Primary aldosteronism and its variants

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Primary aldosteronism is an adrenal abnormality in which there is an excessive production of aldosterone above that required for electrolyte homeostasis which is not driven by known stimulators of aldosterone secretion, although these may retain some degree of modulatory activity on aldosterone secretion. In the early years following the description of primary aldosteronism, the etiology was ascribed to the autonomous production of aldosterone by an adrenal adenoma for which surgical treatment resulted in the resolution of the hypokalemia and cure or improvement of the hypertension in many cases [1]. At this time the possibility of aldosteronism due to adrenal hyperplasia was not recognized. The traditional clinical picture was characterized by salt-sensitive hypertension associated with hypokalemia and suppression of renin secretion [1]. A major emphasis in the selection of patients for consideration for diagnostic procedures for primary aldosteronism was the presence of spontaneous or easily-induced hypokalemia, resulting in an underestimation of the incidence of primary aldosteronism [2,3]. Once identified, normokalemic primary aldosteronism was found to be common; many patients with primary aldosteronism are normokalemic most of the time [2,4,5]. The widespread commercial availability of methods to easily measure aldosterone and plasma renin activity (PRA) allowed the screening of patients with essential hypertension, irrespective of the serum potassium, and has led to the recognition that primary aldosteronism has higher prevalence than previously recognized [2,6,7]. Various stimulatory and localization maneuvers have led to the recognition that there are several types of primary aldosteronism with variable response to surgery [8–10]. The purpose of this mini review is to succinctly address the issues of prevalence, sub types and pathogenesis of primary aldosteronism so that appropriate therapy may be chosen.

1. Incidence of primary aldosteronism

Curable forms of hypertension have a special appeal for clinicians because of the challenge of the diagnosis and the satisfaction of a resulting cure. A real challenge is to avoid low yield and expensive diagnostic chases. The clinical characteristics of hypertension plus hypokalemic alkalosis occurring spontaneously or induced by the high doses of thiazide diuretics used commonly years ago resulted in the identification of severe forms of primary aldosteronism. The description of primary aldosteronism among patients diagnosed with normokalemic essential hypertension reported by Conn et al. [4] led to the suggestion that the prevalence of the disease was more common than previously recognized. This was met with skepticism and claims that the true prevalence of the disease was rare and much lower than 1%. Primary aldosteronism was estimated to occur at a rate of about 0.01% in the screening of 26,589 hypertensive patients at the Mayo Clinic between 1973–1975 [11], re-establishing the impression that primary aldosteronism was a rare form of secondary hypertension.

The documentation of the prevalence of a disease depends upon the zeal and sophistication of the search for it. The presence of primary aldosteronism has mainly been explored in hypertensive patients with spontaneous hypokalemia or in those whose hypokalemia was easily induced by thiazide or loop diuretics. The advent of new therapeutic agents and the decreased use of diuretics has decreased the incidence or severity of hypokalemia in hypertensive patients. So even though normokalemia was recognized early in the description of the disease, and hypokalemia sometimes cannot be documented to occur during the workup of hypertensive patients with primary aldosteronism despite frequent measurements of serum potassium [2], the diagnosis of primary aldosteronism remains rare.
The prevalence of the disease was found to be 1.5% among 4429 patients consecutively studied by David Streten’s group following a protocol which included a minimal of a dynamic test of stimulation of PRA with furosemide and suppression of plasma aldosterone using a saline infusion [7]. The prevalence increased to 2.7% in patients with diastolic BP greater than 100 mm of Hg. In an earlier study by the same group [12], the prevalence of primary aldosteronism in blacks was found to be 8%. Recently, Gordon [5] has suggested that the true incidence of Primary Aldosteronism in patients with hypertension is closer to 12%. The wide discrepancy is not only due to the reliance on the presence of hypokalemia to screen individuals, but also on the type of hormonal measurements combinations used in the screening procedures.

2. Screening and diagnosis for primary aldosteronism

Single determinations of plasma aldosterone are of limited value because of moment to moment and circadian variations [13]. The initial diagnostic procedures in patients with spontaneous or easily-induced hypokalemia relied on the presence of a suppressed response of PRA to stimulation by either upright posture or sodium depletion plus urinary aldosterone excretion rates (Ualdo) which were not suppressed normally by a high sodium diet [1]. Subsequent studies have demonstrated that a significant number of patients with Primary Aldosteronism had stimulated PRA within the normal range [2] and that Ualdo, the acid-labile metabolite of the 18-oxoglucuronide, is an insensitive parameter since it is a relatively minor metabolite of aldosterone (8–12%) [14]. Ualdo is within the normal range in a significant proportion of patients with primary aldosteronism diagnosed using other criteria [6,12,15], including the measurement of tetrahydroaldosterone, the most abundant aldosterone metabolite in urine (30%) [6,14]. Though the measurement of tetrahydroaldosterone significantly improves the chances of diagnosing patients with the disease, the reagents for the tetrahydroaldosterone RIA are difficult to prepare and are not commercially available.

3. Plasma aldosterone/renin ratio (PA/PRA)

PRA and aldosterone tend to change in opposite directions in primary aldosteronism. In 1981, Hiramatsu et al. [16] proposed the calculation of the ratio plasma aldosterone (ng/dl)/PRA (μg/l/h or ng/ml/h) to improve the sensitivity of single collection of samples. A PA/PRA ratio of > 75 (or 2081 pmol/l/μg/l/h) predicted aldosterone-producing adenomas in 348 hypertensive patients studied and was less affected by diet, drug administration or time of day than other parameters [16]. Most hypertensives had a ratio of less than 20. Patients with a ratio between 20 to 75 were suspected to have bilateral zona glomerulosa hyperplasia, an infrequent diagnosis in Japan, but the authors felt that this was of little practical importance because these patients would be treated medically in any case.

In 1991 Gordon et al. reported the results of using the PA/PRA ratio to screen all prospective patients recruited by a newspaper advertisement for an antihypertensive drug trial [3,5]. Six of the 52 respondent patients had an abnormally high ratio and all 6 were documented as having an aldosterone-producing adenoma upon complete work-up. A subsequent screening using a PA/PRA ratio of 30 as the cut-off in 199 relatively ‘unselected’ normokalemic hypertensives found an incidence of at least 9% primary aldosteronism [3,5]. A ratio above 30 is an indication for more definitive testing to establish the diagnosis. The ratio of PA/PRA is greatly influenced by the level of PRA which is frequently very low and determination of the ratio while the patient is upright enhances the yield of patients with primary aldosteronism. In addition to a low PRA, a level of plasma aldosterone of at least 15 ng/dl is useful in increasing the reliability of the test. The administration of Captopril, a converting enzyme inhibitor, prior to sampling has been proposed as a refinement of the PA/PRA ratio test [17]. A ratio of 50 was found to clearly distinguish primary aldosteronism from other forms of essential hypertension, however only patients with florid primary aldosteronism were included and the advantages of this test over the simpler PA/PRA ratio seems minimal. In summary, the determination of the PA/PRA ratio is an easy and excellent screening procedure for searching for patients with primary aldosteronism. Pretreatment with Captopril does not appear to make the test any more reliable.

4. Dynamic tests for primary aldosteronism

These tests are designed to demonstrate autonomy of aldosterone secretion. The most frequently reported has been the Saline Infusion Test. With autonomous aldosterone production, patients retain salt, then reach a state of homeostasis at the higher sodium level due to renal escape from the effects of excess aldosterone. Plasma aldosterone is not decreased appropriately by sodium loading in primary aldosteronism [6,12,15].

In the most common protocol, plasma aldosterone is measured in the morning after 2 h in the upright posture and 4 h after being supine and receiving 2 l of 0.9% sodium chloride solution. Values for plasma aldosterone above 5 ng/dl to 10 ng/dl (138 to 276 pmol/l) [6,15] have been considered abnormal. In a comprehensive study of 1036 patients in which saline infusion was done in 820, the failure to suppress plasma aldosterone below 8.5 ng/dl (235 pmol/l) was indicative of primary aldosteronism, the diagnosis of which was confirmed using the DOC suppression test [12]. When patients with low PRA and plasma...
Aldosterone values between 5 and 10 ng/dl upon suppression by saline infusion were enrolled in a Florinef-suppression protocol using 1 mg/day for 3 days, 47% were found to have an abnormal aldosterone suppression (> 5 ng/dl or 138 pmol/l) [6]. This dose of Florinef corresponds to an approximate equivalent secretion rate of aldosterone of 10 times normal. Most of these patients had bilateral zona glomerulosa hyperplasia [6]. Other authors have used a dose of 0.4 mg/day with similar suppressive results [5]. Failure to suppress plasma or urinary aldosterone by chronic volume expansion induced with DOC or Florinef plus a high sodium diet is probably the most sensitive way of diagnosing primary aldosteronism [5, 6, 12].

5. Sequelae of primary aldosteronism

In our current era of cost containment, it remains practical and important to screen patients with primary aldosteronism since these patients, in addition to suffering the risk factors associated with hypertension per se, are at increased risk for aldosterone-induced myocardial hypertrophy and cardiovascular disease [18]. A significant correlation between left ventricular mass and aldosterone levels has been reported in essential hypertensive patients [18]. Aldosterone induced cardiac hypertrophy and fibrosis has been clearly dissociated from high blood pressure in experimental animals [19]. Lowering the BP with antihypertensives that do not block the direct effects of aldosterone on the heart has no effect on myocardial hypertrophy in animal models [19]. By extension, controlling the blood pressure without reducing aldosterone levels and protecting the heart from direct effects of aldosterone excess may have no beneficial effect on the cardiovascular complications of primary aldosteronism, although this concept remains to be confirmed.

6. Recommended approach to diagnosis and therapy

At this time the consensus is that hypertensive patients should be screened for primary aldosteronism by measuring the PA/PRA ratio in the upright posture. It is preferable, but not absolutely mandatory, that antihypertensive medication be withdrawn as spironolactone, beta blockers, and some calcium channel blockers might interfere with the test (3215). A ratio above 30 supports the tentative diagnosis of primary aldosteronism and the test is repeated. For those with obvious clinical characteristics, a marked increase in ratio (> 70), or moderate elevation of two consecutive PA/PRA, and a plasma aldosterone above 15 ng/dl (414 pmol/l), the next step is to determine the etiology of primary aldosteronism. Patients with severe metabolic and hormonal abnormalities are likely to have aldosterone-producing adenomas. In those with intermediate PA/PRA ratios (30–70) and less severe signs, a saline infusion or a Florinef-suppression test should follow. The 3-day Florinef (0.4 mg/day) suppression test is clearly more sensitive and preferable, and can be done as outpatient, but it is necessary to administer oral potassium supplements to minimize hypokalemia [3, 6].

7. Types and sub types of primary aldosteronism

Surgical removal of aldosterone-producing adenomas results in the cure or significant improvement of the hypertension and hypokalemia [1, 10]. The correct identification of bilateral zona glomerulosa hyperplasia became very important when it was shown that surgical treatment with bilateral adrenalectomy, while resolving the hypokalemic alkalosis of primary aldosteronism, frequently did not result in a significant improvement of the hypertension [10] and created a problem of chronic adrenal insufficiency.

Primary aldosteronism has been classified on the basis of anatomical characteristics and physiological responses as shown in Table 1. Anatomically primary aldosteronism can be divided into neoplastic (adenomas, carcinomas and ectopic) and non-tumorous (unilateral or bilateral zona glomerulosa hyperplasia and glucocorticoid-suppressible aldosteronism). Physiologically they can be divided into angiotensin (or renin) responsive and angiotensin non-responsive, independent of the anatomical lesion. The incidence of the various types is difficult to ascertain since they depend on the sensitivity of the diagnostic procedures used, particularly since zona glomerulosa hyperplasia tends to be associated with a milder clinical syndrome and is almost certainly under-diagnosed [6]. One of the most extensive and carefully conducted series of studies, done over the professional life of Dr. Edward Biglieri, provides a rough idea of the relative prevalence of the various types of primary aldosteronism [8]. State-of-the-art techniques for the time, now known to be relatively insensitive in the diagnosis primary aldosteronism, caused the underestimation of the prevalence of milder syndromes, but his studies

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<th>Table 1 Classification of primary aldosteronism</th>
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<td>Type</td>
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<tr>
<td>Aldosterone-producing adenomas</td>
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<tr>
<td>Classic or angiotensin II unresponsive</td>
</tr>
<tr>
<td>Angiotensin II or renin-responsive</td>
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<tr>
<td>Zona Glomerulosa Hyperplasia</td>
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<td>Bilateral</td>
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<td>Primary adrenal hyperplasia</td>
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<td>Aldosterone-producing adrenal carcinoma</td>
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<td>Aldosterone-producing extra-adenal tumors</td>
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<td>Glucocorticoid-suppressible aldosteronism</td>
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are still a very valuable source of information and many of the following generalizations have stood the test of time and newer techniques.

The response of the adrenal to stimulation by angiotensin II is a useful tool to differentiate aldosterone-producing adenomas and bilateral zona glomerulosa hyperplasia in the majority of patients. The most common aldosterone-producing adenoma is unresponsive to angiotensin II and is sensitive to changes in ACTH, although long term dexamethasone suppression of ACTH does not correct the hypersecretion of aldosterone. Bilateral zona glomerulosa hyperplasia is usually very sensitive to angiotensin II, even when PRA levels in blood are very low [20]. Determination of plasma aldosterone at 8 am and at noon after 4 h in the upright posture helps differentiate between the two forms. In patients with aldosterone-producing adenomas plasma aldosterone at 12 noon is lower than the 8 am in parallel with circadian changes in ACTH. In patients with bilateral zona glomerulosa hyperplasia, the 12 noon plasma aldosterone is higher than the 8 am sample reflecting the stimulatory effects of upright posture on the PRA and the heightened sensitivity of the adrenal to minor changes in angiotensin II. Cortisol is measured simultaneously to detect the possibility of ACTH release by stress mediating changes in plasma aldosterone and spuriously changing the characteristics of the response to the upright posture. The reliability of this maneuver between series has varied between 35 and 85%. Unfortunately, this maneuver has to be done in hospitalized patients which in the current era of cost-containment is difficult to perform.

The finding that some less common patients with aldosterone-producing adenomas behaved like patients with bilateral zona glomerulosa hyperplasia on the postural response led to the identification of angiotensin II-(or renin-) responsive aldosterone-producing adenomas [8,9]. Equally rare are patients with bilateral zona glomerulosa hyperplasia which, like classical aldosterone-producing adenomas, are angiotensin II insensitive. Some of these patients with what has been called Primary Adrenal Hyperplasia, respond well to surgical reduction of adrenal mass [8].

A rare, but increasingly common, form of aldosteronism is Glucocorticoid-suppressible or remediable. In these patients aldosterone is synthesized by a chimeric enzyme created by the expression of a crossover uneven gene recombination between the CYP11B1 and CYP11B2 genes. This enzyme is composed of the promoter region and first 2–4 exons of the 11β-hydroxylase and the last 5–7 exons of the aldosterone synthase genes resulting in the ACTH-regulated expression of the enzyme in the zona fasciculata which can synthesize aldosterone [21]. Dexamethasone administration for a few days results in a consistent normalization of the plasma aldosterone. The incidence of Glucocorticoid-suppressible aldosteronism has been claimed to be as high as 3% of patients with primary aldosteronism and most of the patients are normokalemic [21].

8. 18-Hydroxycorticosterone levels

Plasma concentrations of 18-hydroxycorticosterone are useful in the differentiation between the angiotensin II-responsive and -unresponsive forms of aldosterone-producing adenomas and bilateral zona glomerulosa hyperplasia. Plasma levels of 18-hydroxycorticosterone in patients with non-responsive forms of aldosterone-producing adenomas are usually greater than 50 ng/dl and most are greater than 100 ng/dl. In bilateral zona glomerulosa hyperplasia 18-hydroxycorticosterone levels are less than 100 ng/dl and most are below 50 ng/dl [3,8]. 18-Hydroxycorticosterone is in the pathway of transformation of deoxycorticosterone to aldosterone by the cytochrome P450 aldosterone synthase. The excessive plasma concentration of 18-hydroxy-corticosterone in patients with aldosterone-producing adenomas in comparison to patients with bilateral zona glomerulosa hyperplasia with comparable plasma aldosterone levels seem to be due to the co-expression of the cytochromes P450 aldosterone synthase and 11β-hydroxylase in adrenal tumors [22]. In the normal adrenal, the 11β-hydroxylase is not expressed in the zona glomerulosa with the aldosterone synthase [23]. 11β-Hydroxylase in the tumors produces corticosterone which, when acted upon by aldosterone synthase, generates a higher proportion of 18-hydroxycorticosterone than aldosterone compared to when the normal substrate, deoxycorticosterone, is used [24]. This altered ratio of products (18-hydroxycorticosterone/aldosterone) has been shown to occur experimentally. The incubation of MA-10 cells transfected with the cDNA for the rat [24] and human aldosterone synthase (unpublished) with corticosterone results in a significantly higher ratio of 18-hydroxycorticosterone to aldosterone than do incubations with deoxycorticosterone.

9. 18-Hydroxycortisol and 18-oxocortisol

The excretion of the hybrid steroids 18-hydroxycortisol and 18-oxocortisol has been found to be elevated in patients with aldosterone-producing adenomas which are unresponsive to angiotensin II, as well as those with glucocorticoid-suppressible aldosteronism, but not in patients with angiotensin-responsive bilateral zona glomerulosa hyperplasia [9]. The chimeric enzyme expressed in the zona fasciculata in patients with glucocorticoid-suppressible aldosteronism is exposed to the substrate 11-deoxycorticisol generating excessive quantities of 18-hydroxy and 18-oxocortisol. The increased production of both of these steroids in patients with aldosterone-producing adenomas is not due to the presence of a chimeric enzyme [25], but to the coexpression in the tumor of the aldosterone synthase and 17α-hydroxylase enzymes. Both the angiotensin-unresponsive and -responsive aldosterone-producing adenomas synthesize cortisol in similar amounts [26], but only the angiotensin unresponsive tumors produce excess 18-hy-
10. Pathology and imaging of the adrenals in primary aldosteronism

The determination of the presence of a tumor and its differentiation from bilateral zona glomerulosa hyperplasia more often is done by a combination of the hormonal tests described above and imaging procedures. The most frequently used methods for determining the presence of an adrenal tumor in primary aldosteronism is by CT scan or MRI, which are of similar reliability, and can both detect the presence of a mass greater than 8 mm in the adrenal. Nuclear scanning with 6\(^b\)\(^{123}\)iodomethyl-19-norcholesterol in dexamethasone suppressed individuals is helpful when bilateral zona glomerulosa hyperplasia is suspected and CT scans do not detect an adenoma. The finding of a unilateral mass most often means the presence of an adrenal adenoma. In the current era of cost-containment the demonstration of a clearly abnormal PA/PRA ratio in a hypertensive and hypokalemic patient associated with an adrenal mass by CT or MRI will result in the diagnosis of an aldosterone-producing adenoma and will be removed surgically. This combination of findings leads to the correct management most often than not.

There are several situations where the finding of an adrenal mass by an imaging procedure requires further evaluation. Patients with an adrenal adenoma by imaging in whom the postural response suggests sensitivity to angiotensin II along with normal levels of 18-hydroxycorticoesterone need to be differentiated from patients with bilateral zona glomerulosa hyperplasia with a nonfunctional mass or with unilateral macronodular hyperplasia and contralateral micronodular hyperplasia. The differentiation can be difficult to establish, even by histological examination of the specimen, since many adenomas have coincidental nonfunctional zona glomerulosa hyperplasia including micronodules [27]. The contralateral adrenal by CT scanning might be of normal size but functionally hyperplastic and hyperactive resulting in the persistence of primary aldosteronism. Diagnosis is also problematical in patients with primary adrenal hyperplasia in which the hormonal responses suggest an angiotensin-unresponsive (classic) adenoma despite a negative imaging procedure. A small adenoma that cannot be seen by the imaging procedure is most often the etiology in these cases, but on rare occasions primary adrenal hyperplasia is the cause. A discrepancy by the hormonal studies and the imaging procedure are best resolved by adrenal vein catheterization. Once the diagnosis of primary aldosteronism is made and a CT scan indicates an adrenal mass, surgery is an attractive alternative to further diagnostics, particularly since this decision is going to be correct far more often than not.

The gold standard for establishing if aldosterone is secreted unilaterally from a tumor (or the rare unilateral hyperplasia), or bilaterally by zona glomerulosa hyperplasia, is the measurement of the secretion of aldosterone from both adrenals from samples obtained by adrenal vein catheterizations. This procedure is important when bilateral nodules are encountered by CT scanning. The elderly population have a high incidence of nonfunctional incidentalomas of the adrenal gland which complicates the establishment of the proper diagnosis. Catheterization of the left adrenal vein is most often successful, but the right adrenal vein, being problematic and frequently unsuccessful, requires great experience and skill. Administration of ACTH before the samples are obtained helps minimize the problem of intermittent secretion of aldosterone and the difference in sampling time. Concomitant measurements of aldosterone and cortisol in the effluents of presumed adrenal veins is also very important. Levels of cortisol, which are clearly above the nearly simultaneously obtained samples from the inferior vena cava, confirms that the catheter was in the adrenal vein. The ratio of aldosterone to cortisol is also valuable, particularly in cases where the catheter is near the exit of the adrenal vein and there is significant admixture with inferior vena cava blood.

Bilateral nodules in primary aldosteronism might not represent macronodular hyperplasia but be true bilateral adenomas. Bilateral adrenal adenomas are considered very rare and difficult to differentiate histologically from macronodular hyperplasia. The diagnostic dilemma, after finding bilateral adenomas by imaging, is whether these patients have bilateral zona glomerulosa hyperplasia with nodules but which are not angiotensin II-responsive and behave like classic adenomas (primary adrenal hyperplasia), a unilateral adrenal adenoma with a contra lateral nonfunctional incidentaloma, or bilateral adrenal adenomas. Adrenal vein catheterization will only satisfactorily identify the presence of the unilateral aldosterone-producing adenoma with the contralateral nonfunctional incidentaloma. Therapeutically these patients would be treated medically rather than by surgery. It has been recently reported that immunohistochemistry for the cytochrome P450 11\(^\beta\)-hydroxylase in the removed adrenal can distinguish between the two types. In the case of adrenal adenomas, the 11\(^\beta\)-hydroxylase is expressed only in the adenoma and not in the hyperplastic zona glomerulosa while in the case of macronodular hyperplasia, the 11\(^\beta\)-hydroxylase (aldosterone synthase most likely since the antibody used could not distinguish with the 11\(^\beta\)-hydroxylase) is expressed in both the hyperplastic zona glomerulosa and the macronodules [27].

11. Pathogenesis

There are few studies of the pathogenesis of primary aldosteronism due to bilateral adrenal hyperplasia. By analogy with adrenal zona fasciculata hyperplasia causing
Cushing disease, a great deal of effort has been devoted to the search for a factor(s) responsible for stimulation and hyperplasia of the zona glomerulosa. None of the known stimulators of aldosterone secretion is responsible. In the late 1970’s an aldosterone stimulating factor (ASF) was isolated from human urine and shown to be abnormally excreted in the urine of patients with aldosteronism due to zona glomerulosa hyperplasia [28]. An abstract claimed that ASF was a fragment of chymotrypsinogen [29], but no recent studies have followed this lead. The only new potential candidate is the recently detected aldosterone stimulating factor secreted by endothelial cells, but the structure remains unknown [30].

It is likely that the pathogenic mechanisms leading to bilateral zona glomerulosa hyperplasia will be elucidated once the molecular genetics of recent familial forms of bilateral zona glomerulosa hyperplasia will be elucidated. The potential candidate is the recently detected aldosterone stimulating factor secreted by endothelial cells, but the structure remains unknown [30].

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