Endocrinología, Diabetes y Nutrición 70 (2023) 360–370

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

SCIENTIFIC LETTER

Impact of an endocrine hypertension unit on the diagnosis of primary aldosteronism

Impacto de una consulta de hipertensión endocrina en el diagnóstico del hiperaldosteronismo primario

Arterial hypertension (HT) is the main risk factor for cardiovascular disease and it affects ~50% of the Spanish adult population.[1] Primary aldosteronism (PA) is a chronic, progressive endocrine disorder that is the main cause of HT; it is found in 10–15% of the hypertensive adult population in general[2] and in 30% in cases of severe and/or resistant HT. PA is a major cardiovascular risk factor.[3,4] It increases the risk of death, stroke, coronary heart disease, chronic kidney disease, atrial fibrillation, left ventricular hypertrophy and heart failure more than essential HT and regardless of blood pressure levels. Early detection can therefore save lives and improve the quality of life of those affected.[5,6]

Considering the public health impact of PA, all clinicians should be familiar with its management. However, the reality is that identifying PA can be complex, which partly explains the high rate of underdiagnosis.[7] This seems to be no different among endocrinologists in Spain. Studies from the Spanish PA registry report high rates of hypokalaemia, suggesting that PA is diagnosed in advanced stages, even in very obvious cases.[8] A recent Spanish national survey on the treatment of PA by Spanish endocrinologists[9] showed that there is great variability in this area, and that there is a lack of subtyping studies, findings similar to those reported by other authors.[8] Additionally, it was reported that only 35% of departments had a specific specialist in PA and that, although 67% had an HT clinic/unit at their hospital, these came under other specialist areas. It is likely that the establishment of specific referral centres/units/clinics in HT with endocrinologists subspecialising in PA would improve the management of this condition.

Our department boasts a specific endocrine hypertension clinic (C-HT-Endo), which has been running since January 2022. We report here how this clinic has affected the diagnosis of PA and we discuss our experiences so far.

Operational structure of the clinic

Suspected cases of endocrine hypertension, mainly PA, have been channelled to two endocrinologists since July 2021, and the C-HT-Endo has been running as a specific service two days a week since January 2022. In parallel with the creation of the clinic and once it was up and running, informative sessions were held with the hospital's Nephrology, Interventional Radiology, Internal Medicine, Cardiology, Urology and Pathology departments to coordinate diagnostic-therapeutic strategies. The patients are referred from the Nephrology HT clinic or from our own department. The reason for referral is suspected endocrine hypertension, which includes PA, pheochromocytoma/paraganglioma, Cushing's syndrome and acromegaly. In the case of PA, in addition to clinical suspicion, an aldosterone-renin ratio value >20 ng/dl/ng/mL/ with blood aldosterone (Aldo) >8 ng/dl was agreed on (measured with or without drugs that interfere with the renin-angiotensin-aldosterone system). For the diagnosis of PA, apart from clinical exceptions, two of the following functional tests are performed using the published protocol and cut-off points,[2] in accordance with the latest European consensus:[10] captopril challenge test with captopril 25 mg; oral salt loading test; and intravenous saline loading test. For the study of other causes of endocrine HT, the recommendations of the respective clinical guidelines are followed.

Impact of the C-HT-Endo on the diagnostic approach to PA

From July 2021 to December 2022, 144 patients were seen at the C-HT-Endo, 56 (38.8%) referred from Nephrology and the rest from our department. Of the 144 patients, PA was diagnosed in 46 (31.9%), and no other cause in the rest. With the clinic, compared to previous years, we have seen a markedly progressive increase in the cases investigated and diagnosed with PA, as well as in the number and the diagnostic yield of adrenal venous sampling procedures performed (Fig. 1).

Implications of a C-HT-Endo

First of all, although there are clinical guidelines for the management of HT of endocrine origin, apart from PA, it is still a group of unusual diseases, which are highly heterogeneous from a clinical point of view. The logistical constraints of adapting the approach to the particular situation of each centre and getting a clinic of this type effectively

DOI of original article: https://doi.org/10.1016/j.endinu.2023.02.004

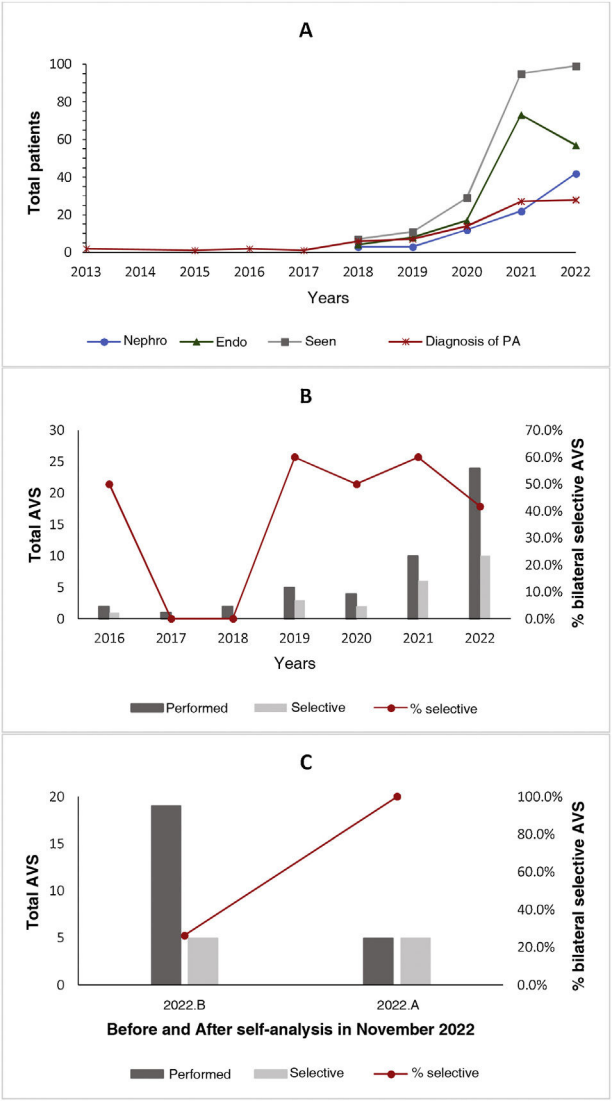

Figure 1 A) Changes in cases seen in the clinic over time according to their origin, referred from the Nephrology (Nephro) or Endocrinology (Endo) departments, and diagnosed with primary aldosteronism. B) Changes over time in the total number of adrenal venous samplings (AVS) performed and in AVS with an adequate bilateral selectivity rate. C) Difference in AVS with adequate bilateral selectivity in the last month of 2022, before and after a multidisciplinary meeting in which the consultation data were self-analysed.

up and running are many. Multidisciplinary coordination with the departments involved is therefore imperative to turn what were initially weaknesses into strengths. Secondly, there is no gold standard for diagnostic or therapeutic action in many of these diseases, especially when ünusual/complicatedcases occur. Moreover, as in the case of PA, the performance of many screening/diagnostic tests can vary depending on pre-analytical factors or cut-off points used, or due to the nature of the disease. In PA, the higher the cut-off point of the aldosterone-renin ratio used for screening, the lower its sensitivity, although the higher its specificity; sitting/standing and some drugs induce different values of aldosterone and renin; and production of aldosterone is not always homogeneous, continuous and completely autonomous. Therefore, doctors who run a C-HT-Endo need to have a thorough knowledge of these situations and be aware that interpreting tests and medical decisions often have to be personalised according to the clinical context. This makes it crucial to have clinical meetings/committees in place for the discussion and study of cases. Lastly, in order to effectively manage endocrine hypertension, it is also necessary to have detailed knowledge of essential hypertension, so training in the field of HT beyond endocrine causes is vitally important.

In conclusion, having a C-HT-Endo has probably led to a more active search for cases of PA by the rest of the physicians, and this would explain the marked increase in the diagnosis of PA in our series. It should also translate into more patients benefiting from better cardiovascular protection after appropriate treatment, which is something we hope to corroborate in the future. We therefore deem the role of an endocrinologist specialising in HT and their participation in HT clinics/units to be vital.

Authors/contributors

1 Conception and design of the manuscript: JGR-S.
2 Data collection: JGR-S and DM.
3 Data analysis and interpretation: JGR-S.
4 Drafting, review and approval of the submitted manuscript: JGR-S and DM.

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Werner syndrome as a crossroads between lipodystrophy, escleroderma-like changes and torpid ulcers in lower limbs

Síndrome de Werner como encrucijada entre lipodistrofia, cambios esclerodérmicos y úlceras tórpidas en miembros inferiores

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Werner's syndrome (WS) or adult progeria is an autosomal recessive hereditary disorder with premature ageing beginning in the person's teens. Its incidence is less than $1/10^6$ births, although it is probably underdiagnosed.[1] Although it was originally described in 1904, its molecular basis was not established until 1996.[2] It is caused by mutations in the *WRN* or *RECQL2* gene, which encodes a DNA helicase. This enzyme is key in DNA repair processes and in maintaining telomere integrity, so a deficiency causes genomic instability, risk of cancer and cellular senescence.[2] The main clinical manifestations are the absence of a puberty growth spurt with short stature, thinning hair with early greying, skin changes, sarcopenia, osteoporosis and glucose and lipid metabolism abnormalities with accelerated atheromatosis.[3] Biallelic mutations in the *WRN* gene are found in 97% of patients. Clinically diagnosed cases in which no *WRN* mutations are found are called atypical WS and in a significant proportion of these, mutations in the *LMNA* gene are identified, with earlier symptoms and more rapid progression.[3]

We present a case of WS diagnosed after association and exclusion of signs and symptoms and the use of next-generation genetic sequencing techniques.

This was a 55-year-old woman who consulted with painful ulcers on both feet. She had never smoked and had been diagnosed with type 2 diabetes mellitus at the age of 29 years, requiring insulin and pioglitazone early, which provided adequate control (HbA1c around 7%). She had surgery for bilateral cataracts at age 50. The patient's height was 147 cm, weight 46 kg, and she had increased abdominal adiposity (circumference 94 cm) with a marked decrease in the fat panniculus around the edges. Her scalp hair was sparse and she had started to go grey in her 20 s. The skin on her hands and feet was thick and hard, with thinning of the underlying tissues, leading to suspicion of scleroderma. She did not have Raynaud's phenomenon and nailfold capillaroscopy showed isolated dilations and capillary ramifications. She had developed the ulcers five years earlier, preceded by hyperkeratosis, which were now chronic, with poor healing and frequent superinfection. The deepest ulcers were located both in the balls and backs of the first and second toes of both feet, some of them deep with bone exposure; ulcers had also developed on the metatarsal heads of the first and fifth toes and on the lateral aspects of her feet. She also had *hallux valgus* and claw toes. Sensitivity in her lower limbs and distal peripheral pulses were normal, with an indeterminate ankle-brachial index due to arterial stiffness. Transcutaneous oxygen pressures (TcPO2) in her feet were 8 and 2 mmHg. Her total cholesterol was 227 mg/dl and triglycerides 289 mg/dl. X-rays of her hands and feet detected osteoporosis and vascular and subcutaneous calcifications, and liver ultrasound revealed steatosis. Further investigations ruled out involvement of the gastrointestinal tract, heart, lungs or kidneys, and autoimmunity tests were negative. There were also no signs of diabetic nephropathy or retinopathy. Added to the intensive treatment of the ulcers (frequent dressings, discharge measures and antibiotics), the patient was started on treatment with bosentan (125 mg/12 h), but with no significant improvement. The associated pain and the need for functional rest had made the use of a wheelchair necessary.

The molecular study with next-generation sequencing of 27 genes associated with hereditary lipodystrophies identified a rare homozygous variant (c.3711del or p.K1237Nfs*11) in the *WRN* gene, classified as pathogenic in ClinVar (ID: 577673). None of the patient's children or siblings and neither of her parents had developed similar conditions. There was no known consanguinity between the parents, although their families were originally from the same town in the province of Ciudad Real.

Although Spain has had some reports of cases of patients with suspected WS, most are old and prior to the discovery of the causative gene. This is the first case in this country with a full clinical description and molecular confirmation. The mutation found in the *WRN* gene, although described as pathogenic, is very uncommon worldwide.[4] In addition, finding it as a homozygous variant has revealed the existence of some previously unknown degree of consanguinity in her parents.

DOI of refers to article: https://doi.org/10.1016/j.endinu.2023.02.005