**Interesting Case**

**Double nucleotidic mutation of the MYH9 gene in a young patient with end-stage renal disease**

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**Introduction**

Alport’s syndrome, a renal disorder with inherited transmission, is characterized by ultrastructural changes of glomerular basement membrane and basement membranes elsewhere. A progressive haematuric nephritis, sensorineural hearing loss and familial occurrence in successive generations are typical of this disorder. X-linked dominant inheritance is quite frequent (85–90% of the families) [1].

Alport-like syndromes identify a group of diseases characterized by thrombocytopenia with ‘giant platelets’ and autosomal dominant transmission. Their distinguishing features consist of the presence of nephritis, cataracts, hearing loss or deafness with or without leucocytic intracytoplasmatic inclusions (named ‘Dhole bodies’). This group of diseases includes: the May–Hegglin anomaly, Fechtner syndrome, Sebastian syndrome and Epstein syndrome. Unlike in Alport’s syndrome, the genetic mutations linked to this group of disorders are in the human non-muscle myosin IIA heavy chain gene (MYH9) [2].

The May–Hegglin anomaly is a rare autosomal dominant disorder characterized by abnormally large platelets, leucocytic inclusions and thrombocytopenia, which predisposes patients to bleeding disorders [3]. The Sebastian and Fechtner syndromes share these features, but patients with the Fechtner syndrome also show high-tone sensorineural deafness, cataracts and nephritis [4], while the May–Hegglin anomaly and Sebastian syndrome are differentiated by an ultrastructural examination of leucocyte inclusions. The Epstein syndrome consists of deafness and nephritis in the absence of cataracts and leucocytic inclusions [2].

**Case**

A 27-year-old girl was admitted to our renal unit with hypertension, thrombocytopenia, proteinuria (non-nephrotic range), microhaematuria and a creatinine of 3.3 mg/dl. She had been diagnosed with thrombocytopenia when she was 1 year old; bilateral hearing loss was found at the age of 6 years. When she was 14 years old, she was treated with steroids after a bone marrow biopsy following a fall in her platelets’ number. She was suspected of suffering from an autoimmune disease. She was found, by ultrasonic tomography, to have (congenitally) only the right kidney. At the age of 19, the occurrence of a mild chronic renal failure with hypertension, probably related to the renal disease, indicated a renal biopsy which the patient refused. Consequently, she was diagnosed as suffering from Alport’s syndrome by exclusion of other diseases. Laboratory tests showed normal immunoglobulins, C3 and C4. The Coombs test, anti-platelet antibodies, anti-nuclear antibodies, extractable nuclear antibodies, anti-mitochondrial antibodies and anti-smooth muscle antibodies were found to be negative. A blood smear, examined within 4 h, was negative for leucocyte inclusion bodies.

In our unit, she underwent clinical and metabolic evaluations. Echocardiography showed an aneurysm of the interatrial septum. She was started on a low protein diet along with anti-hypertensive therapy with calcium antagonists and ACE inhibitors. Her renal function had been stable during the following 2 years. She did not have cataracts. Later, because of worsening renal function, an A-V fistula was created and haemodialysis was started. During the screening for renal transplantation, given the patient’s age, a more complete evaluation was required to exclude nephropathies with high rates of recurrence. Thus, further examinations were performed, including genetic analysis for the gene...
Table 1. The clinical features of Alport’s syndrome, May–Hegglin anomaly, Sebastian syndrome, Fechtner syndrome and Epstein syndrome

<table>
<thead>
<tr>
<th>Feature</th>
<th>Alport</th>
<th>May–Hegglin</th>
<th>Sebastian</th>
<th>Fechtner</th>
<th>Epstein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giant platelets</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Leucocyte inclusions (Döhle-like bodies)</td>
<td>–</td>
<td>+&lt;sup&gt;a&lt;/sup&gt;</td>
<td>+&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Deafness</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cataracts</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Nephritis</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Autosomal dominant transmission (MYH9)</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>X-linked transmission</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

<sup>a</sup>Paracrystalline highly parallel bodies.
<sup>b</sup>Smaller and less organized bodies.

Discussion

Some scientists believe that a clear distinction of the clinical features of the May–Hegglin anomaly, Sebastian syndrome, Epstein syndrome and Fechtner syndrome is impossible. When carefully studied, most patients suffering with the May–Hegglin anomaly or Sebastian syndrome in fact have one or more of sensorineural deafness, microhaematuria or cataracts. In addition, the relatives of patients with the Epstein or Fechtner syndromes can have clinical features that justify a diagnosis of the May–Hegglin anomaly or Sebastian syndrome, because they do not show any significant eye, ear or kidney impairment. Furthermore, the distinction between the Epstein and Fechtner syndromes is not clear, since identifying the intracellular spots depends on their dimensions, and can be subjective. As a matter of fact, cases of Alport-like syndromes (the few cases presenting autosomal recessive or dominant traits) are considered cases of the Fechtner syndrome in the presence of Döhle bodies coupled with macrothrombocytopenia, or Epstein syndrome when no leucocytic inclusions are detected. Molecular biology therefore has a relevant role in the classification and differentiation of these disorders. Alport’s syndrome and the Fechtner or Epstein syndromes in fact are currently considered different entities even though they have similar clinical features. We know that Epstein syndrome and Fechtner syndrome are not genetically related to Alport’s syndrome because they are the result of MYH9 mutations. On the other hand, MYH9 mutations have been also described in the May–Hegglin anomaly and in the Sebastian syndrome, two autosomal dominant forms of isolated macrothrombocytopenia with Döhle bodies in leucocytes and without nephropathy.

The genetic analysis of our patient showed the presence of a double nucleotidic mutation in the MYH9 gene: the first one has been identified inside the 21st exon (2728 A→C) that results in a substitution of a lysine with a glutamine [codon no. 910 (K910Q)]; the second one corresponds to a gene mutation already identified [5] in a family with the Fechtner syndrome, consisting of 4270 G→C, resulting in a substitution of an aspartic acid with a histidine at codon no. 1424 (D1424H). Neither mutation was found in any of 50 normal subjects who were also analysed. Interestingly, the genetic analysis of the patient’s mother revealed the presence of the mutation of the 21st exon which was not found in her father. The novelty of our finding is the presence of another mutation (never before reported in the literature) in a gene that already presents a previously reported mutation. It is not possible to assert that the double mutation in the MYH9 gene caused the hypoplasia of the inferior vena cava and the presence of a single kidney in our patient. The patient’s mother had only microhaematuria as a sign of renal impairment with otherwise normal renal function and with no abnormalities in platelets’ size and number. She did not have proteinuria or cataracts. (Renal biopsy was not performed and her blood smear was not studied.)

In conclusion, while the double mutation in the MYH9 gene of our patient was associated with...
Double mutation in the MYH9 gene in a young patient with CRF end-stage renal disease, only asymptomatic haematuria was observed in her mother, in whom a single mutation in the same gene was found. The condition of our patient can be called an ‘autosomal dominant hereditary nephritis with haematological abnormalities’.

Conflict of interest statement. None declared.

References


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