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Lab bulletin

Clarification of hypertension – Diagnosis of primary hyperaldosteronism

The significance of the aldosterone/renin ratio (ARR) in the diagnosis of normo-alaemic and hypokalaemic primary hyper-aldosteronism, the most common causes of secondary hypertension

Epidemiology of primary hyperaldosteronism

Primary hyperaldosteronism (PH) is the most common cause of secondary hypertension. Apart from hypertension, hypokalaemia was hitherto considered to be the classical cardinal symptom. Its presence was therefore also usually a prerequisite for further diagnostic clarification in respect of PH.

However, numerous studies in normokalaemic hypertension patients now show that serum potassium levels are within the reference range in approximately 90 % of PH patients.

On the basis of the new data, which were obtained by determining the aldosterone/renin ratio (ARR), the frequency of PH in hypertensives (5 – 13 %) is much higher than previously suspected (0.1 – 1 %) [1, 2, 3, 19].

On the cautious assumption that PH is the un-derlying cause in 5 % of all hypertensives, over 1 million people in Germany would be affected by this diagnosis.

Aldosterone-producing adenoma as a cause of hypertension can in principle be cured by surgery.

Aetiology of primary hyperaldosteronism

- Aldosterone-producing adenoma (APA = Conn's syndrome)
  - approx. 30–40 %
  - unilateral
- Idiopathic hyperaldosteronism (IH)
  - approx. 60 %
  - bilateral
- Macronodular adrenocortical hyperplasia (MNH)
  - 1–5 %
  - uni- or bilateral
- Aldosterone-producing carcinoma (adrenal or ectopic, e.g. ovarian)
  - 1 %
- Familial hyperaldosteronism *
  - 1–5 %, typ I (= GSH**) and II
- Further genes that can cause a PH
  - ATP1A1 and ATP2B3
  - CACNA1D
  - MEN1

Fig. 1:
Classification of primary hyperaldosteronism (PH) [1, 2, 3].

The stated frequencies refer to the total PH group (normokalaemic and hypokalaemic). If – as before – only the hypokalaemic PH patients are included, APA is the most common cause, at around 70% [4].

* GSH = glucocorticoid-suppressible hyperaldosteronism

Optimized PH screening: the aldosterone/renin ratio (ARR)

Since the diagnosis of PH opens up effective, inexpensive treatment options, extended laboratory screening with additional determination of the aldosterone/renin ratio (ARR), including normokalaemic patients, is now generally accepted [1, 2, 3, 18].

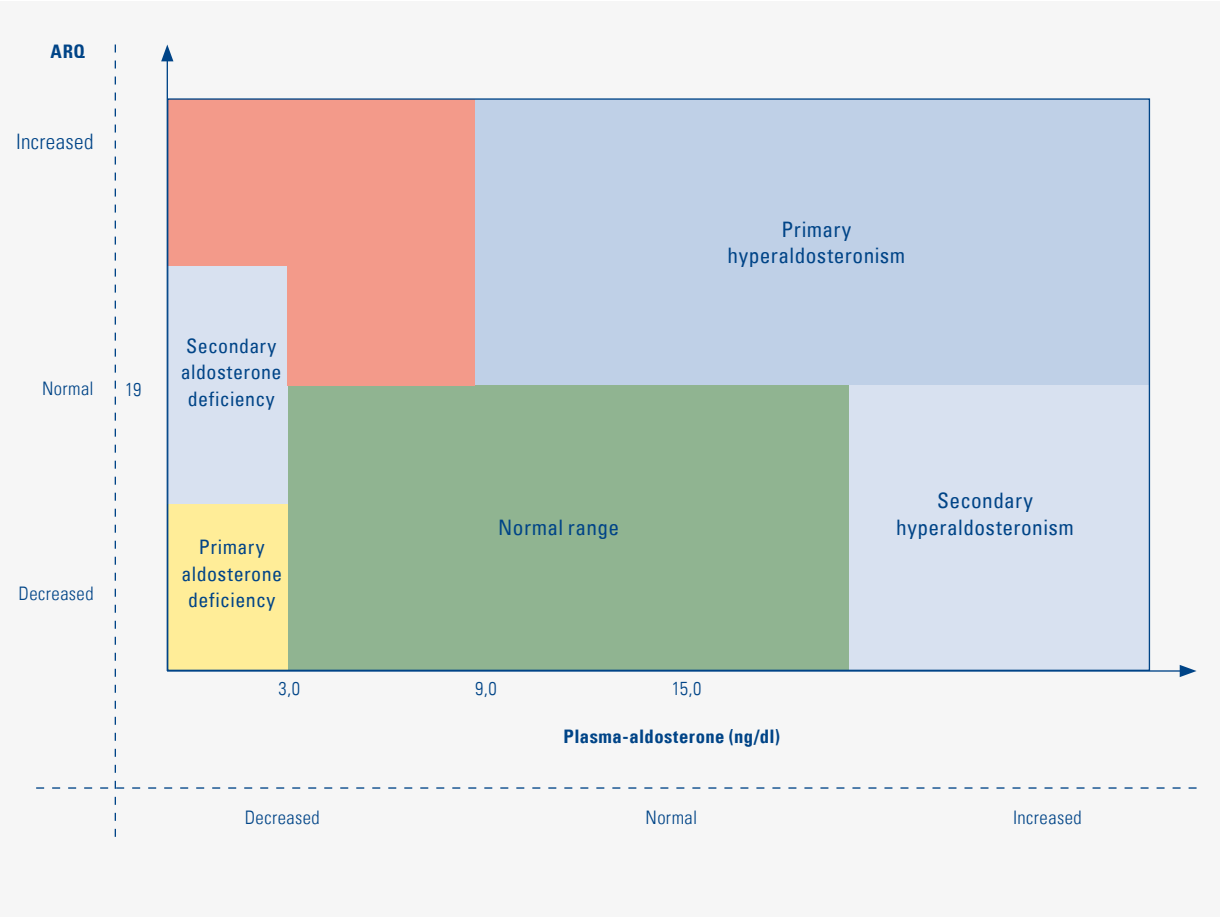

Fig. 1:
Classification of disturbances of the renin-angiotensin-aldosterone system using the aldosterone/renin ratio (ARR) and aldosterone. Marked in are the limits recommended by our laboratory for the identification of patients with PH (ARR: 19; aldosterone 15 ng/dl), according to [1,3]. If the ARR is > 19 and aldosterone is < 15 ng/dl, further clarification in respect of PH may also be indicated and successful, because up to 43% of the patients with PH have a Aldosteronvalue from 9 to 15 ng/dl [1,19].

The following antihypertensives should be discontinued before the aldosterone-renin ratio is determined: [Table 2]:

4 weeks before blood sampling:

- Spironolactone, Epleronone, Amiloride, Triamterene

2 weeks before blood sampling:

- beta-blockers
- AT2-antagonists
- loop diuretics
- Central α-2 receptor-Agonists (Clonidine, α-Methyl-Dopa)
- ACE-inhibitors
- Renin Inhibitors
- Calcium Antagonists (DHP-type)

Alternative medication for treating hypertension during diagnosis is available [Table 3].

Optimized PH screening: target groups

For the following patient groups a PH-Screening with the measurement of the aldosterone/renin ratio (ARR) is recommended [1]:

- sustained blood pressure (BP) above 150/100 mm Hg on each of three measurements obtained on different days
- hypertension (BP > 140/90 mm Hg) resistant to three conventional antihypertensive drugs (including a diuretic)
- controlled BP (< 140/90 mm Hg) on four or more antihypertensive drugs
- hypertension and spontaneous or diuretic-induced hypokalemia
- hypertension and adrenal incidentaloma
- hypertension and sleep apnea
- hypertension and a family history of early onset hypertension or cerebrovascular accident at a young age (< 40 years)
- all hypertensive first-degree relatives of patients with PH

Procedure if a pathological result is obtained in the PH screening

Confirmation of diagnosis

After a positive result in screening, the diagnosis of PH must be confirmed with further testing. The principal confirmatory test recommended, on the basis of its practicability (for outpatients) and evaluation [15], is the salt loading test: 2 litres of isotonic saline is infused into the patient, in a recumbent position, between 8 and 12 o'clock (contraindication: heart failure, state after myocardial infarct; severe, uncontrolled hypertension). At 8 o'clock and 12 o'clock blood is collected for analysis of plasma aldosterone and plasma renin

In patients without autonomous aldosterone secretion, plasma aldosterone is suppressed by at least below 10 ng/ml. In PH, there is no, or no clear, suppression of the elevated baseline aldosterone values. The salt loading test should be performed under the same medication as the screening test [15].
The borderline area is 5 – 10 ng/dl and may require a fludrocortisone suppression test for further clarification.
An aldosterone value of < 5 ng/dl 4 hours after saline burden speaks against primary hyperaldosteronism.

The fludrocortisone suppression test, which has likewise been well evaluated in the literature, is very expensive, because of the need to spend 5 days in hospital. Analysis of aldosterone-18-glucuronide in 24 h urine under oral salt loading should only be carried out as an alternative if the salt loading test is contraindicated/impracticable. Administration of 3 x 2 g NaCl/day in addition to the normal diet (approximately 9 g NaCl/day) for a period of 3 days is recommended for this, to give a daily sodium intake of roughly 260 nmol/day. Since aldosterone-18-glucuronide represents only about 20% of total aldosterone secretion and there are no up-to-date evaluation studies, this test is less conclusive than the salt loading test [15]. On the 3rd day of oral salt loading, aldosterone-18-glucuronide must be in the normal range and urinary sodium in the check on salt supply must be > 200 mmol/ 24 h.

Clarification of the aetiology in cases of confirmed diagnosis

When the diagnosis of PH has been confirmed, the aetiology is further investigated using adrenal vein catheterization and CT of adrenals [see 1, 2, 3].

Selective adrenal venous blood sampling with analysis of aldosterone and cortisol is indicated. Selective adrenal venous blood sampling should always be carried out, however, if surgical treatment is probable [1].

Patients with aldosterone-producing adenoma typically show an aldosterone/ cortisol ratio gradient of more than 2:1 to the adenoma-affected side [1]. Other sources speak of more than 3:1 [1].

If an aldosterone-producing adenoma is present, the treatment of choice is (laparoscopic) adrenalectomy; long-term therapy with spironolactone is an alternative.

For patients with bilateral idiopathic hyperplasia, the only thing left is drug treatment with a mineralocorticoid receptor antagonist (e.g. spironolactone), possibly in combination with ACE inhibitors and beta-blockers [1].

If the hypertension patients who have a PH are initially younger than 20 years or have a cerebral insult under the age of 40 or have a positive family history with a PH in first-degree relatives, a genetic examination on family forms of primary aldosteronism Type 1 (familial hyperaldosteronism type 1 / FH-I syndrome) should be done.

In very young patients (<10 years) with PH, the germline mutation KCNJ5 should be investigated (familial hyperaldosteronism type 3).

In patients with FH type 1, glucocorticoids should be administered to control ACTH.

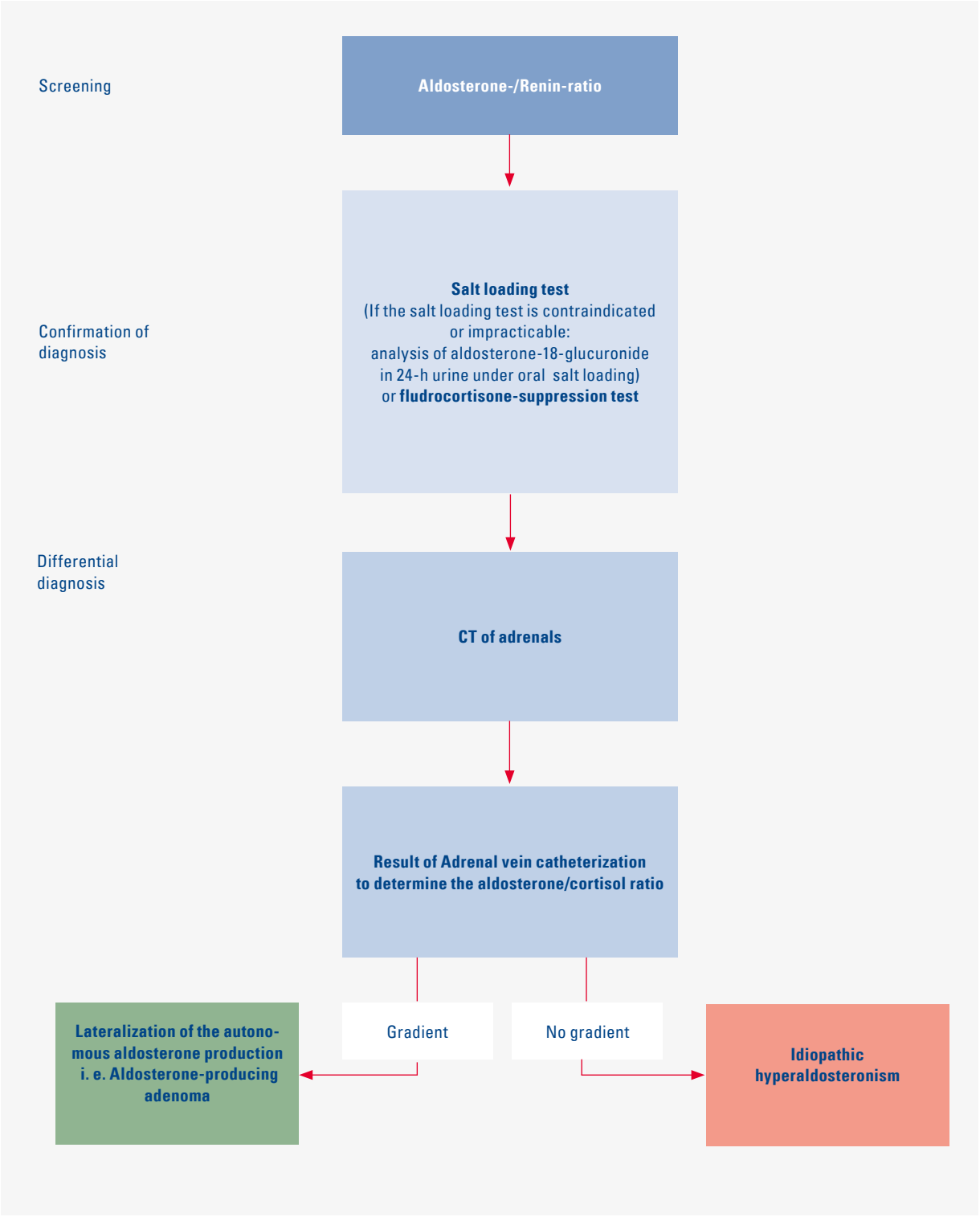

Fig. 2:
Differential diagnosis and clarification of PH [according to 1]
Before surgical treatment, selective adrenal venous blood sampling with determination of the aldosterone/cortisol ratio should always be performed to confirm the diagnosis. The determination of the aldosterone/cortisol ratio first requires the determination of the selectivity index (cortisolgradient adrenal vein to vena cava inferior or peripheral vein) with which the correct catheter position in the AVS will be determined. Only if this has been demonstrated for both AVS the lateralization index can be calculated via the gradient of the aldosterone/cortisol quotients with the lateralization of the aldosterone secretion being detected. However, the selective AVS should always only be carried out if an operative therapy is planned and the patient would be willing to do so.

Medication group	Recommended break
Increase in aldosterone/renin ratio (false-positive results):	
■ Beta rezeptor blockers	At least 2 weeks
■ Imidazoline receptor antagonists (e.g. clonidine, α-Methyl-Dopa)	At least 2 weeks
Decrease in aldosterone/renin ratio (false-negative results):	
■ Loop diuretics	At least 2 weeks
■ ACE inhibitors	At least 2 weeks
■ Calcium antagonists (DHP-type)	-
■ Renin Inhibitors	At least 2 weeks
■ Angiotensin II antagonists (typ 1 receptor) (sartans)	At least 2 weeks
■ Spironolactone, eplerenons, drospirenone, amiloride, triamterene	At least 4 weeks
■ *Also avoid licorice and chewing tobacco 4 weeks before blood collection*	

Table 2:
Effects of antihypertensives on the aldosterone/renin ratio [1, 2, 17]

Drug	Usual dose	Comments
Verapamil slow-release	90–120 mg twice daily	Use singly or in combination with the other agents listed in this table.
Hydralazine	10–12.5 mg twice daily, increasing as required	Commence verapamil slow release first to prevent reflex tachycardia. Commencement at low doses reduces risk of side effects (including headaches, flushing and palpitations).
Prazosin hydrochloride	0,5–1 mg two to three times daily, increasing as required	Monitor for postural hypotension
Doxazosin mesylate	1–2 mg once daily, increasing as required	
Terazosin hydrochloride	1–2 mg once daily, increasing as required	

Table 3:
Medications with minimal effects on plasma aldosterone levels
They can be used to control hypertension during case finding and confirmatory testing for PA

Pre-analysis and sampling for determination of the ARR

- The patient should have been in an erect position (sitting, standing, or walking) for at least 2 h before the blood sampling.
- Blood (EDTA blood) to be collected from the patient in an erect sitting position between 8 and 10 o'clock in the morning after a 15-min phase at rest in a sitting position.
- Since hypokalaemia leads to false-positive results, this must be compensated for beforehand through potassium supplementation [15]. A potassium value of 4 mmol / l should be achieved.
- Creatinine determination, as a restricted renal function can cause a false positive ARR as a result.
- There should be no restriction of sodium in the period before blood sampling
  (sufficient saline = 9 - 15 g per day, corresponds to normal diet).
- Obtain 1 ml EDTA plasma by centrifuging the EDTA blood.
- Transfer the EDTA plasma into a new tube labelled with a bar code with the name of the material ("EDTA plasma") and patient data on.
- Send to Bioscientia FROZEN
- Some antihypertensives should be discontinued for a certain period before blood sampling [see Table 2]. Possible alternative medication, see Table 3.
- If not all medicines potentially influencing the ARR can be discontinued before the blood collection, the blood sampling should nevertheless be carried out and the ARR should be interpreted taking into account possible influencing factors. For example, in patients with severe PH, the mineralocorticoid receptor antagonist (e.g., spironolactone) can not be discontinued because otherwise the patient's health is compromised. In this case, for example, the ARR can still be interpreted as long as the renin is suppressed.
- Request on the request form as: "Aldosterone/ Renin/ratio".

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