

Data availability statement

The data for substantiating the findings of this manuscript are available with corresponding author and can be made available on request.

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Gerry George Mathew^{a,*}, Sharmila Ganesan^b

^a Associate Professor, Department of Nephrology, SRM Medical College Hospital and Research Centre, Kattankulathur, Chengalpattu 603203, Tamil Nadu, India

^b Assistant Professor, Department of Obstetrics and Gynaecology, Chettinad Academy of Research and Education, Chettinad Health City, SH 49 A, Kelambakkam 603103, Tamil Nadu, India

* Corresponding author.

E-mail address: gerrygeorge007@gmail.com (G.G. Mathew).

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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 hyper-

tension. 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, HCO₃ 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 probably pathogenic. Parents 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, 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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Cristina Hernández Tejedor^{a,*}, Yolanda Romero Salas^b,
María Dolores Miramar Gallart^c,
Alberto José Bríngola Moñux^a, María José Sánchez Malo^a,
José Luis Peña Segura^d

^a Servicio de Pediatría, Hospital Universitario Miguel Servet, Zaragoza, Spain

^b Sección de Nefrología Pediátrica, Servicio de Pediatría, Hospital Universitario Miguel Servet, Zaragoza, Spain

^c Sección de Genética Clínica, Servicio de Bioquímica Clínica, Hospital Universitario Miguel Servet, Zaragoza, Spain

^d Sección de Neuropediatría, Servicio de Pediatría, Hospital Universitario Miguel Servet, Zaragoza, Spain

* Corresponding author.

E-mail address: cristinahernandeztejedor@gmail.com
(C. Hernández Tejedor).

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Q fever as a cause of fever of unknown origin in a patient on hemodialysis

Fiebre Q como causa de fiebre de origen desconocido en un paciente en hemodiálisis



Dear Editor,

Q fever is a worldwide zoonosis caused by *Coxiella burnetii* acquired mainly by inhalation.¹ Clinical manifestations of acute Q fever include self-limited flu-like illness, pneumonia, and mild hepatitis. Chronic infection usually presents as a culture-negative endocarditis, but other uncommon forms of persistent focalized infection and secondary non-Hodgkin lymphoma are also possible.^{2,3}

We present the case of a 70-year-old man with a history of hypertension, type 2 diabetes mellitus, and chronic ischemic dilated cardiomyopathy. The patient was also being monitored by Hematology due to a monoclonal gammopathy of undetermined significance and had stage V chronic kidney disease, secondary to mesangiocapillary glomerulonephritis with heavy chain deposition. A Quantiferon-TB Gold plus had been performed with positive results and therefore he had been taking rifampicin 600 mg QD for 4 months as treatment for latent tuberculous infection. Regarding the immunosuppressive treatment, in December 2022 the patient received induction treatment with methylprednisolone pulses and a

single Rituximab dose, due to progressive kidney failure. He finally started chronic hemodialysis program 2 days/week through a tunneled central venous catheter at the end of December 2022. A blood test in January 2023 revealed low IgG (488 mg/dL) with normal IgM and IgA levels.

In April 2023, he consulted after a hemodialysis session complaining of general malaise, impaired mobility, pain in the right hypochondrium and moderate fevers for 2 weeks. The analytical findings suggested an infectious process: C-reactive protein (CRP) 364 mg/L, procalcitonin 1.71 ng/mL, leukocytosis 19,200/mm³, Hb 11.9 g/dL, LDH 300 U/L, GGT 211 U/L, ferritin 1452 ng/mL. He was referred to the emergency department (ED) where an abdominal ultrasound and CT scan were performed, describing multiple small nodular liver images, with a hypodense center and ring enhancement, suggestive of microabscesses. Chest-X ray was normal. The patient was then admitted to our Infectious Diseases Unit and antibiotics stopped. Initial microbiological and analytical results are included in Table 1. After all these diagnostic proceedings yielded no result, a liver biopsy was performed. The patient was sent home pending results and he felt much better without any antimicrobial being started. CRP and procalcitonin declined spontaneously and the patient remained on close monitoring as an outpatient.

6 weeks thereafter (June 2023) the patient visited the ED again complaining of right hypochondrium pain, general