Concise Report

Clinical variability and characteristic autoantibody profile in primary C1q complement deficiency

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Objectives. C1q deficiency is a rare inherited defect in the early part of the complement cascade. In this report, we describe the varied clinical features of patients with this condition as well as the characteristic autoantibody profile.

Methods. A large Pakistani family with a high degree of consanguinity is described in which the father and five sons have C1q deficiency, all with different clinical manifestations.

Results. Clinical features of C1q deficiency can vary from almost no disease to fulminant bacterial infection and localized lupus-like skin, renal or CNS disease. Autoantibodies to ribonucleoproteins such as anti-Sm and Ro, but not dsDNA, were present.

Conclusions. Awareness of the spectrum of clinical disease, autoantibody profiles and tests required to confirm the diagnosis of C1q deficiency are important if this life-threatening immunodeficiency disease is to be managed correctly.

Key words: C1q, Complement, SLE, Vasculitis, Meningitis.

Introduction

C1q deficiency is a rare defect of the first component of complement. C1q normally binds immune complexes and apoptotic cells and promotes their removal from the circulation. Patients with C1q deficiency have an increased risk of fulminant infections with encapsulated bacteria, particularly Streptococcus pneumoniae. Because of the patient’s inability to clear immune complexes and cellular debris [1], they also have an increased risk of autoimmune disease, particularly SLE, as we first reported in 1980 [2]. When we reviewed the literature in 2002, 38 of 41 documented cases (92%) of C1q deficiency had developed this autoimmune complication [3].

In this report, we describe the clinical variability in primary C1q deficiency in a further six patients who present a clinical spectrum from being very well, through mild skin disease (recurrent angioedema or discoid lupus), to the development of chronic glomerulonephritis and renal failure, an acute CNS SLE-like vasculitis, and finally fulminant pneumococcal meningitis. A characteristic autoantibody profile of these patients is presented, as is a possible explanation for the predilection to the CNS in the one case.

Patients and methods

Complement assays

Levels of complement components C1q, C4 and C3 were measured immunochemically by the single radial-diffusion technique with monospecific antisera. CH50 was estimated with the method of Mayer [4].

The proband was the youngest of six brothers who presented at the age of 10 yrs acutely encephalopathic with a global dysphasia, quadra and bulbar paresis, generalized hypertonia and a resting tremor. There was a prodrome of a 5-week history of vomiting, diarrhoea and high fevers up to 40°C, but no specific pathogens were isolated from his stools or blood. Previously he had developed bacterial meningitis at the age of 3 yrs requiring 2 days in intensive care. This had left him with a sensorineural deafness but able to function in mainstream school. At presentation he had an unremitting fever, painful mouth ulcers, a malar rash and the neurological signs detailed above. Blood cultures, ESR, urinalysis and renal function were normal. CSF protein was raised (1.7 g/l), but CSF glucose, PCR for herpes simplex and bacterial pathogens were normal. An MR scan of his brain showed bilateral infarction of his basal ganglia suggestive of a small vessel vasculitis (Fig. 1). He was initially treated with high-dose (30 mg/kg) pulse intravenous methylprednisolone for 3 days with some improvement but as the corticosteroid dose was weaned his fever, mouth ulcers and malar rash recurred and his neurological condition deteriorated. He was therefore started on pulse intravenous cyclophosphamide (500–750 mg/m²/1–3 monthly) as well as high dose (1–2 mg/kg/day) oral corticosteroids and 150mg/day hydroxychloroquine in accordance with current recommendations for treatment of neuropsychiatric SLE [5]. On this treatment his symptoms slowly improved and he is now talking, mobile and back at school. Immunological investigations initially showed raised ESR, ANA, Ro and anti-Sm but not dsDNA, autoantibodies (Table 1). Autoantibodies to cardiolipin, Jo-1, PM-1, Scl-70, RNP, ANCA, mitochondria and smooth muscle were all negative. CH50 was undetectable as was his C1q, but C2, C3, C4 and AP100 were normal. A diagnosis of primary C1q complement deficiency was made, and the proband’s family was screened (Fig. 2).

Because of the high risk of further bacterial infection with the combination of C1q deficiency, immunosuppressant drug therapy and suboptimal pneumococcal antibody levels, he was started on prophylactic amoxicillin as well as replacement immunoglobulin therapy (0.4 g/kg/3 weeks).
The family are very consanguineous with his mother and father, as well both sets of grandparents having married their cousins. His mother is well and has normal Clq levels (82%).

**Father (Ia).** The proband’s father initially presented with abdominal pain, severe hypertension (blood pressure 200/120 mm Hg) and chronic renal failure at the age of 18 yrs. A renal biopsy showed non-specific end-stage chronic glomerulonephritis and he was started on renal dialysis. He also had seizures and a right hemiparesis which were thought to be due to hypertension, as well as an erythematous facial rash for which he saw a local consultant dermatologist but no specific diagnosis was made. At the age of 24 yrs he had a successful cadaveric renal transplant. In subsequent years he was increasingly troubled with coronary vascular disease and heart failure and died in 1998 at the age of 38 yrs of an acute myocardial infarction. There was no history of severe or recurrent bacterial infections. Immunological investigations showed undetectable Clq but normal C3 and C4 complement levels. ANA was not performed but dsDNA antibodies were negative.

**IIa.** At 9 yrs the oldest brother developed a malar rash for which he was seen by the local dermatologist who diagnosed discoid lupus and successfully treated him with the anti-malarial drug mepacrine. There were no other clinical features of SLE. From the age of 13 yrs he was lost to follow-up until he was recently screened for Clq deficiency at the age of 21 yrs. CH50 and Clq levels were undetectable consistent with Clq deficiency (Table 1) and he is now being followed up by the local immunologist. As with the affected proband, he was positive for Ro but not dsDNA or other ENA autoantibodies.

**IIb.** This brother who is now 19 yrs old had recurrent ear infections and tonsillitis as a child but has since been very well. He has no clinical features of SLE or continuing infections. Complement screen revealed undetectable CH50 and Clq levels (Table 1). Renal function, blood pressure and urinalysis were normal.

**IIc.** This boy was well until the age of 17 months when he developed bacterial meningitis and died within 12 h of first developing any symptoms. His complement system was never formally tested.

**IIId.** This brother is fortunately unaffected.

**IIe.** This brother is currently 13 yrs old. He suffers from intermittent mouth ulcers and has had around 20 episodes of angioedema, mainly involving his lower eyelids. He is otherwise well and has no clinical features of SLE. His blood pressure, urinalysis and renal function are normal. He has undetectable CH50 and Clq (Table 1). His C1 inhibitor level and function as well as C4 level were normal, excluding dysfunction of this pathway as a cause of his angioedema.

**Discussion**

This report clearly illustrates the clinical variability of patients with Clq deficiency from being very well to having life-threatening infections and/or autoimmune disease involving their brain and kidneys. The importance of screening the whole family where an index case is found is also apparent, as in this family unfortunately four, and probably five of the six brothers were affected. In this family, as the father was affected and the mother an obligate carrier, the risk of children having Clq deficiency was 50% and not 25%. The father’s five siblings were also screened and fortunately none of them were found to be affected. C3 and C4 are normal in this condition, and therefore it is very important to check the CH50 as a screening test and if abnormal, proceeding to identify the classical pathway component deficiency, in this case Clq.

<table>
<thead>
<tr>
<th>Family member</th>
<th>Clinical details</th>
<th>C1q (70–140)</th>
<th>ANA</th>
<th>dsDNA ab</th>
<th>Sm ab</th>
<th>Ro ab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia—father affected</td>
<td>Chronic glomerulonephritis 38yr post-retrnal transplant</td>
<td>&lt;10</td>
<td>ND</td>
<td>Neg</td>
<td>Neg</td>
<td>ND</td>
</tr>
<tr>
<td>lb—mother unaffected</td>
<td>Well</td>
<td>82</td>
<td>1/100 Homogeneous</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>lla—21 yr brother affected</td>
<td>Discoid lupus</td>
<td>&lt;10</td>
<td>1/1000 Speckled</td>
<td>Neg</td>
<td>Neg</td>
<td>Pos</td>
</tr>
<tr>
<td>llb—19 yr brother affected</td>
<td>Well</td>
<td>&lt;10</td>
<td>1/1000 Speckled</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>llc—deceased brother ?affected</td>
<td>17m Streptococcus pneumoniae meningitis</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td>lld—14 yr brother unaffected</td>
<td>Well</td>
<td>78</td>
<td>1/80 Nucleolar</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
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<td>lle—12 yr brother affected</td>
<td>Recurrent mouth ulcers and angioedema</td>
<td>&lt;10</td>
<td>1/1000 Speckled</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>llf—10 yr proband affected</td>
<td>Bacterial meningitis 3yr severe CNS vasculitis at 10y</td>
<td>&lt;10</td>
<td>1/10 000 Speckled</td>
<td>Neg</td>
<td>Pos</td>
<td>Pos</td>
</tr>
</tbody>
</table>

**FIG. 1.** Cranial MR scan of proband within 1 week of acute encephalopathic episodes showing bilateral basal ganglia changes.

**FIG. 2.** Family pedigree. Black squares indicate affected family members. The grey square is the patient who died of fulminant pneumococcal meningitis before testing for Clq deficiency could be performed.

**TABLE 1.** Clinical features, Clq concentrations and autoantibodies of family with Clq deficiency.
It is interesting to speculate why the proband developed such severe focal CNS vasculitis. CNS vasculitis has been described before in patients with C1q deficiency [6,7]. Although in neural lupus abnormal coagulation may be an important trigger, there was no evidence of lupus anticoagulant/cardiolipin antibodies in this patient or any of his siblings. Sm autoantibodies are associated with an increased prevalence of CNS disease [8], but the mechanism is unclear and immune complex deposition is not thought to be the main pathogenic mechanism in neuropsychiatric lupus [9]. One possibility is that the previous episode of meningitis made his cerebral vasculature prone to further inflammatory damage, although there are only isolated case reports to support such a theory [10]. Against this theory is the fact that previously recorded cases of C1q deficiency who have survived meningitis have not yet gone on to develop a CNS vasculitis [11].

This study also highlights the fact that C1q deficiency is associated with the development of autoantibodies against specific ribonucleoproteins (RNP) such as anti-Sm and Ro, often with no evidence of antibodies to dsDNA. Anti-Sm antibodies bind to core small ribonucleoproteins (snRNP), important in stabilizing larger multimeric snRNP complexes [12]. The presence of these autoantibodies is associated with a speckled pattern of ANA staining on immunofluorescence, as found in all of our patients with confirmed C1q deficiency [13, 14]. Our findings are in keeping with previous reports of increased frequency of anti-RNP antibodies but not dsDNA autoantibodies in patients with complement deficiencies [11, 15]. There is growing evidence to suggest that caspase-mediated cleavage of cellular proteins during apoptosis may induce the formation of immunogenic peptides, which would be expected to promote RNP autoantibody formation [16]. This provides a possible explanation for the formation of these autoantibodies in patients with C1q deficiency who are known to have delayed clearance of apoptotic bodies [1].

This report describes the clinical features of one of the largest families of patients with C1q deficiency. It highlights the importance of measuring CH50, rather than just C3 and C4 if the diagnosis is not to be missed, as well as the characteristic autoantibody profile, which differs from the classical SLE. For rheumatologists used to treating severe vasculitides with high-dose immunosuppressive drugs, it also highlights the need to recognize that patients with C1q have primarily an underlying immunodeficiency disease, and as such will require prophylaxis to counter the high risk of life-threatening bacterial sepsis. Long-term antibiotic prophylaxis, as well as boosting antibody responses to Neisseria meningitides (A, C, Y, W135), Streptococcus pneumoniae and Haemophilus influenzae type b, is often used to help prevent life-threatening infections. However, in patients with C1q deficiency presenting with severe autoimmune disease requiring potent immunosuppression, active vaccination against potential pathogens may not be possible, and thus passive immunization with immunoglobulin replacement therapy in combination with prophylactic antibiotics should be considered as an alternative.

The authors have declared no conflicts of interest.

References