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Multigene involvement in congenital nephrotic syndrome

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To the Editor,

Congenital nephrotic syndrome (CNS) is a serious, rare disease which in most cases has autosomal recessive monogenic inheritance. Several genes are implicated, the most frequent of which are NPHS1, NPHS2, WT1 and LAMB2.^{1,2} It manifests clinically with massive proteinuria, general oedema, hypoalbuminaemia and hypertriglyceridaemia appearing in the first three months of life.³ Here, we present the first case of a CNS patient with multigenic alteration of three of the four most common genes.

CASE REPORT

Our patient was a one-month-old male from Morocco, who came to the Emergency department after presenting symptoms such as vomiting, rejection of food and abdominal distension which had lasted 4 days. The pregnancy was controlled, with no relevant obstetric or perinatal history. The baby was born full-term with the proper weight for his gestational age. On examination the patient's general condition was fair, with cutaneous-mucous paleness and general oedema predominant in the lower limbs. A grade IV/VI polyfocal systolic murmur was auscultated. The abdomen was distended, with the presence of the superficial venous system and ascites. Laboratory analyses revealed normocytic-normochromic anaemia, leukocytosis with a normal formula, creatinine below 0.2mg/dl and 10mg/dl urea, high cholesterol and triglycerides, and reduced total proteins and albumin, as well as hyponatraemia, hypopotassaemia and hypocalcaemia (Table 1). The parathyroid hormone was slightly high. The patient's urine presented nephrotic-range proteinuria with a urine protein:creatinine index of 33.7.

When CNS was suspected, the patient began to undergo intensive diuretic and antiproteinuric therapy, antithrombotic prophylaxis, adjuvant treatment with alfacalcidol, iron, calcium carbonate and levothyroxin, as well as enteral nutrition with hyperprotein, hypercaloric formula. He required treatment with serum albumin and erythropoietin. Moderate pulmonary valve stenosis and atrial septal defect were diagnosed in the cardiology study. The genetic study revealed mutations of the frameshift type for the NPHS1 gene, of the intronic variant type for the NPHS2 gene and of the missense type for the WT1 gene.

At three months of age he was readmitted due to convulsive status epilepticus secondary to severe hypocalcaemia. The high quantities of intravenous calcium which needed treatment via peripheral venous access caused a third-degree burn which required a cutaneous graft to be placed.

Intensive care was required on two occasions, at 4 and 6 months of age, for sepsis secondary to *Staphylococcus hominis* and *Enterococcus faecalis* respectively, which were resolved with empirical antibiotic treatment and then according to the results of the antibiogram.

Finally, the patient died at 8 months of age due to bilateral pneumonia linked to pneumothorax with decompensation of the underlying pathology which caused refractory hypoxaemia.

DISCUSSION

CNS may be suspected in the prenatal period due to high levels of alpha-fetoprotein, maintaining normal figures for cholinesterase from the 15th week of gestation in amniotic fluid and maternal blood.^{2,4} At birth the link between premature birth and a large placenta can provide guidance,⁵ factors which were not present in our patient.

The most frequent cause of this condition is the NPHS1 gene mutation,

with autosomal recessive inheritance, responsible for encoding nephrin.^{2,5,6} This alteration is particularly common in Finland, therefore it has been referred to as CNS of the Finnish type. The NPHS2 gene encodes the protein podocin and is the most common cause of cortico-resistance in childhood.⁷ The WT1 gene plays a crucial role in the embryonic development of the kidney and the genitals and has been linked to the presence of syndromes such as WAGR, Denys-Drash and Frasier.^{1,8} It is considered a monogenic condition and no cases have been described in the literature of more than two genes being implicated, therefore the clinical-pathological importance of the finding we have made in this case is not known.

The method of choice for its diagnosis is genetic analysis, although first secondary causes have to be discarded, such as congenital infections, autoimmune diseases or exposure to toxins during pregnancy.⁹ Knowing this can be useful in the patient's treatment, prognosis and monitoring, and is key to offering genetic counselling to the family.¹⁰ Renal biopsy does not reveal the causes of CNS, as histological findings can occur in various conditions.² CNS is not normally linked to heart malformations, with the exception of a high frequency of ventricular hypertrophy.¹¹ Our patient presented pulmonary valve stenosis and

atrial septal defect, defects scarcely written about in the literature.

The most frequent complications are bacterial infections, especially gram-negative microorganisms.² Our patient presented two septic infections due to gram-positive bacteria, findings that are less frequent but nonetheless described in other publications.²

The number of hospitalizations in these patients continues to be very high because it is difficult to treat and leads to complications, which reduces the patient's quality of life.¹² It is possible that multigenic involvement might entail greater clinical severity, but as there are no findings similar to ours in the literature we cannot confirm these speculations. The aim of treatment is to control the oedema, prevent and treat complications, and provide adequate nutrition to maximize growth and delay replacement therapy, although, in the majority of cases, kidney transplantation is the only curative method of treatment.^{3,5,6}

In conclusion, CNS is a rare, severe pathology that is difficult to treat, the causes of which can include various genes, which may have important implications on clinical severity and associated complications.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the contents of this article.

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Table 1. Analytical parameters upon admission

Parameter	Patient value	Reference values
Urea (mg/dl)	10	0-42
Creatinine (mg/dl)	< 0.2	0.2-1.3
Cholesterol (mg/dl)	226	60-190
Triglycerides (mg/dl)	372	< 155
Total proteins (g/dl)	2.95	5.10-7.30
Albumin (g/dl)	1.38	3.8-5.4
Sodium (mE/l)	125	129-143
Potassium (mE/l)	2.95	3.6-5.8
Calcium (mg/dl)	4.78	9.0-11.0
Phosphorus (mg/dl)	4.70	3.0-6.8
Immunoglobulin G (mg/dl)	44	250-750
Immunoglobulin A (mg/dl)	22.9	10-131
Immunoglobulin M (mg/dl)	149.6	10-70

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Multifactorial hypertension of nephro-urological aetiology. A case study

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To the Editor,

44-year-old patient, nurse, with no history of interest except hypertension (AHT) of 10 years progression, being treated with enalapril 30 mg, nicardipine 10 mg and hydrochlorothiazide 25 mg, without regular monitoring of blood pressure (BP). The patient sought consultation due to raised levels of BP (160-180/95-100mmHg) for 4-5 months with frequent hypertensive crisis that caused admission to the Emergency Department. The patient did not show signs of taking non-steroidal anti-inflammatory drugs, nor history of lithiasis or urinary infection, although chronic inguinal pain on the left side

contributed to dysmenorrhoea and no study was carried out. Examination revealed: body mass index 29 kg/m², BP 167/94 mmHg, 87 bpm, normal cardiopulmonary auscultation, enlarged abdomen and minimal bilateral malleolar oedema.

Complementary examinations were also performed, with the following results:

- Ambulatory BP monitoring (ABPM): diurnal average 151/80mmHg, 61bpm, pulse pressure 70.6mmHg; nocturnal average 137/70mmHg, 57bpm, pulse pressure 66.8mmHg. Maximum diurnal BP 183/99mmHg, maximum nocturnal BP 171/95mmHg. Non-dipper BP pattern.
- Electrocardiogram: sinus rhythm 72bpm; Sokolow-Lyon index <35mm; asymmetric reversal of T-wave.
- Echocardiogram: interventricular septum 12mm.
- Normal thoracic radiographs.
- Normal funduscopy.
- Abdominal ultrasound: right kidney (RK) 13cm, normal differentiation; left kidney (LK) 25cm, hydronephrotic, without corticomedullary differentiation.
- Biochemical tests showed: normal haemogram, hepatic lipid profile, uric acid, ions and glycemia. Urea: 31mg/dl, creatinine 0.79mg/dl, glomerular filtration rate (MDRD-4) >60ml/min/1.73m².
- Plasma renin activity (PRA) 1.35ng/ml/h (normal radioimmunoassay range 0.2-3.3ng/ml/h).
- Urine: proteinuria 0.11g/24hr, creatinine 161mg/d, Na 241mEq/l, fractional excretion of Na 0.78%. Sediment: 5 red blood cells/field, 30 leukocytes/field, negative nitrites; creatinine clearance 113ml/min.
- CT Angiogram (axial computed tomography): lithiasis and maximum ureterohydronephrosis on the left side that caused traction of the ipsilateral renal artery (Figure 1).
- Technetium Tc 99m Dimercaptosuccinic Acid Scintigraphy: DR 100 %, IR 0 %.

The patient was diagnosed with moderate risk stage 2 HBP, initially of renovascular aetiology and failure of the RK, and it was decided to carry out laparoscopic nephrectomy on the left side which went smoothly. The anatomical pathology of the specimen reported a hydronephrotic kidney with lithiasis, chronic pyelonephritis in the stage of exacerbation, acute fibrinohemorrhagic pyelonephritis, uriniferous cysts and chronic erosive urethritis (Figure 2).

Progress from a clinical point of view was favourable. Renal clearance and creatinine slightly and temporarily deteriorated following nephrectomy, returning to their baseline levels in less than 15 days. BP dropped significantly. Postoperative renogram revealed a RK with good vascularisation and radiotracer uptake capacity, as well as adequate response to the diuretic. Sequential images and the renographic curve showed adequate elimination, without ectasia or obstructive behaviour. At present, three years after surgery, BP remains well controlled (self-measurement and ABPM) with lecanidipine 20mg/day (10mg in the summer), and presents 1.1mg/dl of creatinine, clearance of 71ml/min and proteinuria 0.09g/day. The patient has not re-experienced inguinal pain.

DISCUSSION

Nephrolithiasis, in spite of techniques such as ureteroscopy, lithotomy or lithotripsy, is one of the causes that lead to the development of chronic renal failure.¹ The asymptomatic form is more frequent than expected, reaching 11 % prevalence in a study carried out in potential donors.² The evolution of these "healthy carriers" of nephrolithiasis has not been studied, the risk of chronic kidney disease being controversial, which seems to relate to the size, the composition and the location of the calculus, among other factors.³⁻⁷ The same occurred with the asymptomatic bacteriuria, whose need for antibiotic and/or surgical treatment is dependant on, in addition to microbiology and the age of the patient, the existence or not