Adolescent with Alport syndrome and congenital hemolytic anemia

Adolescente con síndrome de Alport y anemia hemolítica congénita

Abbreviations: BP, Blood pressure; HR, Heart rate; BPM, Beats per minute; HIV, Human immunodeficiency virus; HCV, Hepatitis C virus; HBV, Hepatitis B virus.

Alport syndrome is characterized by hematuria, proteinuria, progression to chronic kidney disease, sensorineural hearing loss and ocular disorders, manifestations related to pathogenic nucleotide variants in type 4 collagen. Over time, it may present anemia in relation to chronic kidney disease, without evidence of hemolysis. Hereditary spherocytosis is a congenital hemolytic anemia due to mutations in genes encoding erythrocyte membrane proteins, including ankyrin (autosomal dominant inheritance in 75% of cases).

13-year-old woman with pallor, asthenia and febrile catarrhal episode (48 h of evolution). Weight 47 Kg (37th percentile), height 153 cm (26th percentile), BP 112/54 mmHg (lower 90th percentile),[1] HR 96 BPM, Tanner Stage 5.[2] Did not look well, cutaneous-mucosal pallor. Jaundice, malar hypertrophy and splenomegaly. Personal history highlights: Peruvian origin, admitted for non-immune jaundice (first 24 h of life), diagnosis of hemolytic anemia at 5 years, hemoglobin 8–10 g/dL, has required a transfusion. Family history includes: mother 36 years, 3 gestations (case G1, twin G2, G3), Abortions 0, 3 live births, mild iron deficiency anemia, serum creatinine 0.72 mg/dL, albumin/creatinine urine 0.56 mg/mmoL, no hematuria, no hearing loss or eye disorders; father unknown history; no consanguinity; healthy male siblings 11 and 9 years (normal blood/urine analysis, no hearing loss), brother died at 2 months due to pneumonia (previously healthy).

The following tests were performed upon admission: positive PCR for influenza B, ultrasound (kidneys normal size and echogenicity, cholelithiasis, splenomegaly of 18 cm), blood count (hemoglobin 5.1 g/dL, VCM 80 fL, reticulocytes 10%, smears: spherocytes), Coombs direct negative, blood biochemistry (urea 131 mg/dL, creatinine 1.77 mg/dL, potassium 3.9 mmoL/L, total bilirubin 1.3 mg/dL (direct 0.5 mg/dL), haptoglobin 0 mg/dL; ferritin 686 ng/mL, calcidiol 12,5 ng/mL), serology (HIV, HCV and HBV negative, IgG Parvovirus positive, IgM negative), urine (density 1007, pH 5, protein positive, red blood cells positive, red blood cells 12 cells/field; protein/creatinine 122 mg/mmol).

Red blood cell concentrate is transfused. Diagnosis of bilateral sensorineural hearing loss, no ocular alterations. Serum creatinine decrease to 1.23 mg/dL (stable >3 months), cystatin C 2.19 mg/L (estimated glomerular filtrate Schwartz[3] 51.37 mL/min/1.73 m^2, Chehade[4] 41.52 mL/min/1.73 m^2, creatinine clearance 47.85 mL/min/1.73 m^2). Associated hyperuricemia, serum phosphorus 4.5 mg/dL, PTH 84.9 pg/mL, polyuria (volume by renal glomerular filtration-FGR-3.6 mL/100 mL FGR), urinary osmolality 393 mOsm/L, protein/creatinine 113 mg/mmol and microscopic hematuria.

The suspected diagnosis is congenital hemolytic anemia (spherocytosis) and chronic kidney disease stage 3 (Alport syndrome). Clinical exome is performed: two variants in heterozygosity:

- *COL4A3* gene: exon 30, chromosome 2: g.227280441 of NM_000091.3, variant not previously described. A deletion that causes a premature stop codon. Probably pathogenic variant. Alport syndrome, autosomal dominant (OMIM 104200).
- *ANK1* gene: exon 26, chromosome 8: g.41696520 G > A NM_020476.2. Substitution of the amino acid arginine at position 935 of the polypeptide chain with a premature stop codon. Variant described in patients with hereditary spherocytosis with an autosomal dominant inheritance pattern (OMIM 182900).[5]

Segregation study (study of relatives except the father): mother and 9-year-old brother are carriers in heterozygosis of variant c.2225 of the *COL4A3* gene of the index case; non-carriers of the *ANK1* gene variant. Brother 11 years: not carrying either variant.

Treatment with calcidiol, calcium carbonate, folic acid and ursodeoxycholic acid, enalapril as an antiproteinuric (withdrawn due to asthenia and feeling of instability). After 5 months splenectomy and cholecystectomy are performed with normalization of red blood cells. The objective of the surgery is to reduce transfusions that could sensitize the patient to a future kidney transplant and improve adherence to antiproteinuric treatment, which we restarted without incident.

The coexistence of Alport syndrome with hemolytic anemia in a contiguous gene syndrome has been previously described: AMME (Alport, Mental retardation, Midface hypoplasia and Elliptocytosis) associated with microdeletions

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in the Xq22.3 region.[6,7] However, in our case the neurological assessment was normal, the facial alterations (malar hyperplasia) were attributed to extramedullary hematopoiesis and the alterations in the peripheral blood smear were suggestive of spherocytosis (not elliptocytosis).

So far no previous case with coexistence of Alport syndrome and hereditary spherocytosis has been described. Thanks to advances in genetic techniques, both pathologies are diagnosed with a single assay (clinical exome). The management of chronic hemolytic anemia can improve survival of future renal transplant, decreasing the patient's sensitization with transfusions. In addition, splenectomy (and normalization of serum hemoglobin levels) appears to improve tolerance to the antiproteinuric.

We describe a new unknown mutation in *COL4A3*. The absence of clinical-analytical alterations in the mother and sibling affected by the same mutation in *COL4A3* has been previously described (poor genotype-phenotype correlation even in families with the same mutation)[8] and may be due to environmental factors or other unknown genetic alterations. Since we have not been able to study the father, we do not know whether the *ANK1* mutation is de novo or inherited.

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Conflict of interest

The authors declare that they have no competing interests.

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