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MANAGEMENT OF PRIMARY HYPERADOSTERONISM : DON'T WAIT UNTIL IT'S TOO LATE

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ABSTRACT **Introduction:** Arterial hypertension by primary hyperaldosteronism is the most frequent cause of endocrine hypertension. It is responsible for 10% of endocrine arterial hypertension. In our context, there is a delay in the diagnosis of primary hyperaldosteronism because it is under traked and also because of the high cost of check-ups. The aim of our study is to highlight the challenges in the management of these patients. **Material And Method:** This observational study includes patients admitted at the department of endocrinology of Sheikh Khalifa Ibn Zayd universitary hospital for primary aldosteronism between January 2019 and January 2021. Primary hyperaldosteronism was defined according to the Consensus on Primary Hyperaldosteronism of The French Society of Endocrinology (SFE), in collaboration with the French Society of Hypertension (SFHTA) and the French Association of Endocrine Surgery (AFCE). For all patients, we collected demographic characteristics, familial history of hypertension and cardiovascular diseases, patient's history of hypertension and its complications. We performed biological assessments and imaging investigations. **Results:** We included 10 patients .The mean age of patients was 42.5 years (+/-12.06). 7/10 of patients was males. We found a family history of hypertension in 7/10 of the cases . The mean age of onset of arterial hypertension was 36.4 years (+/-7,87) . Grade 3-hypertension was found in 4/10 of the cases. Hypokalemia was found in 6/10 of the cases. The etiological investigation found bilateral adrenal hyperplasia in 4/10 of the cases. Among them 5/10 have performed catheterization of the adrenal veins, which revealed lateralization of aldosterone secretion. Conn's adenoma was found in 4/10 of the cases and unilateral adrenal hyperplasia in 2/10 of the cases. **Conclusion:** Our study illustrate the value of screening for primary hyperaldosteronism in young subjects with severe hypertension associated with hypokalemia and also given the curable and reversible nature of hypertension.

KEYWORDS :

INTRODUCTION :

Primary hyperaldosteronism is a syndrome described by Conn in 1955, which is characterized by hypertension with or without hypokalemia. This syndrome is caused by inappropriate autonomic secretion of aldosterone with suppression of renin levels. The prevalence of primary hyperaldosteronism has been underestimated in the past (approximately 1%). This prevalence has increased to reach currently 10% of arterial hypertension [2].

In our context, primary hyperaldosteronism is under-diagnosed because of the high cost of check-ups, particularly biological and radiological examinations, and especially the inaccessibility of catheterization of the adrenal veins in our country.

Consequently, there is a delay in the diagnosis of primary hyperladosteronism with the over-evidence of complications of arterial hypertension. The aim of our study is to describe the clinical, biological, imaging characteristics and clinical outcomes of patients with primary aldosteronism. As well as to highlight the challenges in the management of these patients.

MATERIAL AND METHOD

Study Design And Over View:

This observational study included all patients admitted for primary hyperaldosteronism in the department of endocrinology at the Sheikh Khalifa Ibn Zayd international universitary hospital between January 2019 and January 2021. Primary hyperaldosteronism was defined according to the Consensus on Primary Hyperaldosteronism of The French Society of Endocrinology (SFE), in collaboration with the French Society of Hypertension (SFHTA) and the French Association of Endocrine Surgery (AFCE) (1). The diagnosis of primary hyperaldosteronism was based on demonstration of low or undetectable renin levels and inappropriate high levels of aldosterone whether or not they had hypokalemia.

For all patients , we collected demographic characteristics (age, gender), familial history of hypertension and cardiovascular diseases. We also collected patient's history of hypertension and its complications. We performed , for all patients, biological assessments including dosage of aldosterone and renin with the calculation of the aldosterone/direct renin ratio.

The conditions for carrying out the blood test were as follows:
- Blood test in the morning more than 2 hours after waking up.
- Patient in a sitting position for 5 to 10 minutes.
- Normosodium diet with natriuresis between 100 and 200ml/24hrs.
- Normokalemia.
- Adjustment of the treatment of high blood pressure (A two-week stop of Converting enzyme inhibitors, angiotensin II antagonists, renin inhibitors, beta-blockers and potassium-sparing diuretics. And 6 weeks stop of spironolactone treatment).
- A six weeks stop of Estrogen progestins

For the diagnosis of primary hyperaldosteronism, we considered the following cut-off values:
- direct renin >5mUI/L
- plasma aldosterone > 415.5pmol/L
- Aldosterone/renin ratio (ARR) > 64 (for plasma aldosterone in pmol/L and direct renin in mIU/L)

Concerning the assay techniques, we have used Radioimmunology on EDTA tubes for the determination of aldosterone and chimiluminescence on EDTA tubes for the determination of direct renin.

For the etiological diagnosis, we performed adrenal CT-scan and adrenal venous catheterization in order to identify the lateralization of

the aldosterone secretion. we established the indication for catheterization of the adrenal veins in patients with bilateral adrenal hyperplasia . We referred patients eligible for surgery in accordance with the Consensus on Adrenal Surgery in Primary Hyperaldosteronism of The French Society of Endocrinology (SFE), in collaboration with the French Society of Hypertension (SFHTA) and the French Association of Endocrine Surgery AFCE (3).

We also conducted an assessment of hypertension complications for all patients, including a renal check-up, ophthalmological examination, abdominal angioscan, electrocardiogram and cardiac ultrasound.

Exclusion Criteria:
- Patients lost to follow-up
- Patients who have not been able to perform complete explorations for primary hyperaldosteronism.

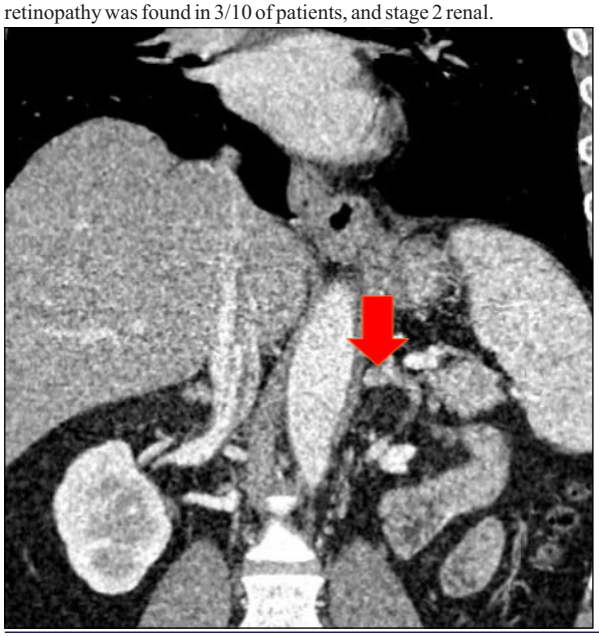
Ethics:
We obtained oral consent from all patients. Data confidentiality and patient anonymity were maintained at all stages of the study. We deleted Patient-identifying information before analyzing the database. Informed consent was obtained for all patients prior to inclusion.

Statistical Analysis
Data were analyzed using SPSS (V.20.0). Qualitative data are expressed aspercentages. Quantitative data are expressed as means and standard deviation.

RESULTS:
We included 10 patients .The mean age of patients was 42.5 years (+/- 12.06). 7/10 of patients was males. We found a family history of hypertension in 7/10 of the cases .The main arterial cardiovascular complications found in family history were myocardial infarction(2/10) ischemic Stroke (7/10) and sudden death (4/10) at a young age in first-degree relatives. The mean age of onset of arterial hypertension was 36.4 years (+/-7,87) . Hypertension was discovered during a hypertensive spike in 7/10 . Grade 3-hypertension was found in 40% of the cases . Resistant hypertension was found in all of patients . The mean duration of arterial hypertention was 6,2 years (+/- 5,24). Hypokalemia was found in 6/10 of the cases, with a mean level of hypokaliémia of 2.9mmol/L.

The etiological investigation found bilateral adrenal hyperplasia in 4/10 of the cases. Among them 5/10 have performed catheterization of the adrenal veins, which revealed lateralization of aldosterone secretion.

Conn's adenoma was found in 4/10 of the cases and unilateral adrenal hyperplasia in 2/10 of the cases. 7/10 of patients received medical treatment and 3/10 received surgical treatment. Complications of hypertension were hypertensive heart in 5/10 of patients , anevrysmal dilatation of the ascending aorta in 1/10 of patients. Hypertensive retinopathy was found in 3/10 of patients, and stage 2 renal.



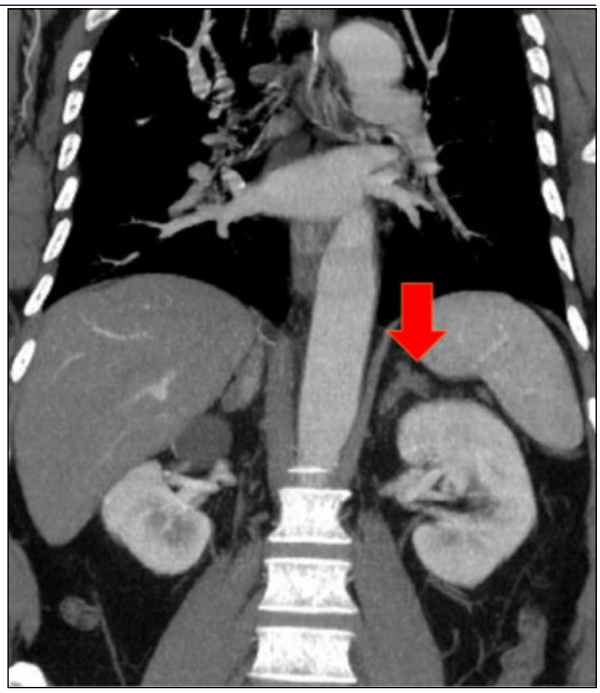


Figure 1. Enhanced Computed Tomography Demonstrating A Left Adrenal Adenoma Showing As An Homogenous Nodule With Minimal Enhancement (Red Arrows).

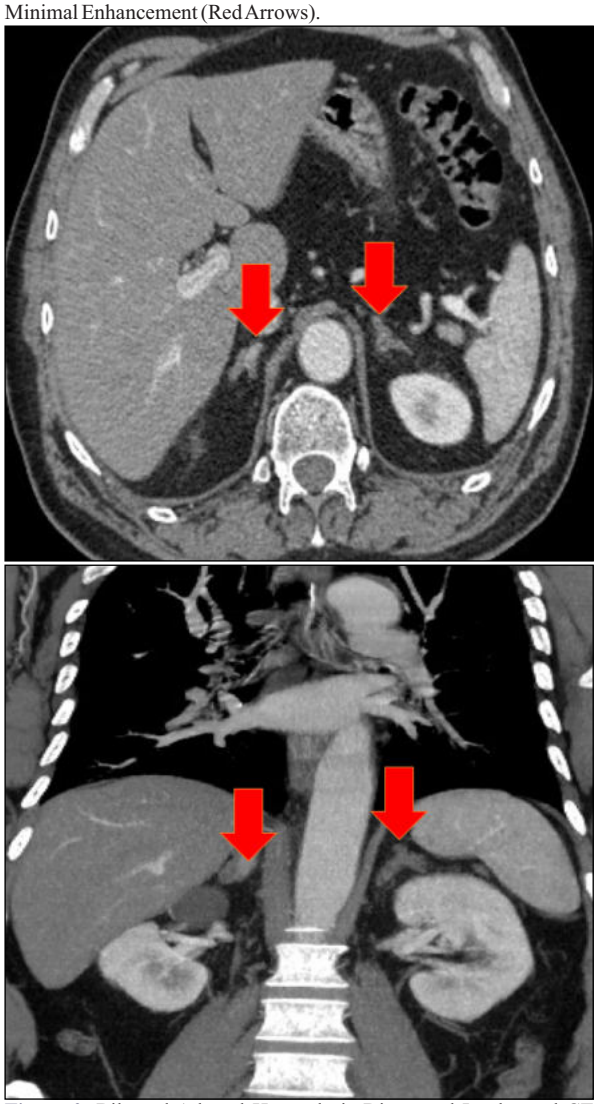


Figure 2. Bilateral Adrenal Hyperplasia Diagnosed Isenhanced CT

Images In Coronal And Axial Plans Showing Markedly Enlarged Adrenal Limbs And Bodies Bilaterally.

Insufficiency in 6/10 of cases and stage 3 renal insufficiency in 2/10 of cases and stage 4 renal insufficiency in 2/10 of cases. And we found a positive proteinuria in 3/10 of the cases.

Post-operative follow-up was simple and uncomplicated. There was a normalization of postoperative kalemia with a decrease in plasma aldosterone in the operated patients.

DISCUSSION:

Primary hyperaldosteronism is an important and increasingly prevalent cause of hypertension. It is characterized by unregulated aldosterone excess (4). The diagnosis of primary hyperaldosteronism is based on the biological assay of aldosterone and renin. In compliance with the sampling conditions, in particular, normokalemia and the normosalted diet, the dosage after sitting for 15 minutes instead of sitting upright. The dosage also requires stopping or changing the antihypertensive treatment between 2 and 6 weeks. In our cohort, all the patients had to modify the antihypertensive treatment before the tests were carried out. This has the consequence of further delaying the diagnosis. In the sample of STOWASER al. patients of Diuretic drugs (including spironolactone and amiloride) were ceased for at least 4 weeks, and ß-adrenoreceptor blockers, alpha-methyldopa, clonidine and dihydropyridine-type calcium channel antagonists were ceased for at least 2 weeks before the aldosterone : renin ratio test. During this period, other agents (such as hydralazine, prazosin or slow-release forms of verapamil), which have a lesser effect on the aldosterone : renin ratio. were used as required in order to maintain control of hypertension.(5)

Primary hyperaldosteronism is classically diagnosed as arterial hypertension associated with hypokalemia. In our sample of patients, all had arterial hypertension resistant to three or more antihypertensive agents, but hypokalemia was present in only 60% of cases. in the sample of patients of STOWASER al. 53% of patients had hypertension resistant to three or four antihypertensive agents, and hypokalemia was present in only 13% of patients.(5) These arguments testifies to the fickle nature of hypokalemia in primary hyperaldosteronism.

Primary hyper aldosteronism is a common cause of hypertension, but frequently overlooked. It increase the incidence of cardiovascular events, particularly atrial fibrillation(6). In our patient sample we found complications of arterial hypertension in 100% of our patients. This finding can be explained by the long duration of hypertensive evolution. Indeed in our study the duration of evolution was of 6.2 years (+/- 5.24. This joins the literature data, in the patient sample of STOWASER and al. the mean of duration of arterial hypertension ranged from 7.8 to 11.6 years (5). Which is indicative of the diagnotic delay of primary hyperaldosteronism. which highlights the importance of early screening for primary hyperaldosteronism. This screening will make it possible to stabilize or even definitively treat arterial hypertension. In the stowasser sample, it was shown that patients who stabilized their blood pressure after surgery were 50% and none in the medically treated group (5). In our patient sample, only 10% were able to treat high blood pressure, and the rest were able to stabilize their blood pressure numbers with one antihypertensive agent instead of three or four antihypertensive agents. There was a normalization of blood pressure figures and kalemia . among the group of patients treated medically 1/7 patient had renal failure on ALDACTONE. We then modified the treatment and put the patient on EPLERENONE.

It is important to define the etiology of hyperaldosteronism because unilateral damage is treated by surgery, while bilateral damage is treated by medication.(2) Primary hyperaldosteronism can be caused by a uni- or bilateral adenoma (30%), or adrenal hyperplasia (70%), which is often bilateral, but can be unilateral. Other, rarer causes that can lead to primary hyperaldosteronism, are familial hyperaldosteronism and ovarian tumors or adrenal carcinomas that secrete aldosterone(4). In our study the most common diagnosis was bilateral adrenal hyperplasia, and the same in the STOWASER.al sample. (7)

PA is currently underdetected for several reasons. First, there is still a quite popular misconception that PA is “a needle in a haystack” (8), notwithstanding clear evidence showing the opposite: the PAPY (Primary Aldosteronism Prevalence in Hypertension) study. That is the first large prospective survey that used a rigorous methodology to diagnose PA and aldosterone- producing adenoma (APA), reported a rate of 11.2% in consecutive newly diagnosed hypertensive patients (5, 7), indicating that PA was the most common curable endocrine form of hypertension.

When primary hyperaldosteronism is diagnosed and treated at an early stage, radical treatment of this syndrome can be provided, even when it is resistant to medical treatment. This justifies the need to establish strategies for early detection of primary hyperaldosteronism with a simplified algorithm. They can be particularly beneficial in some subgroups of hypertensive patients, as those who are at highest cardiovascular risk. However, identification of the surgically curable cases of PA and achievement of optimal results require subtyping with adrenal vein sampling, which, as it is technically challenging and currently performed only in tertiary referral centers, represents the bottleneck in the work-up of PA(10). In our context, catheterization of the adrenal veins is a technique that is not developed, which limits management.

CONCLUSION:

It is therefore necessary to establish systematic despitation of hyperaldosteronism in all patients at risk, particularly young subjects with resitant arterial hypertension associated with hypokalemia. Early detection as soon as hypertension is discovered will make it possible to reduce the delay in treatment and increase the chances of reversibility of hypertension and avoid complications. In our context, it is also necessary to improve access to care, in particular by developing dosage techniques in national laboratories, imaging techniques, notably adrenal scintigraphy and catheterization of the adrenal veins.

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