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Letter to the Editor

A case report of apparent mineralocorticoid excess, with nephrological and neurological symptoms since birth, and with a new probably pathogenic variant in *HSD11B2* gene

A propósito de un caso de exceso aparente de mineralocorticoides, con clínica nefrológica y neurológica desde el nacimiento, y con nueva variante probablemente patogénica en gen *HSD11B2*

Apparent mineralocorticoid excess (AME) is a rare form of pseudohyperaldosteronism characterised by early hypertension, hypokalaemia, metabolic alkalosis and low levels of renin and aldosterone, due to low or no activity of the enzyme 11-beta-HSD2.[1]

This was a male who, after a full-term caesarean section, required advanced cardiopulmonary resuscitation. Newborn weight percentile less than 3. Healthy, non-consanguineous parents. He presented with severe neonatal pulmonary hypertension. On the sixth day, myoclonus and epileptiform electroencephalographic signs were observed, for which the patient received phenobarbital. Due to the patient's high blood pressure, he was started on nifedipine in the first week of life. With signs of heart failure, digoxin, furosemide and potassium were added after 18 days.

At 13 and 18 months of age, he presented with seizures in the context of fever. At age 16 months, sustained hypokalaemia (K 2.2 mEq/l) with metabolic alkalosis (pH 7.49, HCO_3 33.1 mmol/l and BE 10.5 mmol/l) and arterial hypertension with inhibition of plasma renin (0 ng/ml/h) and aldosterone (22 pg/ml) raised suspicion of Liddle's syndrome (LS), owing to which treatment with amiloride was started. At age 19 months he suffered his first afebrile seizure and was prescribed valproic acid. Despite treatment, the frequency and type of seizure increased at 22 months. Dravet syndrome spectrum was suspected and topiramate was added, resulting in seizure remission.

At 11 years of age, a genetic study was performed, detecting a heterozygous variant p.Glu197Lys (c.589G > A) in exon 3 of the *SCNN1G* gene, one of the most frequently associated with LS.[1] This nucleotide change had previously been described as a variant associated with the development of LS with autosomal dominant inheritance. The mother, asymptomatic to date, is a carrier of the variant. In a subsequent database review (LOVD, ClinVar, VarSome), this variant was classified as benign.

At 16 years of age, the study was expanded with trio-exome sequencing, identifying a homozygous variant in the *HSD11B2* gene c.176_196delinsTCCAGCC; p.(Ala59Valfs*28) in exon 1 of chromosome 16q22. Variants in *HSD11B2* are associated, with an autosomal recessive inheritance pattern, with AME.[1,2] This variant has not previously been reported in the literature or in population databases (gnomAD) and is classified as p̈robably pathogenic.P̈arents are carriers of the mutation.

A hemizygous variant is also detected in the *TBC1D8B* gene c.126dupC; p.(Thr43Hisfs*9) on chromosome Xq22 associated with nephrotic syndrome type 20, probably pathogenic, without presenting with corresponding symptoms.[3]

Amlodipine was required at 12 years of age, with progressive increase in dose, replacing amiloride with spironolactone after genetic diagnosis. The latest ultrasound scans show hyperechoic kidneys, with decreased corticomedullary differentiation, without lithiasis. The patient intermittently presents with high-limit urinary calcium, owing to which initiation of thiazides will be considered. During follow-up, adequate height development was evident, but weight and head circumference at birth and in the first months of life were below the 3rd percentile. At 17 years of age, follow-up was required in nephrology, neurology (intellectual disability,

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language disorder and executive dysfunction) and cardiology (mild aortic insufficiency and aortic root ectasia).

Reviewing the literature, Leventoğlu et al.[4,5] describe a case of a patient with AME associated, as in our case, with low birth weight and cardiological problems. Their patient also presented with dysmorphic features and a pathogenic variant in the *SMARCA4* gene consistent with Coffin-Siris syndrome was identified. Our patient had no associated dysmorphic features on examination, nor a pathogenic variant in the *SMARCA4* gene.

To date, just over a hundred cases of AME have been described, with more than 50 different variants in the *HSD11B2* gene.[6] Most are located in exons 3–5, but in our patient it is located in exon 1. The different clinical and analytical presentation can be explained by the presence of a classic and a non-classic form.[7,8]

No association has been identified between LS, AME and the development of epilepsy, but there is a reported case of a variant in exon 5 of the *HSD11B2* gene and seizures.[9]

Although the abolition of 11-beta-HSD2 leads to abnormal cortisol metabolism and decreased urinary metabolites,[2] subjects with AME may have a normal serum cortisol concentration, since its prolonged half-life may lead to low cortisol secretion by regulation of the hypothalamic-pituitary-adrenal axis.[6] Our patient had normal cortisol levels (8.79–14.6 μg/dl). There are no data available on cortisone or urinary metabolites.

Amiloride, triamterene, spironolactone or eplerenone and, occasionally, dexamethasone are used as treatment.[10] They may initially require potassium. Thiazides are recommended in subjects with hypercalciuria or nephrocalcinosis.

Multidisciplinary monitoring of complex patients is necessary, and the diagnosis must be reconsidered in the face of progressive changes. Nowadays, properly interpreted genetic studies can provide aetiological diagnoses, allowing for early treatment to improve patient outcomes.

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