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Case report

The need for genetic study to diagnose some cases of distal renal tubular acidosis☆

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ABSTRACT

We describe the case of a young woman who was diagnosed with advanced kidney disease, with an incidental finding of nephrocalcinosis of unknown aetiology, having been found asymptomatic throughout her life. The genetic study by panels of known genes associated with tubulointerstitial disease allowed us to discover autosomal dominant distal renal tubular acidosis associated with a *de novo* mutation in exon 14 of the SLC4A1 gene, which would have been impossible to diagnose clinically due to the advanced nature of the kidney disease when it was discovered.

Necesidad de estudio genético para el diagnóstico de algunos casos de acidosis tubular renal distal

Palabras clave:
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RESUMEN

Describimos el caso de una mujer joven, que fue diagnosticada de insuficiencia renal avanzada, con un hallazgo casual de una nefrocalcinosis sin una etiología clara, al haberse encontrado asintomática a lo largo de su vida. El estudio genético por paneles de genes conocidos asociados a enfermedad tubulointersticial permitió descubrir una acidosis

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tubular renal distal autosómica dominante, asociada a una mutación *de novo* en el exón 14 del gen SLC4A1, que hubiera sido imposible diagnosticar clínicamente por lo avanzado de la enfermedad renal cuando fue descubierta.

Introduction

Nephrocalcinosis—i.e. a generalised increase of calcium in the kidney—is the result of several factors which contribute to renal damage (nephrolithiasis: elevated urine calcium/oxalate/phosphate, in particular due to serious metabolic defects).[1] The main inherited causes of nephrocalcinosis include adenine phosphoribosyltransferase deficiency, cystinuria, Dent's disease, familial hypomagnesaemia-hypercalciuria-nephrocalcinosis, renal tubular acidosis (RTA) and primary hyperoxaluria.[2,3]

Amongst the latter causes, primary or hereditary distal RTA has gained particular interest in recent years due to de increased understanding of molecular mechanisms that allows to known mutations in the main proteins involved in acid–base transport. RTA is manifested in two hereditary forms: autosomal dominant (AD) and autosomal recessive (AR), which are associated with mutations in the SLC4A1, ATP6V1B1, CA2 and ATP6V0A4 genes. It is characterised by hyperchloraemic metabolic acidosis, which is caused by a failure to excrete hydrogen ions (H^+) *via* the urine. The main symptoms that accompany distal RTA are growth retardation, vomiting/diarrhoea or constipation, poor appetite, polyuria and polydipsia, and nephrocalcinosis. The prognosis for distal RTA is good if diagnosed and treated with bicarbonate/potassium citrate at an early age.[4] However, in asymptomatic patients it may be difficult to establish a diagnosis, through just clinical studies/laboratory tests, once advanced renal failure is established, which is also associated with a poor prognosis. In such situations the diagnosis can be obtained through a genetic diagnosis that includes all the known genes associated with the disease.

In this article we describe the case of a young woman with no family history of kidney disease, no prior nephrological examination, who was asymptomatic throughout her life, and, when advanced renal failure was detected, she was diagnosed with renal parenchymal calcification. She underwent a genetic study of all known genes associated with nephrocalcinosis, and was diagnosed with autosomal dominant RTA, identifying a *de novo* mutation in the SLC4A1 gene as the primary cause of nephrocalcinosis.

Case report

Background

26-Year-old woman with no relevant history or chronic treatment, who was seen by Primary Care Physician because of malaise, cramps and numbness in the hands and feet, and, during the last 2 days, she was unable to open her left eyelid. Lab test was requested which revealed a serum creatinine of 4.6 mg/dL (the only previous test recorded available at this centre was 6 years earlier, with creatinine at 1.5 mg/dL). Therefore the patient was sent to the emergency room. No family history of kidney disease.

Clinical course

Her blood pressure was 135/67 mmHg, heart rate 120 bpm and temperature 37.5 °C, without relevant finding in the physical exam. The blood test was repeated and confirmed the impaired renal function (creatinine 5.1 mg/dL and urea 245 mg/dL), together with sodium 124 mmol/l; potassium 3.5 mmol/l; pH 7.08; bicarbonate 5.9 mmol/l; pCO_2 20 mmHg; corrected calcium ion 0.69 mmol/l (normal: 1.13–1.32); magnesium 1 mg/dL; WBC 14,060; and a normal CBC and clotting test. Subsequent lab tests showed calcium 7.4 mg/dL; phosphorus 5.6 mg/dL; iPTH 298 pg/ml; vitamin D 18.27 ng/ml and uric acid 8.8 mg/dL. The immunological exam (immunoglobulins, ANA) was normal. Blood electrophoresis: decreased immunoglobulin. Serological testing for B and C viruses and HIV was negative. In a systematic urine test, pH was 6.0, blood+, and WBC+++. In the 24-h urine protein test, proteinuria was 0.73 g, creatinine clearance 12 ml/min, uric acid 600 mg, urine calcium < 4 mg/kg and urine oxalate 10 mg (normal: 4–31).

The electrocardiogram showed sinus rhythm with an ST elevation of 1 mm in all leads. The chest X-ray was normal. In plain abdominal X-ray, there were extensive bilateral renal calcifications (Fig. 1). After correcting the hypocalcaemia, hypomagnesaemia and metabolic acidosis, the patient was discharged, with no significant incidents during admission. Lab test values at discharge were creatinine 3.6 mg/dL; sodium 142 mmol/l; potassium 4.4 mmol/l; pH 7.43; bicarbonate 24.6 mmol/l; calcium 8.6 mg/dL; corrected calcium ion 1.16 mmol/l; phosphorus 2.9, iPTH 103 ng/ml and magnesium 1.9 mg/dL. Treatment at discharge was: calcium carbonate 2.5 g every 8 h; calcitriol 0.5 mcg/day; sodium bicarbonate 1 g/day and oral potassium and magnesium supplements.

Approximately 48 h after being discharged from the Nephrology Department, she came to emergency room because she was not able to talk or move her tongue. In addition, the patient reported that the previous night she had trouble controlling the movements of her right hand. She also reported trouble swallowing and severe asthenia. She had no fever or headache. The physical exam showed blood pressure 102/72 mmHg, heart rate 75 bpm, baseline oxygen saturation 98%, and all else was normal. The blood test showed creatinine 3.6 mg/dL; sodium 141 mmol/l; potassium 4.4 mmol/l; pH 7.43;