INVITED COMMENTARY

Would wider screening for primary aldosteronism give any health benefits?

Pierre-François Plouin¹ and Xavier Jeunemaitre²¹Hypertension Unit and ²Department of Genetics, Hôpital Européen Georges Pompidou, Paris, France

(Correspondence should be addressed to P F Plouin; Email: pierre-francois.plouin@egp.ap-hop-paris.fr)

Abstract

Fifty years ago, Jerome Conn described 'a new clinical syndrome which is designated temporarily as primary aldosteronism' in a young patient with hypertension, severe hypokalaemia and a benign adrenocortical tumour, for whom an adrenalectomy cured both the hypertension and hypokalaemia. His report identified the condition known as aldosterone-producing adenoma, a form of curable hypertension. According to Conn, the prevalence of primary aldosteronism in the hypertensive population referred to his department was 20%, but this estimate was subject to referral bias. Primary aldosteronism has long been considered rare, with an estimated prevalence of 0.5–2% among unselected hypertensive patients. During the past 10 years, however, the apparent prevalence of the condition increased dramatically, up to 30% in some series. Overall, the prevalence of primary aldosteronism in series dealing with at least 100 screened hypertensive patients averaged 6%, with one patient in two harbouring an aldosterone-producing adenoma. This increase in prevalence reflects the fact that hypokalaemic and normokalaemic patients are now screened for primary aldosteronism, with the aldosterone to renin ratio used as a screening tool. The current 'epidemic' of primary aldosteronism raises several questions and concerns.

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What is primary aldosteronism?

Primary aldosteronism is the most common cause of mineralocorticoid hypertension, a condition comprising hypertension, hypokalaemia and suppressed renin concentrations (1). In primary aldosteronism, the mineralocorticoid is aldosterone and diagnosis relies on the patient displaying the following combination of signs: high blood pressure, which is present in virtually all patients; spontaneous or diuretic-induced hypokalaemia, which is absent in many patients (1–4); high concentrations of aldosterone in the plasma or urine; low concentrations of renin. The hallmark of primary aldosteronism is the dissociation between aldosterone and renin concentrations (2), which gives a high aldosterone to renin ratio (ARR; high aldosterone and low renin concentrations). Although logical and convenient, this test has several drawbacks. First, the ARR relies on the concentration of renin present and thus, although aldosterone concentrations may be within the normal range, the value determined may be abnormally high in patients in whom the renin concentration is low. In extreme cases in which renin is undetectable, for example in some elderly patients or some patients with a high sodium intake or those taking β -blockers, the ARR is infinity. Secondly,

in normal individuals and in patients with an aldosterone-producing adenoma (APA), aldosterone is secreted in bursts; therefore the plasma aldosterone concentration and ARR can change within minutes, making the results from a single ARR test unreliable. Thus several ARR readings are required and the diagnosis should depend on the presence of a combination of high ARR values plus an increased excretion of aldosterone. Thirdly, renin concentrations can be determined as plasma renin activity or active renin concentration, and aldosterone can be determined using iodinated or tritiated markers, with or without using an extraction step; consequently, reference values and diagnostic thresholds for renin, aldosterone and the ARR should be determined within each laboratory. Finally, the ARR is not reliable in patients who are being treated with a variety of antihypertensive agents, including diuretics, β -blockers and inhibitors of the renin–angiotensin system, or in patients with renal insufficiency. These drawbacks have been highlighted in a review by Montori & Young (5), who reported that ARR cut-off values for diagnosing primary aldosteronism ranged from 200 to 2774 pmol/l per ng/ml per h – that is, a variation of 14-fold. Similarly, Seiler *et al.* (6) reported, in a recent issue of this journal, that various indexes derived from

renin and aldosterone determinations yielded sensitivities of 0.53–0.94 for the diagnosis of primary aldosteronism, leading to twofold variations in prevalence estimates for the same population.

Basing the diagnosis of primary aldosteronism on ARR determinations implies that primary aldosteronism is a quantitative trait like hypertension or hypercholesterolaemia, and not a qualitative disease like malaria or pheochromocytoma. This is confirmed by clinical and pathological studies. There have been many attempts to discriminate between inappropriate aldosterone secretion, detected by a high ARR, and autonomous aldosterone secretion, in which suppression tests, using exogenous mineralocorticoids or intravenously or orally administered salt, failed to decrease aldosterone concentrations to the normal range (3, 4). Unfortunately, there exists neither a bimodal distribution of post-test aldosterone concentrations that discriminates between low renin hypertension and primary aldosteronism nor a bimodal distribution that discriminates between idiopathic aldosteronism and APA among patients with primary aldosteronism. There is overlap in the post-suppression aldosterone concentrations of patients with low renin hypertension, idiopathic aldosteronism or APA (7). There is also evidence that some patients with APA are responsive to angiotensin II (1) and that the resection of angiotensin-responsive APA may cure primary aldosteronism, hypokalaemia and, most importantly, hypertension (8). In fact, there is no consensus as to whether suppression tests should be included in the definition of primary aldosteronism, and no gold standard for defining the condition (1, 3–5). The pathological characteristics defining primary aldosteronism are also unclear. Adrenals may be nodular in individuals without primary aldosteronism, and the index of nodularity increases with age and blood pressure (3). Patients with primary aldosteronism may have APA, idiopathic hyperaldosteronism or, in rare cases, unilateral primary adrenal hyperplasia or an aldosterone-producing adrenal carcinoma. In patients with apparent solitary adenomas, pathological studies of the removed adrenal frequently show hyperplasia of the adjacent zona glomerulosa or the presence of several smaller nodules throughout the gland (3, 4, 7). Inherited familial hyperaldosteronism, in which patients bearing the same mutation (9) or mutations linked to the same locus (10) may display different clinical, biological or computed tomography (CT) scan characteristics, provides an example of the variety of pathological presentations possible.

What hope is there for patients with primary aldosteronism and for physicians?

Primary aldosteronism is a potentially curable, or at least specifically treatable, form of hypertension.

In patients in whom aldosterone hypersecretion is unilateral, hypertension may be cured by unilateral adrenalectomy. Unilateral aldosterone secretion can be detected by adrenal vein sampling, but this test is frequently omitted in patients in whom primary aldosteronism is evident and CT scans reveal a unilateral adrenocortical mass that is presumed to be an APA. It must be kept in mind, however, that the presence of a unilateral tumour is not synonymous with unilateral aldosterone secretion. The aim of surgery is to suppress aldosterone hypersecretion, not to resect an adenoma that may be present with or without primary aldosteronism. Only three preoperative characteristics of patients have been conclusively linked to the blood pressure outcome of surgery: patient age (the older the patient, the less good the blood pressure response to adrenalectomy), unilateral aldosterone secretion detected at adrenal venous sampling, and the preoperative blood pressure response to large doses of spironolactone (4). In patients who are not candidates for surgery, aldosterone receptor antagonists – spironolactone and, more recently, eplerenone – in theory offer a specific treatment for primary aldosteronism. Unfortunately, many patients with primary aldosteronism have idiopathic adrenal hyperplasia and show little blood pressure response to monotherapy with spironolactone. In addition, that drug is poorly tolerated in the long term, and there is no evidence that high doses of eplerenone are more effective and better tolerated in patients with primary aldosteronism.

Will there be any health benefits from wider screening for primary aldosteronism?

This is both the last of our questions and the main concern.

The ultimate outcome for patients and physicians is the control of blood pressure. Although rare cases of APA without hypertension exist, hypertensive patients are usually tested for primary aldosteronism, with the aim of proposing surgical treatment for hypertension in those in whom an APA is demonstrated. Hypokalaemia is generally treated successfully with potassium supplements at the time of the diagnostic work-up, or with amiloride or spironolactone in patients who are not going to undergo surgery. As the treatment of hypertension requires lifelong medication, correction of primary aldosteronism that is associated with persistent hypertension has only academic relevance. In an earlier issue of *European Journal of Endocrinology*, Enberg and colleagues describe their analysis of the postoperative outcome of 27 patients who underwent adrenalectomy for primary aldosteronism, taking in account the expression of steroidogenic enzymes in resected adrenals (11). This expression was analysed by

in situ hybridisation, a technique that allows the location of gene expression to be visualised but does not allow accurate quantification. Higher levels of *CYP11B2* gene expression would be expected in patients with an APA (12). Also, it would be expected that this alteration in expression be related to the production of aldosterone. In the series studied, the expression of steroidogenic enzymes was closely associated with the cure of primary aldosteronism, but not with the cure of hypertension. In the light of the current epidemic of primary aldosteronism (3), the results reported by Dr Enberg also raise the question of the ultimate objective of screening for the condition: the correct identification of patients who will benefit from adrenal surgery.

Overall, only one in two of patients operated on show a clear improvement or are cured of hypertension (reviewed in (4)), the others still requiring antihypertensive medication. This disappointing outcome has several explanations. First, aldosterone hypersecretion may be bilateral rather than unilateral, even in patients in whom the adenoma appears typical on the CT scan. Secondly, the blood pressure phenotype associated with primary aldosteronism may vary in a manner dependent on the polymorphisms of the steroidogenic enzymes, particularly aldosterone synthase (7). Finally, the most frequent explanation for the failure to normalize blood pressure is non-specific and relates to the poor reversibility of cardiovascular remodelling with age, long-standing hypertension, or both. In older patients or those with long-standing hypertension, aetiological intervention has only a limited effect on secondary hypertension (hypertension linked to any 'curable cause' – occurring in APA and in renal artery stenosis or pheochromocytoma). This was the most likely explanation for the failure of surgery to control blood pressure in the series of patients reported by Enberg and colleagues, as 11 of their 23 patients who were cured of primary aldosteronism still needed antihypertensive medication at follow-up (11).

The potential benefits of surgery must be weighed against the financial costs of screening for primary aldosteronism, of the tests for discriminating between APA and the other variants of the condition, and of the direct costs of admission to hospital, surgery and any complications (3). Patients who may benefit from surgery – relatively young individuals with resistant hypertension or symptomatic hypokalaemia – need to be screened for primary aldosteronism. In addition, robust, reproducible and redundant diagnostic tests need to be used and adrenal venous sampling needs to be performed to document unilateral aldosterone hypersecretion in most – if not all – candidates for surgery. It is hoped that preoperative molecular tests will make it possible to differentiate between those individuals who may benefit from surgery and those who may not. With this in mind, the C344T polymorphism of the *CYP11B2* gene, interesting because of its

potential *in vitro* and *in vivo* functionality, has been analysed in search of an association with primary aldosteronism, hypertension and a variety of cardiovascular diseases (7). However, even in the case of such an attractive polymorphism, most results, including our own (unpublished), indicate that it will not be usable as molecular marker for screening tests for primary aldosteronism.

Additional studies of large cooperative cohorts are needed, to test the hypothesis that steroidogenic enzyme polymorphisms have a prognostic value in primary aldosteronism. In addition, microarray technology could be used to analyse tissue-specific gene expression, and comparative genomic hybridisation should assist in the identification of genes and molecular pathways specific to adrenocortical tumorigenesis (13).

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