

Coagulation disorder and persistent microhematuria in a 17-year-old male patient

*Alteración de la coagulación y microhematuria persistente
en un varón de 17 años*

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Abstract

We report the case of a 17-year-old male patient with constant alteration of the prothrombin time and episodes of self-limited macrohematuria. After several studies we found out a deficiency of Factor X levels, whereas all other coagulation factors levels were normal. We continued with the study of the hematuria with urine and blood analysis, imaging tests and viral serologies, which finally made it possible to rule out any other primary or secondary glomerulopathies and to focus on IgA nephropathy as the most likely diagnosis.

In this release we explain in detail the diagnostic tests performed. We have also reviewed the two entities separately and together, in search of a genetic disease which associates both pathologies.

Palabras clave: Hematuria. Déficit de Factor X. Nefropatía por IgA.

Keywords: Hematuria. Factor X deficiency. IgA nephropathy.

Factor X(FX) is a protease which requires vitamin K for its synthesis, which takes place in the liver. It plays an essential role in the coagulation system since it is the first enzyme of the common pathway and the most important activator of the prothrombin¹. FX deficiency may be congenital or acquired (through vitamin K deficiency, treatment with anticoagulant drugs, severe hepatopathies, multiple myeloma, tumors, drugs, infections or amyloidosis)².

In children, hematuria is a sign of disease, malformation or lesion in the urinary tract. Most diseases which affect the urinary system involve microscopic or macroscopic hematuria at some stage in their evolution, and its origin may be found in the kidney (glomerulus, tubules, interstitium, vessels) or at any level of the urinary tract (from the calyces to the anterior urethra). Its causes may be congenital (hereditary or not) or acquired, and it may have a very varied nature (infection, immunological alteration, metabolism, tumor, etc). It is commonly classified into two large groups: glomerular and non-glomerular hematuria³.

We report the case of a 17-year-old male patient who presented with constant alteration of the prothrombin time as well as with self-limited episodes of macrohematuria with persistent microhematuria.

The patient was referred to the Service of Internal Medicine upon finding that from childhood he had presented with episodes of self-limited macrohematuria without any other accompanying symptom, and with normal results in the physical examination. The urine analysis revealed microhematuria without proteinuria or erythrocyte dysmorphism, and a prothrombin activity in blood of 54%, with normal results in the rest of the analysis. A wider study of coagulation showed that

the activated partial thromboplastin time was normal, and in the assessment of coagulation factors, the levels of active FX were 41% (normal values in laboratory between 60-120%). All other factors were normal. In order to define the etiology of the FX deficiency, we ruled out the main causes of acquired deficiency, and we suspected a hereditary disorder. We carried out a genetic study of the patient and his mother (paternal serum could not be analyzed). The analysis of the panel for the diagnosis of hereditary bleeding diathesis through next-generation sequencing technology revealed 2 genetic variants in the FX gene which led to compound heterozygosity. In exon 5, the change of the c.424G>A nucleotide led to the amino acid change p.Glu142Lys (described by Marchetti G et al)⁴, which affected the catalytic domain of the FX (Figure 1). In exon 8, the change of nucleotide c.1351A>C caused a new change of amino acid p.Ile451Leu (this amino acid change was also found in the mother, who did not present with an alteration of FX) (Figure 2).

Since the factor X deficiency was mild and did not justify the hematuria of the patient, we continued with our study. A complete study of urine was carried out with systematic analysis and analysis of sediment and erythrocyte morphology and assessment of calciuria and proteinuria, which were normal, with the only exception of the persistent microhematuria. Imaging studies were also performed: abdominal ultrasound, magnetic angioresonance and intravenous urography, which ruled out any structural alterations in the kidneys. The autoimmunity study, complement study and viral serologies were normal, which finally made it possible to rule out any other primary or secondary glomerulopathies and to focus on IgA nephropathy as the most likely diagnosis (benign familial hematuria seemed

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Fig 1. Exon 5, change in the nucleotide c.424G>A.

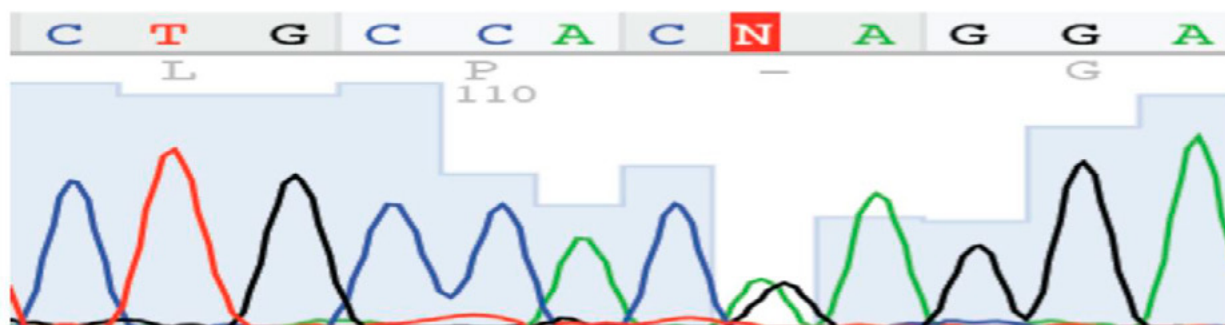
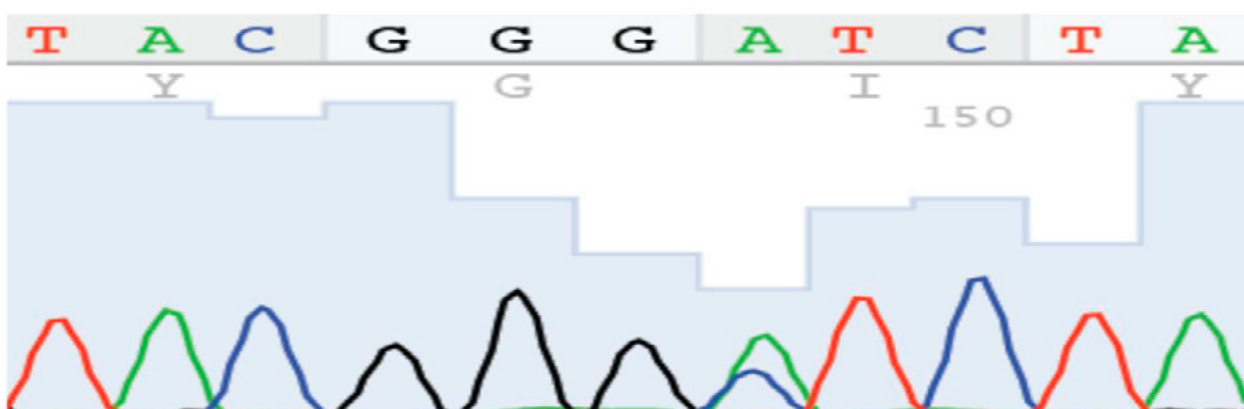


Fig 2. Exon 8, change in the nucleotide c.1351A>C.



less likely due to its rare incidence, but it was not completely ruled out because the paternal branch of the family could not be contacted).

Congenital deficiency of factor X is a rare coagulation disorder with an autosomal recessive inheritance pattern. The prevalence of homozygous deficiency is approximately 1 case per 1 million people in the general population, whereas the heterozygous deficiency appears in 1:500 people¹. The factor X gene has 22 kb and is located in chromosome 13, more specifically in locus 13q34-ter, 2.7 kb beyond the gene of factor VII with which it maintains a close relation. Its structure is similar to that of other vitamin K-dependent proteins: the sequence of the gene is divided into 8 exons, each of which encodes a specific domain inside the protein (the signal peptide, the catalytic domain, etc.)⁵. More than 100 mutations have been described, most of which affect exon 8. The diagnosis is based on the measurement of the coagulating activity of factor X (FX:C) through prothrombin time and aPTT, as well as through the measurement of factor X antigen plasma levels (FX:Ag). Therefore, we can establish a difference between type I deficiency, when there is a parallel decrease in the figures of FX:C and FX:Ag, and type II deficiency, when there is a discrepancy between low values of FX:C and normal or elevated levels of FX:Ag.⁶

Clinical manifestations depend on the circulating levels of active factor X. A deficiency with activity below 20% is considered severe, and it may be accompanied by hemarthrosis, intracranial bleeding in the neonatal period, hematuria, etc¹. In these cases it may be convenient to use prothrombin complex, which contains factor X, and which is effective in these patients and improves their symptoms⁶. Our patient showed a factor X level of 41%, which was classified as a mild deficiency which consequently did not require treatment, because it is not normally associated to spontaneous hemorrhage⁷.

IgA nephropathy has an excellent clinical evolution in most cases. Several studies have shown that, when microhematuria is accompanied by normal kidney function and absence of proteinuria (as in the case of our study), a progression towards kidney failure appears in few cases. Therefore, a renal biopsy is not recommended as part of the diagnostic study⁸. It is advisable to keep the patient under close monitoring in case that arterial hypertension or proteinuria may appear during the evolution, because they are prognostic markers of a progression towards kidney failure, and in those cases a renal biopsy would be indicated⁸.

It is worth mentioning the question of the association between nephropathy and factor X deficiency. A search in Pubmed returned only one article which described the case of a patient

with membranoproliferative glomerulonephritis and factor X deficiency⁹. There is no genetic disease described which associates both pathologies and, therefore, we believe that there is no such association, and that it is a casual finding when studying the coagulation of a patient with hematuria.

Therefore, we conclude that our patient had a congenital mild deficiency of coagulation factor X caused by a double heterozygosis in the gene of the factor and probably a concomitant and independent IgA nephropathy which caused a persistent microhematuria which was not related to the coagulation alteration, because the figures of active factor X did not justify the hemorrhagic symptoms.

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