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Apparent Mineralocorticoid Excess (AME) diagnosis using Mass Spectrometry analysis:

AME could be the underlying cause of many patients with hypertension, hypokalemia, low renin, low aldosterone

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Apparent mineralocorticoid excess (AME) was first defined in 1977 by New et al. (*New 1977*) in their assessment of a young Zuñi female patient with hypertension, hypokalemia, low renin and low aldosterone. Subsequently, it was demonstrated that AME is caused by impaired activity of 11beta-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which converts biologically active cortisol into inactive cortisone. The 11β-HSD2 enzyme is co-expressed with the Mineralocorticoid Receptor (MR) in renal tubular cells. With the elucidation of the pathophysiology of this disease it was established that the specificity of the Mineralocorticoid Receptor function depends on a metabolic enzyme (11β-HSD2) rather than the receptor itself, a new concept in receptor biology. The Mineralocorticoid Receptor binds aldosterone (A) and cortisol (F) with equal affinity. Plasma F concentrations exceed those of A by 1000 fold. The enzymatic action of 11β-HSD2 guarantees the selectivity of the MR for A by converting F to its inactive metabolite cortisone (E), (E.does not bind to the MR.) See Fig. 1. In the case of impaired 11β-HSD2 activity, F binds inappropriately to the MR, thus acting as potent mineralocorticoid, leading to sodium resorption, potassium excretion, and severe hypertension.

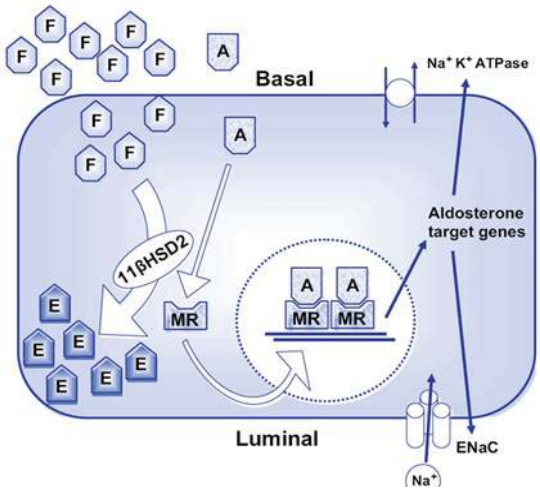

Fig 1- Schematic depiction of aldosterone action in a cell of the renal cortical collecting duct. (Hammer & Stewart 2006, Best Pract Res Clin Endocr Metab 22:337)

Laboratory analysis: Measurement of urinary free cortisol (F), and cortisone (E) by Liquid Chromatography-Tandem Mass Spectrometry (LC-Tandem MS). This methodology has a remarkable accuracy and sensitivity. A spot urine is all what is needed for the diagnosis of AME (for Cushing you must collect a 24hs sample)

Interpretation of results: The deficit of the enzyme 11β-HSD2 generates a significant low or even non detectable level of cortisone. Moreover, the quotients of cortisone to cortisol are better indicators of the disease.

	Free cortisone (E)/Free cortisol (F)
Typical AME	0.01*
Mild AME	0.3*
Controls	2.1-6.3

Table 1 Ratios of urinary cortisone to cortisol in AME patients and healthy controls.
**The values indicated are examples of representative results*

Indications for the analysis of urinary cortisol and cortisone: AME is usually considered a rare disease. About 100 cases were reported in the last 30 years (*Hammer F 2006*). More cases probably exist and are not diagnosed because AME is not always included in the differential diagnosis of low-renin hypertension, what is associated with the difficulty to accurately

measure cortisone metabolites in urine. The principal indication for this analysis is low-renin levels and hypertension. Essential hypertension has been estimated to occur in 15 million residents in the United States, and approximately 40% are associated with low renin.

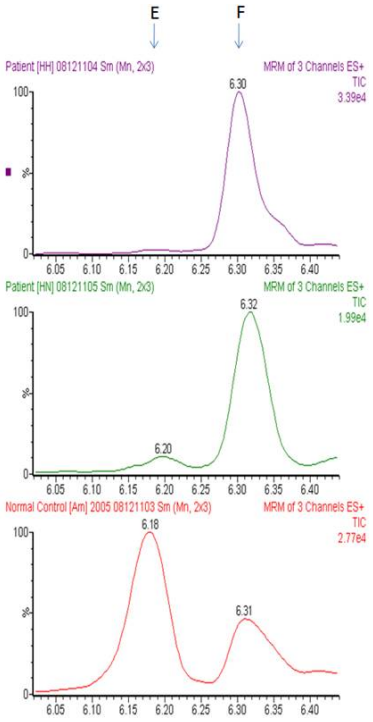

Fig 2- Chromatograms of two AME patients and a normal control performed in our Lab. [A]: severe AME; [B]: milder AME; [C]: normal control. The first peak is free cortisone (E), the second is free cortisol (F). Note that cortisone is almost absent in A and significantly reduced in B.

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