Case Report

Factor H deficiency and fibrillary glomerulopathy

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Factor H deficiency is reported infrequently, however, it has been associated with a variety of renal diseases [1]. Here we report the second case of factor H complement deficiency presenting with fibrillary glomerulonephritis.

Case

A 12-month-old boy presented to a local hospital with periorbital oedema and microscopic haematuria. He was pale and hypertensive and had low serum complement C3. He was treated for and followed with the diagnosis of acute post-streptococcal glomerulonephritis. The patient’s parents were second-degree relatives of each other, but his family history was entirely negative for renal disease, hypertension and anaemia. When he was 17 months, he was referred to our unit for persisting haematuria and periorbital oedema. Physical examination revealed a pale, oedematous boy with a blood pressure of 180/90 mmHg.

His laboratory values included: urea 35 mg/dl, creatinine 0.54 mg/dl, albumin 4.3 g/dl, cholesterol 175 mg/dl, haemoglobin 6.3 g/dl, MCV 77.7 fl, reticulocyte count 0.52%. His platelet count was normal, and a peripheral blood smear showed no evidence of microangiopathy. The direct Coombs’ test was positive; the test for cold agglutinins was negative. Urinalysis revealed haematuria and proteinuria. Creatinine clearance (Ccr) was 122 ml/min/1.73 m², serum cholesterol of 242 mg/dl, urea 53 mg/dl, creatinine 0.3 mg/dl, haemoglobin 9.2 g/dl and albumin 3.8 g/dl. He was treated with 30 mg/kg doses of i.v. methyl prednisolone for 3 days, and afterwards with i.v. 500 mg/m² cyclophosphamide—monthly six times—and prednisolone 1.5 mg/kg/day on alternate days. Enalapril was prescribed for hypertension. Microscopic haematuria and nephrotic-range proteinuria persisted over the 6 months of this therapy. He required hospitalization to control a sudden severe hypertensive crisis at the end of 6 months; and his blood pressure was regulated with 2 mg/kg/day nifedipine, 25 mg/day atenolol and 0.5 mg/kg/day enalapril. Microhaematuria and nephrotic-range proteinuria persisted with high serum cholesterol, but he still had a normal Ccr.

A second renal biopsy was performed at the age of 2.5 years. Cyclosporine A (CyA) at a dose of 5 mg/kg was started, and alternate-day prednisone, nifedipine, enalapril and atenolol were continued. Serum cyclosporine levels were controlled against C₀ and C₂ levels. Cyclosporine doses were adjusted to maintain C₀ < 50 ng/ml and C₂ around 400 ng/ml. At the end of the second week, when C₀ was 15 ng/ml and C₂ was 434 ng/ml, urine protein began to decrease from the nephrotic-range, and microscopic haematuria disappeared. After 3 months of cyclosporine therapy, urine was protein-free and serum albumin and cholesterol normal; therefore, prednisolone and anti-hypertensive drugs were decreased gradually. CyA therapy was terminated at the end of 15 months of follow-up when he was 3.5 years old. He is still being followed-up, and has been on no medications for 6 months. His blood pressure, Ccr, serum cholesterol and serum albumin are at normal levels and his urine is protein-free; but he still has low complement—C₃ (160 mg/l).
Methods

Some elements of the complement system (CH50, AP50, C3, B, C5, H, I, P) were studied by the Centre Hospitalier Universitaire de Grenoble, Laboratoire d’Immunologie. Serum C3 and B were measured with a nephelometric technique (Dade Behring, Paris La Defense, France). Serum factor H was measured by radial immunodiffusion (antiserum from Bio-Rad, France). Tissues from the two biopsy specimens were processed for light and immunofluorescence microscopy. In addition, tissue from the second renal biopsy specimen was processed for electron microscopy.

Results

The patient’s pedigree is shown in Figure 1. His parents are second-degree relatives. The complement system of the family is profiled in Table 1. The father and the second sister, who were healthy and did not have proteinuria, have half the normal levels of factor H while the mother and the first sister have levels in the lower normal range. The data indicate a heterozygous carrier state. The proband, who has almost undetectable levels of factor H, probably has inherited two defective alleles, one from each parent.

The pathologic results of the first and second renal biopsies were as follows.

Biopsy 1 under light microscopy yielded 18 glomeruli, which included two globally sclerotic glomeruli. The others were severely lobulated with mesangial hypercellularity. Capillary loops were obliterated with diffuse thickening of the basal membranes and showed double contour. Necrosis, thrombosis and crescents were absent. Immunofluorescence studies showed granular staining of the glomerular basement membrane for C3.

Biopsy 2 under light microscopy yielded 40 glomeruli under light microscopy, which included seven globally sclerotic glomeruli. The others showed mesangial hypercellularity, capillary obliteration, basal membrane thickening and duplication. Immunohistochemical studies showed severe granular C3 staining of glomeruli, basal membranes and the mesangium. Ultrastructural examination (electron microscopy) revealed glomerular basement membrane thickening and lamellation. No electron-dense deposits were identified. Mesangial hypercellularity and matrix increase was present. Mesangial areas and basal membranes showed thin

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Table 1. Serum complement profile of the familya

<table>
<thead>
<tr>
<th></th>
<th>CH50</th>
<th>AP50</th>
<th>C3</th>
<th>B</th>
<th>C5</th>
<th>H</th>
<th>I</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>82–102%</td>
<td>84–150%</td>
<td>825–1140 mg/l</td>
<td>140–200 mg/l</td>
<td>120–160 mg/dl</td>
<td>80–120% of reference</td>
<td>80–120% of reference</td>
<td></td>
</tr>
<tr>
<td>Mother</td>
<td>102</td>
<td>34</td>
<td>1280</td>
<td>211</td>
<td>144</td>
<td>72</td>
<td>150</td>
<td>144</td>
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<tr>
<td>Father</td>
<td>80</td>
<td>29</td>
<td>1000</td>
<td>124</td>
<td>128</td>
<td>57</td>
<td>120</td>
<td>83</td>
</tr>
<tr>
<td>1st daughter</td>
<td>95</td>
<td>71</td>
<td>1310</td>
<td>170</td>
<td>144</td>
<td>74</td>
<td>130</td>
<td>121</td>
</tr>
<tr>
<td>2nd daughter</td>
<td>93</td>
<td>83</td>
<td>881</td>
<td>163</td>
<td>101</td>
<td>48</td>
<td>110</td>
<td>120</td>
</tr>
<tr>
<td>3rd daughter</td>
<td>93</td>
<td>85</td>
<td>1740</td>
<td>178</td>
<td>141</td>
<td>135</td>
<td>110</td>
<td>134</td>
</tr>
<tr>
<td>The son (patient)</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>80</td>
<td>44</td>
<td>97</td>
<td>&lt;10</td>
<td>170</td>
<td>35</td>
</tr>
</tbody>
</table>

aStudied in CHU Grenoble, Laboratoire d’Immunologie, France.
Discussion

Haemolytic uraemic syndrome (HUS), MPGN, collagen type III glomerulopathy and systemic lupus erythematosus (SLE) have been reported in association with homozygous factor H deficiency, whereas Ig A nephropathy, vasculitis and HUS have been reported associated with heterozygous factor H deficiency [2–4]. The functions and functional moieties of factor H are numerous. Caprioli’s report might lead to the speculation that different point mutations could lead to different renal histopathologies [5].

To date, factor H deficiency has been reported in association with MPGN in five patients. Levy et al. [6] reported two Algerian brothers with low normal plasma factor H levels and type II MPGN. Lopez-Larrea et al. [7] reported a kindred with three factor H deficient siblings, all of whom had MPGN. Other reported factor H deficient cases had HUS and SLE [2].

Only Vogt et al. [8] have described type III collagen glomerulopathy in a factor H deficient child. He was a native American child who at 13 months of age presented with hypertension, anaemia, haematuria, proteinuria and hypocomplementaemia. His plasma complement profile revealed undetectable factor H levels. Renal biopsy showed mesangial hypercellularity, endothelial proliferation and thickening of the capillary loops with double contouring. In addition, there was endothelial cell swelling and sub-endothelial widening by multiple layers of membrane-like material. Immunofluorescence studies showed minimal staining for C3 in the mesangium, capillary loops, and along the basement membrane. However, there was abundant staining for type III collagen in the mesangium and capillary loops. This patient was followed-up without immunosuppressive therapy, and progressed to renal failure over a 5-year period.

Although the immunofluorescence study of our patient’s biopsy revealed granular staining of the glomerular basement membrane for complement C3 and light microscopy gave the impression of MPGN, electron microscopy excluded MPGN (absence of electron-dense deposits) and revealed thin non-amyloid fibrillary materials. Our findings in light microscopic, immunohistochemical and electron microscopic evaluations resembled those of Vogt et al. [8], but we did not have the chance to stain for anti-type-III collagen.

In the reports by Vogt [8] and Levy [6], both patients presented with anaemia without the histopathologic features of HUS. Our case also did not show the histopathologic features of HUS—with low-grade haemolysis and anaemia recalling complement-mediated haemolysis without microangiopathy. It could be speculated that decreased factor H levels most likely induce decreased factor H binding on the surface of red blood cells, with consequent decreased inhibition of local C3 activation and complement-mediated red blood cell damage.

Our patient’s proteinuria and haematuria remitted with CyA, although anaemia persisted with normal GFR and normal serum creatinine during a 3-year period of follow-up. CyA has been reported to have beneficial effects in improving renal function and delaying the onset of renal failure in canine X-linked Alport syndrome and human Alport syndrome [9,10]. Reduced glomerular filtration pressures and reduced matrix degradation could have been the protective mechanisms underlying the outcome. Pickering et al. [11] showed that mice deficient in factor H spontaneously develop MPGN, and are hypersensitive to developing renal injury caused by immunocomplexes. This information invites the supposition that CyA influenced our patient through its immunosuppressive effect. Nevertheless, electron microscopy did not show any electron-dense deposits to prove this idea, for it only found thin non-amyloid fibrils. Therefore, the efficacy of CyA is assumed to be related to its intrarenal protective effects. Our patient is still in remission. It is obvious that CyA therapy is effective in this form of glomerulopathy, although the mechanism of its action is unclear.

In conclusion, factor H deficiency leads to several distinct histopathologic forms of renal disease with different prognoses. It seems that anaemia is a common finding, and CyA therapy is effective for the prevention of the progression of renal failure in fibrillary glomerulonephritis.

Conflict of interest statement. None declared.

References


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