Primary adrenal insufficiency due to X-linked adrenoleukodystrophy diagnosed in adulthood☆

Insuficiencia suprarrenal debida a adrenoleucodistrofia ligada al cromosoma X diagnosticada en la edad adulta

X-linked adrenoleukodystrophy (ALD-X) is a hereditary disorder seen in male children/adolescents. Adult cases are less common. Primary adrenal insufficiency (PAI) is present in over 50% of the affected patients, and constitutes the sole manifestation in 10% of the cases.[1,2]

We present the case of a male diagnosed with PAI at 61 years of age, followed 6 years later by the diagnosis of ALD-X. His history comprised dyslipidemia, parkinsonian syndrome for the last three years indicative of Parkinson's disease (PD) without imaging test data due to patient claustrophobia, and PAI for the last 6 years, subjected to treatment with hydrocortisone. The blood pressure was 128/99 mmHg, with no significant variation on standing up from dorsal decubitus, and the laboratory tests revealed normal sodium and potassium levels. Examination of the medical history did not reveal the etiology of PAI. Complementary tests were therefore requested. The aldosterone concentration was 3.7 ng/dl (reference range 3.7–43), with renin 17.6 μU/ml (2.3–99), DHEA < 15 μg/dl and testosterone 6.2 ng/ml (1.4–9.2). Anti-21 hydroxylase (anti-21OH) antibodies proved negative, and the abdominal CAT scan revealed normal adrenal glands. Considering the negative results of these two tests in a male with neurological alterations in which the underlying etiology could not be established by imaging techniques, we suspected a genetic cause and requested the determination of very long chain fatty acids (VLCFAs) in plasma, which were found to be elevated: C22:0 70.3 μmol/l (51–113), C24:0 109.5 μmol/l (44.5–9.4), C26:0 4.7 μmol/l (0.2–0.8), C24:0/C22:0 ratio 1.5 (0.5–0.8) and C26:0/C22:0 ratio 0.06 (0.004–0.02). The genetic study revealed the mutation E292 K c.[874G > A] (p.Glu292Lys) in exon 1 of the *ABCD1* gene located in the long arm of chromosome X (Xq28), described in the ALD-X database (http://www.x-ald.nl). The skin biopsy revealed elevated VLCFAs in the fibroblasts, with a decrease in peroxisomal transmembrane protein (adrenoleukodystrophy protein [ALDP]). The open brain MRI scan revealed no white matter alterations. The DATscan (isotopic neuroimaging with ^{123}I-ioflupane) revealed intense alteration of the bilateral nigrostriatal pathway. The patient had a 24-year-old son and a 30-year-old daughter. The daughter presented elevated VLCFAs in plasma and the same mutation of the *ABCD1* gene. Since she expressed a wish to have children, she was referred for genetic counseling.

Primary adrenal insufficiency is due to gradual destruction of the adrenal gland cortex – the clinical manifestations developing when at least 90% of the cortex has been lost. Adrenal gland sex steroid, mineralocorticoid and glucocorticoid deficiency is observed. The most common underlying cause is autoimmune adrenalitis (AA), which accounts for 70–90% of all cases, either isolatedly or in the context of an autoimmune polyglandular syndrome, followed by infections and other less frequent diseases: bilateral adrenal metastases, bilateral adrenal hemorrhage, infiltrating diseases, genetic alterations, drugs and surgery.[3]

The diagnosis of PAI involves complementary tests based on algorithms in which the first step is the determination of anti-21OH antibodies.[4] These antibodies are present in 100% of the cases of AA for up to 15 years after the diagnosis. They subsequently decrease to under 60% and may even disappear. In such cases the absence of antibodies would not rule out autoimmunity.[3]

X-linked adrenoleukodystrophy is estimated to affect one out of every 17,000 newborn infants. The disease is characterized by altered beta-oxidation of the VLCFAs ≥ 22 C in the peroxisomes, with their consequent accumulation in plasma and other tissues such as the white matter of the brain, spinal cord, adrenal cortex and Leydig cells of the testicles, where they cause cell damage. The disorder is caused by a mutation of the *ABCD1* gene located in chromosome X. The mutation results in the absence or dysfunction of ALDP, which is in charge of transporting the acylated esters of the VLCFAs from the cytosolic compartment to the peroxisome. Six hundred different mutations have been described, and there appears to be no genotype/phenotype correlation. There are a number of phenotypes: presymptomatic forms, isolated adrenal insufficiency, cerebral adrenoleukodystrophy (ALD) (childhood, adolescent and adult forms), adrenomyeloneuropathy (AMN), and female carriers. The phenotypes are not static. Almost all presymptomatic males will develop cerebral ALD, AMN or PAI over time. Males with isolated adrenal insufficiency can develop cerebral ALD or AMN, while males with AMN may show brain involvement.[1,5,6]

X-linked adrenoleukodystrophy is a rare cause of PAI, but can account for up to 5–10% of all cases. An etiological diagnostic delay of as long as 29 years has been observed as a result of the above.[2,7,8] Primary adrenal insufficiency manifests in 50–86% of the cases, and at any age (20% in adults).[6,9] The management of PAI in ALD-X is based on the administration of glucocorticoids. However, not all patients require mineralocorticoids, as in our case, since there is less VLCFA accumulation in the glomerular zone of the adrenal cortex, and this deficit is present in approximately 50% of the patients.[1,3,9] Unlike once believed, female carriers are not always asymptomatic. Fifty percent suffer neurological manifestations such as AMN from the age of 40–50 years onwards - the presentations in some cases being severe.[10] Primary adrenal insufficiency is very rare (incidence 1%).

The scientific literature contains other cases similar to our own, described in studies on the etiology of PAI. The most extensive sample, published by Horrn et al., identified three cases of ALD-X among 202 male adults with PAI.[8]

The patient presented an isolated adrenal insufficiency phenotype, because the neurological manifestations were more consistent with Parkinson's disease than with AMN or

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cerebral ALD, and the DATscan findings supported the diagnosis of Parkinson's disease.

In the event of PAI in a male with negative anti-21OH antibodies and normal adrenal glands as evidenced by the CAT study, we must suspect ALD-X as the underlying cause, independently of the age of the patient. The diagnosis is relevant not only because of the treatment implications, but also due to transmission of the disorder to the offspring. It is important to detect female carriers in order to ensure adequate clinical follow-up and genetic counseling, as in the daughter of our patient.

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