol by adrenocortical carcinomas. In some cases the disease is associated with secondary hyperaldosteronism due to a direct activation of the renin angiotensin system by glucocorticoids.

The effective treatment of hypercortisolism and the use of MR-blockers can reverse the situation.

2.5 Other Endogenous Causes of Pseudohyperaldosteronism

Chrousos syndrome is a rare familial or sporadic condition, characterized by generalized, mostly partial, target-tissue insensitivity to glucocorticoids, due to mutations in glucocorticoid receptor (GR) gene. This condition leads to compensatory increased secretion of ACTH, which stimulates cortisol and/or DOC synthesis, leading to an AME-like condition, associated with adrenal hyperandrogenism.

Treatment with dexamethasone can normalize ACTH levels and adrenal steroids production [11].

The Geller's syndrome is due to a mutation of MR that alters its specificity and allows progesterone to bind MR, causing severe hypertension particularly during pregnancy, where progesterone levels are very high [12].

Gordon's syndrome (also known as pseudohypoaldosteronism type 2—PHA2) is a rare genetic form of hypertension, characterized by hyperkalemia, normal renal function, low renin and normal aldosterone levels. It is caused by an increased activity of the thiazide-sensitive Na–Cl co-transporter in the distal tubule, due to different mutations correlated to different phenotypes. Mutations of at least four genes have been identified, including WNK1 and WNK4 (members of a family of serine-threonine kinases), associated to PHA2C (OMIM 614492) and PHA2B (OMIM 614491) respectively, and KLHL3 and CUL3 (components of the cullin/Ring E3 ligase ubiquitination pathway) associated to PHA2D (OMIM 614495) and PHA2E (OMIM 614496) respectively. Additional mutations in chromosome 1 have also been described, associated to PHA2A (OMIM 145260).

The treatment is based on the administration of thiazide diuretics and/or dietary sodium restriction, which effectively improve hypertension and electrolytic alterations [13].

3 Exogenous Causes of Pseudohyperaldosteronism

3.1 Intake of Corticosteroids with Mineralocorticoid Activity

Fludrocortisone or fluoroprednisolone can mimic the action of aldosterone, causing plasma volume expansion, increase of blood pressure and suppression of renin and aldosterone. This

situation is usually the consequence of an excess of fludrocortisone intake in Addison's disease or during inappropriate use of inhalatory mineralocorticoids for rhinitis or asthma. Treatment with glucocorticoids (for example prednisone or prednisolone) for rheumatic diseases can also induce pseudohyperaldosteronism by binding GR and/or MR.

3.2 Pseudohyperaldosteronism from Licorice, Grapefruit and Carbenoxolone

Abuse of licorice is one of the most common causes of exogenous hypertension. The main component of licorice is the glycyrrhetinic acid that binds MR and blocks 11-HSD2 at the level of classical target tissues of aldosterone [14]. The syndrome is related not only to the common licorice products as sweetening, but also to laxatives or ocular drops containing glycyrrhetinic acid [15].

High assumption of naringenin, a component of grapefruit, can also block 11-HSD2 [16].

Finally, carbenoxolone is a glycyrrhetinic acid derivate with a steroid-like structure, able to bind MR and block 11-HSD2 [17]. It is usually used for the treatment of gastrointestinal ulcerations and inflammation.

3.3 Contraceptives

Other common situations associated with pseudohyperaldosteronism are the use of some particular contraceptives in predisposed patients. Estrogens can retain sodium and water by different mechanisms, causing increased blood pressure values and suppressing the renin aldosterone system. However, contraceptives usually cause hypertension through a secondary hyperaldosteronism due to the stimulation of the synthesis of angiotensinogen.

3.4 Other Exogenous Common Causes of Pseudohyperaldosteronism

An expansion of volume, due to exaggerated water and/or sodium intake, can cause hypertension and induce suppression of the renin aldosterone system. In surgical and neurosurgical units the excess of fluid infusion can cause hypertension with hyponatremia and hypokalemia due to blood dilution. It is also very important to consider any other pathological conditions associated to volume expansion, such as hypothyroidism.

4 Particular Causes of Hypertension with Low Renin and Aldosterone

Hypertension with glomerulosclerosis is frequent in diabetic microangiopathy or in the elderly. This situation can increase blood pressure despite that renin is low, juxtaglomerular apparatus being sclerotic (secondary hypoaldosteronism).

Prolonged use of FANS can increase blood pressure, blocking the prostaglandin secretion.

Low-renin essential hypertension is very frequent and its pathogenetic mechanism is still unknown. Some authors have hypothesized a genetic higher sensitivity to aldosterone or sodium. This clinical condition is frequent in African American hypertensive people or in subjects consuming high sodium diets, as for example in China. The disease is characterized by suppression of renin angiotensin system and by subnormal aldosterone levels: in these cases the measurement of renin aldosterone ratio (ARR) is not indicated, thus excluding primary aldosteronism.

5 Diagnosis and Management of Pseudohyperaldosteronism in a Hypertensive Patient

An accurate history must be always performed in patients with hypertension, asking for water/sodium intake, use of licorice, grapefruit juice, contraceptives, glucocorticoids, not only by oral intake, but also by inhalator or topical use. In pediatric hypertensive patients, sex hormone alterations must be considered in case of ambiguous genitalia. Pseudohyperaldosteronism should also be suspected in case of familiarity, resistant hypertension, diabetes, aging and hypokalemia.

In cases with aldosterone at the low levels of normal range and suppressed renin, the differential diagnosis with hyperaldosteronism should be considered, being primary aldosteronism in some cases associated with these parameters [18]. This finding can support the theory that the primary aldosteronism is a disease that evolves from a situation of low renin essential hypertension in idiopathic hyperaldosteronism and adrenal adenoma, as we suggested in a previous study of our group [19, 20].

Biochemical exams should always include the evaluation of renin, aldosterone, cortisol, sodium and potassium, considering possible interfering drugs. Use of diuretics, ACE-inhibitors, sartanics, MR-antagonists, β-blockers, corticosteroids and contraceptives should be avoided for a correct interpretation of the results in endogenous disease. In patients affected by exogenous pseudohyperaldosteronism the diagnosis is done during the intake and it is confirmed by the normalization of the clinical and biochemical picture after the suspension of the substance for at least one month to demonstrate their influence on the renin aldosterone system. Finally, particular measurements should be performed based on the history and the physical examination, as for example the ratio of cortisol to cortisone and of THF + 5αTHF/THE, the measurement of

glycyrrhetinic acid or of minor mineralocorticoids, like DOC, corticosterone and 18-hydroxycorticosterone, specific genetic mutations and the morphological study of adrenals and genitalia.

6 Conclusive Remarks

Syndromes that mimic aldosterone excess are not rare and pseudohyperaldosteronism is a very important clinical situation not only for hypertension and/or endocrinology specialists, but also for general doctors. The evaluation of electrolyte balance and of renin aldosterone system should always be considered, and an accurate history is mandatory for correct diagnosis, avoiding unnecessary exams or mistreatments.

The most important point to consider is that the knowledge of a disease can lead to a correct diagnosis.

Compliance with Ethical Standards

Conflict of interest There are no conflict of interest and no financial disclosure to disclose.

References

1. Armanini D, Strasser T, Weber PC. Characterization of aldosterone binding sites in circulating human mononuclear leukocytes. Am J Physiol. 1985;248:E388–90.
2. Bordin L, Donà G, Sabbadin C, Ragazzi E, Andrisani A, Ambrosini G, Brunati AM, Clari G, Armanini D. Human red blood cells alterations in primary aldosteronism. J Clin Endocrinol Metab. 2013;98:2494–501.
3. Armanini D, Calò L, Semplicini A. Pseudohyperaldosteronism: pathogenetic mechanisms. Crit Rev Clin Lab Sci. 2003;40:295–335.
4. Scaroni C, Opocher G, Mantero F. Renin-angiotensin-aldosterone system: a long-term follow-up study in 17 alpha-hydroxylase deficiency syndrome (17OHSD). Clin Exp Hypertens A. 1986;8:773–80.
5. Zhao LQ, Han S, Tian HM. Progress in molecular-genetic studies on congenital adrenal hyperplasia due to 11beta-hydroxylase deficiency. World J Pediatr. 2008;4:85–90.
6. Osmond JM, Dorrance AM. 11β-Hydroxysteroid dehydrogenase type II inhibition causes cerebrovascular remodeling and increases infarct size after cerebral ischemia. Endocrinology. 2009;150:713–9.
7. Calò LA, Zaghetto F, Pagnin E, Davis PA, De Mozzi P, Sartorato P, Martire G, Fiore C, Armanini D. Effect of aldosterone and glycyrrhetinic acid on the protein expression of PAI-1 and p22(phox) in human mononuclear leukocytes. J Clin Endocrinol Metab. 2004;89:1973–6.
8. Pizzolo F, Friso S, Morandini F, Antoniazzi F, Zaltron C, Udali S, Gandini A, Cavarzere P, Salvagno G, Giorgetti A, Speziali G, Choi SW, Olivieri O. Apparent mineralocorticoid excess by a novel mutation and epigenetic modulation by HSD11B2 promoter methylation. J Clin Endocrinol Metab. 2015;100:E1234–41.
9. Ronzaud C, Staub O. Ubiquitylation and control of renal Na^+ balance and blood pressure. Physiology (Bethesda). 2014;29:16–26.
10. Ferraù F, Korbonits M. Metabolic comorbidities in Cushing's syndrome. Eur J Endocrinol. 2015;173:M133–57.
11. Charmandari E, Lino T, Chrousos GP. Primary generalized familial and sporadic glucocorticoid resistance (Chrousos syndrome) and hypersensitivity. Endocr Dev. 2013;24:67–85.
12. Geller DS, Farhi A, Pinkerton N, Fradley M, Moritz M, Spitzer A, Meinke G, Tsai FT, Sigler PB, Lifton RP. Activating mineralocorticoid receptor mutation in hypertension exacerbated by pregnancy. Science. 2000;289:119–23.
13. Glover M, Ware JS, Henry A, Wolley M, Walsh R, Wain LV, Xu S, Van't Hoff WG, Tobin MD, Hall IP, Cook S, Gordon RD, Stowasser M, O'Shaughnessy KM. Detection of mutations in KLHL3 and CUL3 in families with FHHt (familial hyperkalaemic hypertension or Gordon's syndrome). Clin Sci (Lond). 2014;126:721–6.
14. Armanini D, Lewicka S, Pratesi C, Scali M, Zennaro MC, Zovato S, Gottardo C, Simoncini M, Spigariol A, Zampollo V. Further studies on the mechanism of the mineralocorticoid action of licorice in humans. J Endocrinol Invest. 1996;19:624–9.
15. Scali M, Pratesi C, Zennaro MC, Zampollo V, Armanini D. Pseudohyperaldosteronism from liquorice-containing laxatives. J Endocrinol Invest. 1990;13:847–8.
16. Palermo M, Armanini D, Delitala G. Grapefruit juice inhibits 11beta-hydroxysteroid dehydrogenase in vivo, in man. Clin Endocrinol (Oxf). 2003;59:143–4.
17. Armanini D, Karbowiak I, Krozowski Z, Funder JW, Adam WR. The mechanism of mineralocorticoid action of carbenoxolone. Endocrinology. 1982;111:1683–6.
18. Stowasser M, Ahmed AH, Pimenta E, Taylor PJ, Gordon RD. Factors affecting the aldosterone/renin ratio. Horm Metab Res. 2012;44:170–6.
19. Armanini D, Fiore C, Pellati D. Spontaneous resolution of idiopathic aldosteronism after long-term treatment with potassium canrenoate. Hypertension. 2007;50:e69–70.
20. Armanini D, Fiore C. Some considerations about evolution of idiopathic primary aldosteronism. J Endocrinol Invest. 2009;32:623–5.