Apparent Mineralocorticoid Excess Syndrome: An Overview

revisão

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ABSTRACT

Apparent mineralocorticoid excess (AME) syndrome results from defective 11α-hydroxysteroid dehydrogenase type 2 (11α-HSD2). This enzyme is co-expressed with the mineralocorticoid receptor (MR) in the kidney and converts cortisol (F) to its inactive metabolite cortisone (E). Its deficiency allows the unmetabolized cortisol to bind to the MR inducing sodium retention, hypokalemia, suppression of PRA and hypertension. Mutations in the gene encoding 11α-HSD2 account for the inherited form, but a similar clinical picture to AME occurs following the ingestion of bioflavonoids, licorice and carbenoxolone, which are competitive inhibitors of 11α-HSD2. Reduced 11α-HSD2 activity may explain the increased sodium retention in preeclampsia, renal disease and liver cirrhosis. Relative deficiency of 11α-HSD2 activity can occur in Cushing's syndrome due to saturation of the enzyme and explains the mineralocorticoid excess state that characterizes ectopic ACTH syndrome. Reduced placental 11α-HSD2 expression might explain the link between reduced birth weight and adult hypertension. Polymorphic variability in the HSD11B2 gene in part determines salt sensitivity, a forerunner for adult hypertension onset. AME represents a spectrum of mineralocorticoid hypertension with severity reflecting the underlying genetic defect in the 11α-HSD2; although AME is a genetic disorder, several exogenous compounds can bring about the symptoms by inhibiting 11α-HSD2 enzyme. Substrate excess as seen in Cushing's syndrome and ACTH ectopic production can overwhelm the capacity of 11α-HSD2 to convert F to E, leading up to an acquired form of AME. **(Arq Bras Endocrinol Metab 2004;48/5:687-696)**

Keywords: Hypertension; 11α-HSD2; AME syndrome; Cortisol; Cortisone

RESUMO

Síndrome do Excesso Aparente de Mineralocorticóides: Uma Revisão.

A síndrome do excesso aparente de mineralocorticóides (SEAM) resulta de defeito na 11α-hidroxisteróide desidrogenase tipo 2 (11α-HSD2). Esta enzima é co-expressa com o receptor mineralocorticóide (RM) nos rins e converte cortisol (F) em cortisona (E), seu metabólito inativo. Deficiência desta enzima permite que o cortisol não metabolizado se ligue ao RM, induzindo retenção de sódio, hipocalemia, supressão da APR e hipertensão. Mutações no gene que codifica a 11α-HSD2 são responsáveis pela forma herdada, mas um quadro clínico semelhante de SEAM ocorre durante ingestão dos bioflavonóides, alcaçuz e carbenoxolona, que são inibidores competitivos da 11α-HSD2. Redução na atividade da 11α-HSD2 pode explicar o aumento da retenção de sódio na pré-eclâmpsia, na doença renal e na cirrose hepática. Deficiência relativa de atividade da 11α-HSD2 pode ocorrer na síndrome de Cushing devido à saturação da enzima e explicar o estado de excesso mineralocorticóide que caracteriza a síndrome do ACTH ectópico. Redução da expressão placentária da 11α-HSD2 poderia justificar a ligação entre baixo peso ao nascer e hipertensão no adulto. Variabili-

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dade polimórfica no gene HSD11B2 determina, em parte, a sensibilidade ao sódio, um preditor do surgimento da hipertensão no adulto. A SEAM representa um espectro de hipertensão mineralocorticóide cuja severidade reflete o defeito genético de base na 11α-HSD2; embora a SEAM seja uma doença genética, vários compostos exógenos podem provocar os sintomas pela inibição da 11α-HSD2. O excesso de substrato, visto na síndrome de Cushing e na produção ectópica de ACTH, pode sobrepujar a capacidade da 11α-HSD2 de converter F em E, levando a uma forma adquirida de SEAM. **(Arq Bras Endocrinol Metab 2004;48/5:687-696)**

Descritores: Hipertensão; 11α-HSD2; Síndrome do EAM; Cortisol; Cortisona

APPARENT MINERALOCORTICOID EXCESS SYNDROME (AME) is characterized by clinical features suggesting excessive production of a mineralocorticoid-like substance with hypertension, plasma volume expansion, hypokalemic alkalosis and a suppressed renin-angiotensin-aldosterone system (1). It can be classified on the basis of whether it is congenital or acquired, but the two forms share the same pathophysiology: AME is the outcome of defective 11α-hydroxysteroid dehydrogenase type 2 (11α-HSD2) (2,3). This enzyme is predominantly expressed, together with the mineralocorticoid receptor (MR), in the renal distal tubules and collecting ducts (4), in the distal colon, in the salivary glands and also in the placenta where it protects the fetus from an excessive amount of maternal cortisol (F) (5,6) (figure 1). 11α-HSD2 converts F to its inactive metabolite cortisone (E). Since F, but not E, is a potent agonist of epithelial type 1 mineralocorticoid receptors, reduced activity or total deficiency of the enzyme exposes the kidney to an excess of F, which can then act as a potent mineralocorticoid (7,8). Mineralocorticoid receptor (MR) has the same affinity for F and aldosterone *in vitro* (9), and the inactivation of cortisol to cortisone by 11α-HSD2 at the site of the MR enables aldosterone to bind to this receptor *in vivo* (figure 2) (10). Aldosterone is not metabolized by 11α-HSD2 because it forms a C_{11}-C_{18} hemi-ketal group in aqueous solution.

	11α-HSD type I	11α-HSD type II
Location	Liver, adipose tissue	Kidney, colon, placenta
Cofactor	NADP+	NAD+
Substrate affinity	Low	High
Bi-directional?	Yes, mainly reductase	No, only dehydrogenase
DNA	1287 bp	1840 bp
Aminoacids	292	405
Molecular mass	34 kDa	45 kDa
Chromosome	1	16

Figure 1. 11α-Hydroxysteroid dehydrogenase (11α-HSD) isozymes.

Circulating levels of adrenal corticosteroids and 11α-HSD2 activity are then involved in blood pressure regulation. Their importance is highlighted by pathophysiological situations such as Cushing's syndrome or ectopic production of ACTH, but even in essential hypertension decreased activity of 11α-HSD2 has been described.

A distinct isozyme of 11α-hydroxysteroid dehydrogenase exists (11α-HSD1). It is widely distributed, but most abundant in liver and adipose tissue. It functions mainly as an oxoreductase, converting cortisone to cortisol, and plays a crucial role in the organ-specific modulation of F effect (11) (figure 1).

This review discusses the consequence of congenital or acquired deficiency of 11α-HSD2 activity, in humans.

CONGENITAL DEFICIENCY OF 11α-HSD2

Apparent Mineralocorticoid Excess Syndrome

Cortisol metabolism

To understand the metabolic consequence of defective 11α-HSD2 activity, it is important to know the normal metabolism of F.

Cortisol is interconverted with cortisone by 11α-HSD2 and the principal site of conversion is the kidney (12), whilst the liver is the place where corti-

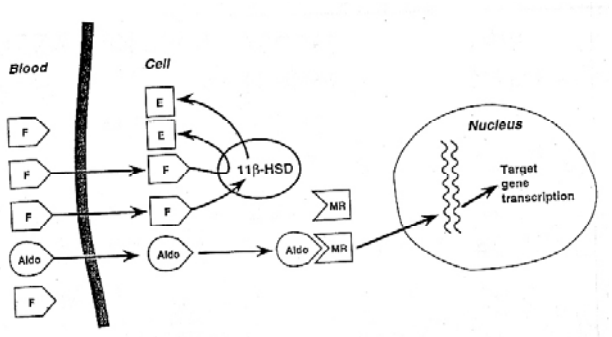

Figure 2. Pathophysiology of apparent mineralocorticoid excess syndrome. The mineralocorticoid receptor (MR) binds aldosterone (A) and cortisol (F) with equal affinity. Plasma F concentrations exceed those of A by a 100-fold. 11α-HSD by inactivating F to E, enables aldosterone to bind to MR. After binding of A to the MR, the A-MR complex binds to DNA hormone response elements and increases transcription of target genes. In the case of impaired 11αHSD2 activity, F binds inappropriately to the MR and increases transcription of MR target genes leading to sodium resorption and potassium excretion.

sone is mainly converted to cortisol by 11α-HSD1. Both are substrates for a series of enzymatic activities in the liver, including the reduction of α^4 double bond (yields 5α- and 5α-dihydrocortisol and 5α- and 5α-dihydrocortisone), reduction of 3-keto group (yields 5α- and 5α-tetrahydrocortisol and 5α- and 5α-tetrahydrocortisone), reduction of 20-keto group (yields to 20α- and 20α-DHF, cortols and cortolones) (figure 3). Most of the products are excreted in the urine as glucuronides. Only a small part of cortisol metabolites is excreted unconjugated mainly as 3-oxo-4-ene steroids (36).

In the case of AME (partial or complete deficiency of 11α-HSD2), urinary steroid metabolite profiles indicate that the majority of cortisol metabolites are excreted as A-ring reduced metabolites of cortisol itself (5α-tetrahydrocortisol (THF) and 5α-THF or allo-THF) with very low or absent levels of tetrahydrocortisone (THE) in the urine. The excretion of 5α-cortisol metabolites exceeds that of 5α-cortisol metabolites and results in a high urinary allo-THF/THF ratio suggesting an additional defect in 5α-reductase activity (13,14). The incremental increase in the THF+allo-THF/THE compared to the allo-THF/THF ratio, however, is much larger, with typical THF+allo-THF/THE ratios ranging from 3 to over 70 in AME (normal ratio is approximately 1). The THF+allo-THF/THE ratio has been used in the past in the diagnosis of AME (13,14), but probably provides an index of "global" 11α-HSD activity within the body, i.e. principally 11α-HSD1 in the liver and 11α-HSD2 in the kidney. The conversion of cortisone to cortisol mediated by 11α-HSD1 is normal in AME (67). The plasma half-life of [11-^{3}H]-cortisol (which when metabolized by 11α-HSD yields tritiated water and cortisone) may more accurately reflect renal 11α-HSD2 activity (10), as may the ratio of urinary free cortisol/urinary free cortisone (UFF/UFE) (15). Normal subjects excrete 2-3-fold more UFE than UFF, reflecting the significant activity of renal 11α-HSD2. In AME, however, UFE excretion is virtually undetectable (16) resulting in a high UFF/UFE ratio. Plasma cortisol half-life is prolonged (120-190min vs. 70-90min in controls), but patients with AME are not cushingoid; the cortisol secretion rate falls often to very low levels due to a normal intact negative feedback mechanism. This maintains normal circulating concentrations in the face of impaired cortisol metabolism.

A variant of AME, so-called "type II AME" has been documented in several patients (17,18). This variant is characterized by a milder phenotype, with onset in late adolescence or early adulthood and only a mildly deranged urinary THF+allo-THF/THE ratio. However, the UFF/UFE excretion is high in the type II variant, and the metabolism of 11-triated cortisol

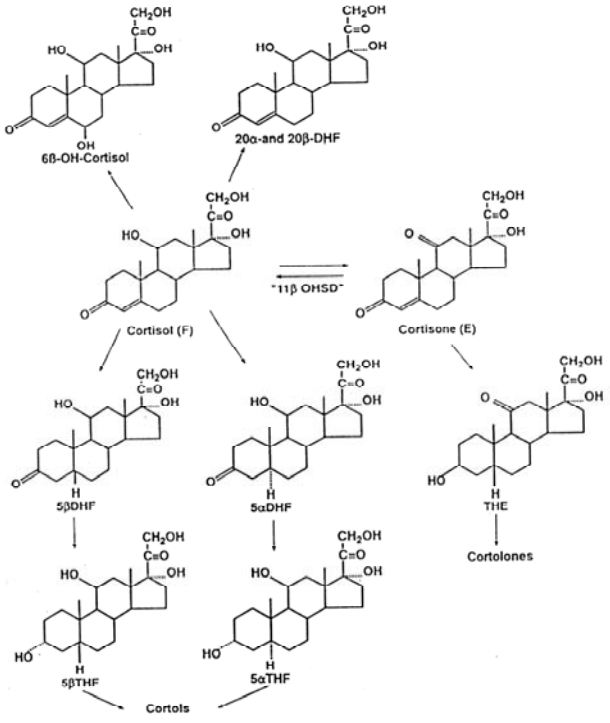

Figure 3. Cortisol metabolism. 11α-HSD2 deficiency reduces the production of THE; as a consequence, (THF+allo-THF)/THE ratio increases. Despite normal circulating cortisol levels, patients with AME show a decrease in the total urinary excretion of cortisol metabolites reflecting a reduction secretion rate consequent upon a prolonged plasma half-life. In addition, 5α-reduced cortisol metabolites predominate over 5α-reduced cortisol metabolites consistent with a reduction of 5α-reductase activity in patients with AME.

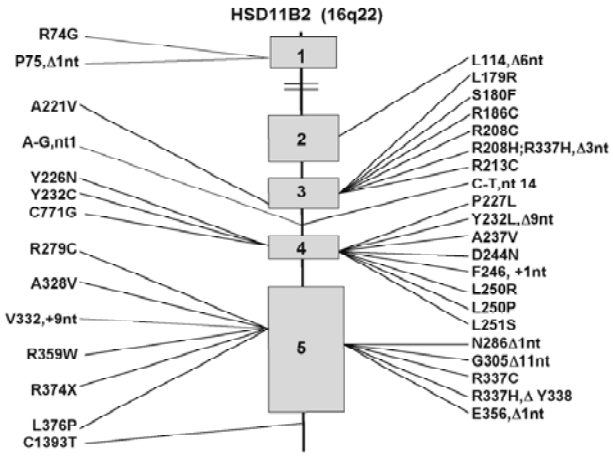

Figure 4. Mutations and their location in the HSD11B2 gene leading to Apparent Mineralocorticoid Excess (AME) syndrome. Exons= gray squares.

(directly reflecting 11α-HSD2 dehydrogenase activity) is grossly deranged, confirming deficiency of 11α-HSD2 (16) (figure 5A).

Pathophysiology

The pathophysiology of AME has now been satisfactorily explained in terms of its clinical, biochemical and genetic basis. An inability of the renal 11α-HSD2 enzyme to inactivate F to E is the cause of sodium retention, PRA and aldosterone suppression and hypertension.

Firstly, in 1974 Werder et al. (19) described a child with features similar to primary hyperaldosteronism, but presenting suppressed plasma aldosterone. Afterwards, New et al. (20) and Ulick et al. (21) described other children presenting similar clinical pictures. The distinctive feature of the patients was the high excretion of 11α-hydroxycortisol metabolite (THF and cortols) to the extremely low excretion of 11-oxo-metabolites (THE and cortolones). Since hypertension, low renin and hypokalemia, but low levels of aldosterone and deoxycorticosterone were present, the term "Apparent Mineralocorticoid Excess" (AME) was coined. In 1983, Oberfield et al. (22) documented the mineralocorticoid effect of hydrocortisol and the marked hypotensive effect of spironolactone and metyrapone. For these reasons, they suggested the presence of a defective conversion of F to E and a mineralocorticoid-like action of cortisol on MR (22). In 1985, the first adult case of AME was reported. It was described the beneficial effect of dexamethasone and the deleterious action of hydrocortisone on blood pressure and hypokalemia in this patient, confirming the involvement of a deranged cortisol metabolism in the pathogenesis of the syndrome (23). The physiological explanation of this theory was given by the demonstration that the MR has the same affinity for cortisol and aldosterone *in vitro*, but 11α-HSD protects the MR *in vivo* by the action of F hundreds of times higher in concentration compared to aldosterone (9,24). This enzyme was then proposed as the one responsible for the syndrome. In 1989, Ulick et al. (25) described the case of 4 Italian children with the same clinical presentation of classical AME, but less severe biochemical features. They called this syndrome AME type II (25). On the basis of the markedly decreased ring-A reduction constant (THF+allo-THF/F), they indicated the impaired ring-A reduction and/or defective interconversion of F and E in both directions (F to E and E to F, leaving the ratio between 11-α and 11-oxo steroid unchanged) as the principal abnormalities of AME (25,26). In 1995-1996, information on the structure and sequence of the HSD11B2 gene has enabled the identification of mutations in AME patients. HSD11B2 is 6.2kb in length containing five exons and is located on chromosome 16q22 (27,28). At present, more than 30 different mutations have been defined within the HSD11B2 gene in approximately 60 affected kindreds (figure 3) (3,28-30). Genetics entirely explain the clinical and biochemical features of AME.

The congenital form of AME is thus attributable to deficiency of 11α-HSD2. Cortisol and aldosterone have similar affinities *in vitro* for the type I MR and 11α-HSD2 confers aldosterone specificity on the intrinsically non-specific MR by converting cortisol to its inactive metabolite cortisone. This way, 11α-HSD2 *in vivo* protects MR from the hundreds of times higher circulating levels of cortisol.

AME is an autosomal recessive inherited form of hypertension. Most type I AME patients are homozygous for HSD11B2 mutations causing full, or partial loss of activity. It is most commonly found in consanguineous families (3,28,30,31).

Type II AME is also explained on the basis of mutations in the HSD11B2 gene (32,33). In an extensive Sardinian kindred, a novel homozygous mutation (R279C) was found in all 4 affected cases. In keeping with the mild phenotype the mutation resulted in a mutant enzyme with only minor disturbances in activity. Classification of AME into distinct variants is therefore inappropriate (figure 5A). In keeping with this, a close correlation is reported between disease phenotype (as measured by the THF+allo-THF/THE ratio, serum potassium and blood pressure) and genotype (34). Patients with mutant 11α-HSD2 cDNAs that demonstrate little or no activity *in vitro*, present in early life with severe, often life-threatening, hypertension and hypokalemia. In contrast patients presenting in late adolescence or early adulthood with so-called "mild" forms of AME have been found to have mutations that result in an 11α-HSD2 protein with only attenuated activity.

Clinical Picture

In its full expression AME is rare, with fewer than 100 cases reported worldwide, but presentation is dramatic. Usually patients are children with low birth weight, failure to thrive, short stature, and severe, often fatal, hypertension with hypokalemic metabolic alkalosis and muscle weakness. Hypokalemic nephropathy sometimes causes nephrocalcinosis, polycystic kidney and nephrogenic diabetes insipidus manifesting as thirst and polyuria. Renal insufficiency is not rare. Severe hypertension causes left ventricular hypertrophy, car-

diomegaly and hypertensive retinopathy. The mortality is more than 10%, due to stroke, cerebral hemorrhage and infarction. Less severe forms in adults have been described. These patients were in the past included in the type II AME. The less severe biochemical and clinical features in type II patients compared to type I appear to be explained on the basis of mutations, which result in some residual functional enzymatic activity. The decision to assign the individual patients to AME type I or II group is therefore rather arbitrary (35,18) (figure 5A).

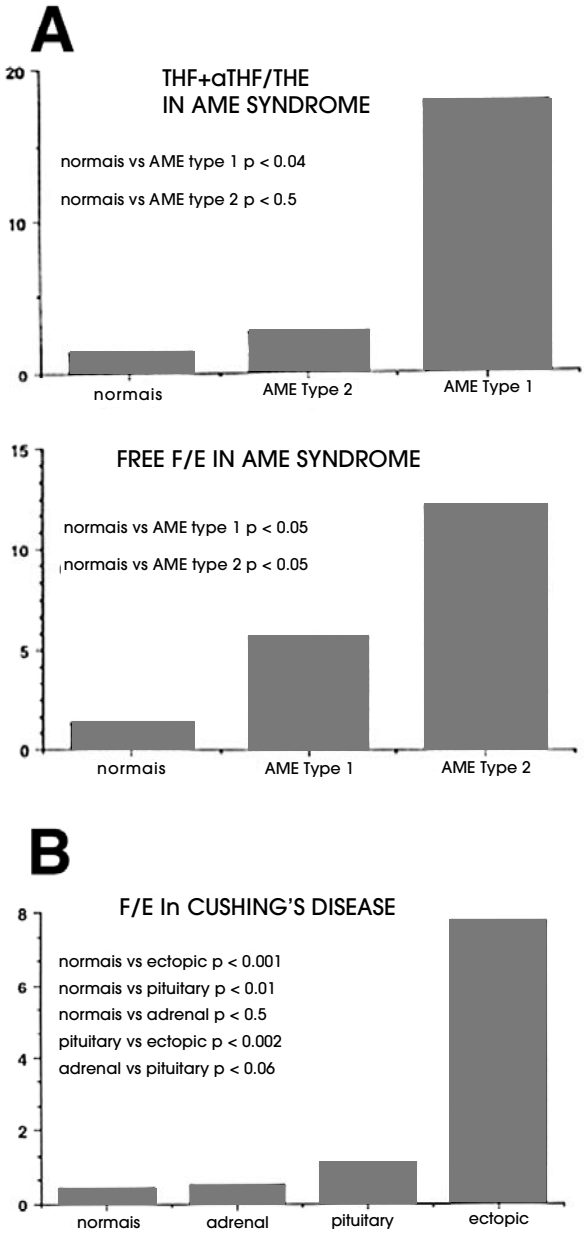

Figure 5. A) (THF+allo-THF)/THE and UFF/UFE are significantly increased both in AME type I and type II. **B)** 11α-Hydroxysteroid dehydrogenase is saturated by substrate excess. Increase in UFF/UFE ratio depends by the amount of circulating cortisol.

Diagnosis

Biochemical abnormalities comprise suppressed PRA, undetectable serum aldosterone levels and hypokalemia. Traditionally, the THF+alloTHF/THE ratio has been used in the diagnosis of AME. A very high ratio can be found (normal ratio ranges from 1 to 3) together with evidence of a more general defect in steroid ring-A reduction (i.e. a higher allo-THF/THF ratio and a lower ring-A reduction constant THF+allo-THF/F).

The "net" *in vivo* conversion of F to E involves both isoforms of 11α-HSD in tissue expressing these enzymes. As AME is a disorder of the renal 11α-HSD2, a direct measure of the ratio of urinary free cortisol/free cortisone fractions (UFF/UFE) should better reflect 11α-HSD2 isozyme activity with respect to the ratio of liver-reduced metabolites (THF+allo-THF)/THE (15,16,36). As a consequence, UFF/UFE ratio proves extremely sensitive and accurate when used as an index of clinical disorder. In 24 patients suffering from AME syndrome, where urinary E is virtually absent, THE was always detectable although 12 subjects had undetectable UFE (16). This suggests that UFE may be more sensitive than THE in the diagnosis of AME. Moreover, if used in monitoring the enzymatic activity in heterozygotes, we often found a significant increase in UFF/UFE ratio, but not in the (THF+allo-THF)/THE ratio (37). A comparison of the UFF/UFE to (THF+allo-THF)/THE ratios in patients with AME after licorice ingestion or in patients suffering from ectopic ACTH syndrome, shows that any deviation from normal in the (THF+allo-THF)/THE ratio resulted in a much more marked change in UFF/UFE (15). The higher sensitivity of UFF/UFE probably occurs because it derives from the activity of the renal isozyme 11α-HSD2, expressed together with the MR in the distal tubule and collecting duct, whereas the reduced fraction THF, allo-THF and THE are products of the hepatic metabolism of F (38).

AME patients are not cushingoid because they have a normal intact negative feedback mechanism. This maintains normal circulating concentration in the face of impaired cortisol metabolism.

Figure 6 illustrates how AME might be diagnosed in a patient presenting with mineralocorticoid excess.

Therapy

Therapy is directed at correcting life-threatening

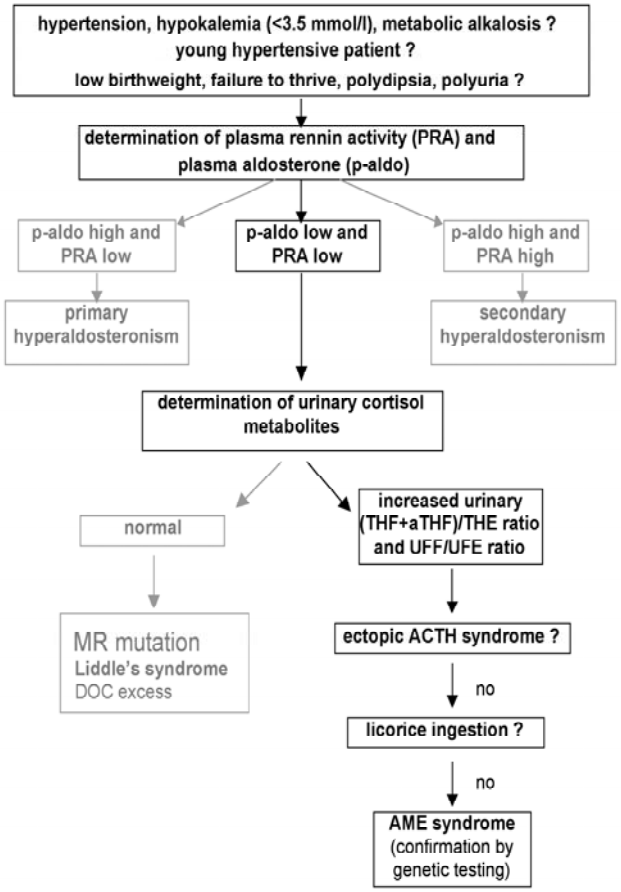

Figure 6. Flowsheet with guidelines for detecting Apparent Mineralocorticoid Excess (AME) syndrome. THF= tetrahydrocortisol; aTHF= allo-tetrahydrocortisol; THE= tetrahydrocortisone; UFF= urinary free cortisol; UFE= urinary free cortisone.

hypokalemia and hypertension (18,35). Dexamethasone is the treatment of choice. Doses ranging from 1.5 to 2mg/day brought serum potassium levels to normal in 7-10 days in approximately 60% of cases by suppressing cortisol and progressively decreasing blood pressure. Additional antihypertensive medication may be required. Patients have been successfully treated with the potassium sparing diuretics triamterene and/or amiloride. Thiazide diuretics are indicated when hypercalciuria and/or nephrocalcinosis are present. Spironolactone, a MR antagonist, has been of variable benefit, presumably because very high doses are required to block the mineralocorticoid effects of cortisol on the MR. Its side effects include menstrual disturbances in women, gynecomastia, impotence and decreased libido in men and are mainly due to its inhibition of steroid biosynthetic P-450 enzyme and its action as an antiandrogen. Sometimes it is important to reduce dietary sodium. AME was reported "cured" in one patient following kidney transplantation due to the normal 11α-HSD2 activity of the transplanted kidney (39). The case suggests a new strategy in a selected cohort of patients such as drug-unresponsive children and in patients with end-stage kidney failure.

11α-HSD2 and "Essential" Hypertension

Although patients with essential hypertension do not have overt signs of mineralocorticoid excess, some positive correlations between blood pressure and plasma sodium levels or a negative correlation with serum potassium levels have been described.

Regarding 11α-HSD2, studies have demonstrated variations in 11α-HSD activity in hypertensive subjects with either increases in the plasma [11˜-^{3}H]-cortisol half-life or the THF+allo-THF/THE ratio (40,41), but mineralocorticoid excess in patients with impaired 11α-HSD2 activity could not be demonstrated.

Recently, association and linkage studies have been performed. One study has reported an association between a microsatellite marker close to the HSD11B2 gene and hypertension in African Americans with hypertensive end stage renal disease (42). These data were confirmed using a polymorphic restriction site in exon 3 of the HSD11B2 gene. In terms of hypertension per se, however, linkage and/or association studies have been negative (43,44).

Increased sensitivity to salt is a forerunner to "essential" hypertension. Salt sensitive individuals appear to have impaired 11α-HSD2 activity as measured by increased urinary cortisol/cortisone ratios. Studies have evaluated a microsatellite within intron 1 of the HSD11B2 gene, and documented association with salt sensitivity in both normal subjects and patients with hypertension (45,46). Short microsatellite alleles were more common in salt sensitive compared to salt resistant subjects. The same phenomenon was observed in Blacks compared to Caucasians (47), in keeping with the predisposition to low-renin, salt-sensitive hypertension in this ethnic group.

In addition to enhanced renal sodium retention, the modulation of active glucocorticoid concentration by 11α-HSD in vascular smooth muscle cells could be an additional factor underlying hypertension (48). *In vitro* and *in vivo* studies indicate that 11α-HSDs regulate vascular tone at an autocrine level through the amplification of responses to vasoconstrictors (49). Inhibition of 11α-HSD2 in vascular smooth muscle cells resulted in increased responses to angiotensin-II (50) and phenylephrine (51). 11α-

HSD2 knockout mice demonstrate increased arterial reactivity to norepinephrine and decreased endothelium-derived nitric oxide synthase activity (52).

ACQUIRED DEFICIENCY OF 11α-HSD2

Licorice

Licorice roots and their extract have been used for over one thousand years as a medical herb product and as sweeteners and mouth fresheners (53). The active ingredient of licorice is glycyrrhizic acid, which is hydrolyzed into its aglicone glycyrrhetinic acid *in vivo*. Licorice products are made from peeled and unpeeled dried root. There are powdered and finely cut root preparations; the most important are the liquid and the dry extracts. These formulations have different concentrations of the active ingredient, glycyrrhizic acid, and can vary from 20% to trace amount, based on the extraction process. In addition, a number of commercial preparations containing licorice are available such as herboristic and cosmetic; moreover some preparations are used as a cough remedy and are usually mixed with Arabic gum, sugar, alcohol and tobacco. A preparation of the root of the licorice plant was successfully used to treat patients with peptic ulceration. Such observations were the basis for the development of the effective anti-ulcer drug, carbenoxolone, which is a hemisuccinate derivative of 18α-glycyrrhetinic acid. Licorice possesses some endocrinological effects such as glucocorticoid activity, antiandrogen effect, and estrogenic activity. Whorwood (54) described an inhibitory effect of licorice on prolactin gene expression *in vivo*. Its mineralocorticoid effect was first documented in the 1940's. Patients consuming excessive quantities of licorice present with hypertension and hypokalemia, which may be severe enough to cause myopathy and cardiac arrhythmia. Both PRA and aldosterone levels are suppressed and exchangeable sodium levels are increased. The condition responds to spironolactone and is reversible upon stopping licorice ingestion (55). Glycyrrhizic and glycyrrhetinic acids have a very low affinity for the MR, but are very potent competitive inhibitors of 11α-HSD2 (Ki of approx. 5-10nM) (56). Licorice administration to normal volunteers results in a mineralocorticoid excess state, an increase in the urinary THF+allo-THF/THE ratio, an increase in plasma cortisol half-life, and a decrease in circulating cortisone values, indicative of inhibition of 11α-HSD2 *in vivo*. Thus it is now established that licorice induces an acquired and milder form of AME, causing its mineralocorticoid effects through inhibition of 11α-HSD2.

Flavonoids Consumption

The flavonoids naringin and its aglycone naringenin present in some kind of fruits, such as grapefruit, seem to have an inhibitory effect on 11α-HSD2 similar to licorice. In sensitive individuals, 250mg/day of grapefruit juice for 7 days causes significant inhibition of the enzyme causing an increase in the UFF/UFE ratio, reduction of PRA and mild hypokalemia (57).

OTHER DISEASES

Ectopic ACTH Syndrome

Eighty per cent of patients with Cushing's syndrome have hypertension, and in the subgroup of patients with ectopic ACTH syndrome this increases to over 95%. The severity of hypertension is a key factor in predicting morbidity and mortality from the disease, yet its pathogenesis has been poorly understood. The ectopic ACTH syndrome is characterized by mineralocorticoid excess, with hypokalemic alkalosis found in 95-100% of cases, in contrast to < 10% in other forms of Cushing's syndrome. Although elevated plasma levels of deoxycorticosterone have been postulated to play a role, it is the level of cortisol secretion, which correlates best with the degree of mineralocorticoid excess.

ACTH has no direct effect on 11α-HSD2, but the enzyme is saturated in ectopic ACTH syndrome by very high concentrations of ACTH-dependent 11α-HSD substrates such as cortisol and corticosterone. Both the urinary ratio of THF+allo-THF/THE and UFF/UFE are elevated, not because of impaired 11α-HSD2 activity, but because of substrate saturation (58) (figure 5B). In severe hypercortisolism all available cortisol cannot be inactivated to cortisone and "spills over" onto the MR to cause mineralocorticoid hypertension (15).

Renal Disease

The human kidney is the principal site of cortisol to cortisone metabolism *in vivo*. Patients with chronic renal failure have a prolonged plasma cortisol half-life (2.9 hours compared to 2.1 hours in controls) (59). The same is true for prednisolone, but not for dexamethasone, no doubt reflecting the observation that cortisol and prednisolone are better substrates than dexamethasone for 11α-HSD2. Plasma cortisone concentrations are reduced in patients with renal disease (60) with an inverse correlation between cortisone values and plasma creatinine. Because of the negative feedback mechanism and concomitant fall in cortisol secretion rate, plasma cortisol concentrations remain

unchanged. Impaired 11α-HSD2 activity in patients with renal disease might underpin the increased sodium retention observed in some pathologies, notably nephrotic syndrome. ACE inhibitors are known to increase renal 11α-HSD2 activity and this, in part, may explain their natriuretic effect (61).

Liver Disease

Activation of MR in patients with liver cirrhosis leads to renal sodium retention and hypokalemia. The same is described during alcoholic and non-alcoholic chronic liver disease or bile duct obstruction where an increase in (THF+allo-THF)/THE ratio is present as a consequence of an inhibitory effect of bile acid on 11α-HSD2 activity (62).

Fetal Growth

Glucocorticoid excess in uterus decreases fetal growth and the high levels of placental 11α-HSD2 may protect the fetus from maternal glucocorticoid excess. Impaired enzymatic activity causing an excess of glucocorticoid in uterus can lead to the poor growth rate seen in many children with AME (63). Impaired placental 11α-HSD2 activity has been associated with intrauterine growth restriction and with programming of hypertension in adult life (64).

Preeclampsia

Sodium retention is a feature in preeclampsia and pregnancy-induced hypertension caused probably by activation of MR. Progesterone and its metabolites can favor this by inhibiting 11α-HSD2 (65). Reduced 11α-HSD2 expression has been reported in placentas of women with preeclampsia and pregnancy induced hypertension (66).

CONCLUSION

11α-HSD is a key enzyme for cortisol metabolism. Its activity in converting F to its inactive metabolite E regulates at "pre-receptor" site the action of glucocorticoid steroids in the body. The isozyme type II is involved in sodium and potassium homeostasis giving specificity to aldosterone for the mineralocorticoid receptor. AME syndrome is caused by total or partial 11α-HSD2 deficiency and is characterized by hypertension, suppressed PRA and aldosterone and hypokalaemia. It represents a spectrum of mineralocorticoid hypertension with severity reflecting the underlying genetic defect in the 11α-HSD2, from very severe and life threatening to mild. Several acquired forms of AME exist. Licorice, carbenoxolone and flavonoids may cause sufficient 11α-HSD2 inhibition to produce metabolic and clinical disorders. Mineralocorticoid excess is also a feature of the ectopic ACTH syndrome, because 11α-HSD2 is overwhelmed by its substrate cortisol. Polymorphic variability in the HSD11B2 gene determines salt sensitivity and might play a role in patients with "essential" hypertension. Impaired 11α-HSD2 activity in patients with renal or hepatic disease or in preeclampsia might be involved in sodium retention in these diseases.

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