Impaired IgG responses in a child with homozygous C2 deficiency and recurrent pneumococcal septicaemia

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Case report

The patient presented at the age of 3 mo with drowsiness, fever and poor feeding. Blood cultures grew S. pneumoniae and she was successfully treated with intravenous benzylpenicillin. She developed two further episodes of pneumococcal septicaemia at the ages of 4 mo and 13 mo respectively, both of which also responded to antibiotic therapy. Each episode of septicaemia was caused by a different serotype of S. pneumoniae, namely 33, 19 and 6. She was commenced on ampicillin prophylaxis, but subsequently developed two episodes of urinary tract infection (UTI) due to enterococcus. These were successfully treated with co-amoxiclav; antibiotic prophylaxis was also changed to co-amoxiclav following the second UTI. Up to the age of 10 y the patient had not developed any further serious infections or evidence of autoimmune disease.

In the absence of infection, white cell counts revealed normal percentages of neutrophils, monocytes and lymphocytes as well as B and T cell subsets. A neutrophil leukocytosis occurred in response to the pneumococcal septicaemia and in vitro analysis of neutrophil function was normal. A positive response to a Mantoux test following BCG vaccination was consistent with normal T cell function. Immunoglobulin class analysis revealed appropriate levels of IgG and IgG subclasses, as well as IgA, IgM and IgE. A normal-sized spleen was present and Howell-Jolly bodies were absent from the peripheral blood.

Analysis of the classical pathway of complement activation by the CH50 assay demonstrated undetectable levels of haemolysis, whereas alternative pathway activity was within normal limits. All components of the classical pathway were normal except for C2, which was undetectable. Tests for anti-nuclear antibodies and antibodies to extractable nuclear antigen were negative.

We next examined specific antibody responses to S. pneumoniae. Despite three episodes of pneumococcal septicaemia, there was no evidence at this time of an IgG anti-pneumococcal antibody response. However, total IgM levels were increased during one infectious episode as compared to levels obtained when the patient was well (1.98 g/l vs 1.02 g/l, respectively; normal range: 0.47–1.90 g/l), suggesting a primary IgM response to S. pneumoniae.

The patient was vaccinated at 18 mo old with Pneumovax II (Merck, Sharpe and Dohme), a polyvalent pneumococcal vaccine. Examination of antibody responses by ELISA showed complete absence of a post-vaccination rise in anti-pneumococcal antibodies (Table 1). Vaccination at 27 mo with HibTITER (Lederle Laboratories), an H. influenzae type b (Hib) polysaccharide-tetanus toxoid conjugate vaccine, induced only a slight rise in anti-Haemophilus total IgG antibody as measured by ELISA (Table 1). She was revaccinated at the age of 4 y, 8 mo with both the pneumococcal vaccine and the Hib conjugate vaccine. The post-vaccination IgG response to H. influenzae was adequate, while total IgG antibodies to S. pneumoniae
rose four-fold. However, IgG2 anti-pneumococcal anti-
body levels rose from less than 10 units to 10 units, sug-
suggesting that the IgG2 response remained impaired (Table 1).

Absence of the G2m(23) allotype of IgG2 has also 
been independently associated with poor responses to 
polysaccharide antigens such as the H. influenza type b 
polysaccharide vaccine (5). However, allotyping for 
IgG2 showed the patient to carry the G2m(23) allotype.

### Discussion

Although our patient had normal levels of IgG subclasses, an association between C2 deficiency, recurrent infection and IgG2 deficiency has been previously described in a child who also lacked the G2m(23) IgG2 allotype (2). Low IgG4 levels have been also been found in association with C2 deficiency (3, 4) and in one of these cases, in which recurrent pneumo-
coccal septicaemia occurred following splenectomy, 
neither pneumococcal infection nor vaccination with a 
pneumococcal vaccine resulted in protective levels of 
anti-pneumococcal antibody, although this patient also 
lacked the G2m(23) IgG2 allotype (3). We have 
recently identified another family including four 
children with C2 deficiency, all of whom have undetectable 
levels of IgG4 (unpublished data). Furthermore, in some 
cases of C3 deficiency the levels of IgG4 are signifi-
cantly reduced, with IgG2 levels also reduced, although 
to a lesser extent (6). In a study of anti-pneumococcal antibodies in complement-deficient individuals, three 
out of four cases of C3 deficiency displayed low levels of 
anti-pneumococcal antibodies (7). Moreover, this 
was associated with reduced levels of total IgG2 in each 
case and all had a history of recurrent pneumococcal 
infection. Recently, IgG subclass levels have been 
shown to be highly related to the Gm allotype, 
especially G2m, in which G2m(23) demonstrates a 
retarded rate of development in childhood (8). There-
fore, IgG subclass levels must be interpreted with 
cautions in the absence of knowledge of the Gm 
allotypes present.

Immunization of C2-deficient guinea pigs leads to 
suboptimal primary and secondary antibody responses 
and failure of switching of the antibody response from 
IgM to IgG, a T cell-dependent event (9). To some 
extent these defects can be overcome by increasing the 
antigen dose (9). Similarly, a C2-deficient individual 
immunized with the bacteriophage φX 174 displayed 
impaired IgG responses in addition to absence of an 
IgM to IgG switch (9).

C3b and C4b covalently linked to tetanus toxin have 
been shown to reduce the amount of antigen required 
to induce antigen-specific T cell proliferation via a mecha-
anism requiring expression of the complement receptors 
CR1 and CR2 on the antigen-presenting cell (10). 
Follicular dendritic cells (FDCs) also express both CR1 
and CR2, and localization of antigen to FDCs is largely 
dependent on the formation of complement-containing 
immune complexes (11). Furthermore, it has recently 
been shown that C3d when fused to antigen can act as 
a powerful adjuvant in B cell responses in mice (12). 
Taken together, these findings suggest that complement 
plays a critical role in both T cell and B cell immune 
responses and that there is a causal relationship between 
complement deficiency and impaired antigen-specific 
IgG responses.

Our patient’s poor IgG responses to the pneumococ-
cal and Hib conjugate vaccines might be ascribed to a 
physiological delay in the maturation of the immune 
system associated with her young age. Children as old as 5 y may respond poorly to the pneumococcal vaccine 
(13). However, most children over the age of 18 mo 
respond well to a single injection of the protein-based 
Hib conjugate vaccine (14). We favour the view that our 
patient’s impaired responses to vaccination are directly 
related to her C2 deficiency, especially given her 
unexpectedly poor response to the Hib conjugate 
vaccine at 27 mo. It is possible that C2 deficiency leads 
to a more pronounced delay in the maturation of 
antibody responses, which would explain the occur-
rence of infection in young C2-deficient children (1).

<table>
<thead>
<tr>
<th>Age</th>
<th>Vaccines</th>
<th>Anti-S. pneumoniae:</th>
<th>Pre-vaccination</th>
<th>4–8 wk post-vaccination</th>
<th>Normal response</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IgG total</td>
<td>77</td>
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<tr>
<td></td>
<td></td>
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<td>17</td>
<td>5</td>
<td>&gt;160</td>
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<td>18 mo</td>
<td>Pneumovax II</td>
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<td>27 mo</td>
<td>HibTITER</td>
<td>Anti-H. influenza b:</td>
<td>IgG total</td>
<td>58</td>
<td>&gt;640</td>
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<tr>
<td>4 y, 8 mo</td>
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<td>Anti-S. pneumoniae:</td>
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<tr>
<td></td>
<td>HibTITER</td>
<td></td>
<td>IgG total</td>
<td>40</td>
<td>&gt;40</td>
</tr>
</tbody>
</table>

Specific immunoglobulin responses to S. pneumoniae and H. influenzae were measured by ELISA. Values represent arbitrary units.

a Different ELISA assays were used at the third vaccination, producing different arbitrary units compared to the earlier assays.
deficient individuals, this has been shown to be associated with persistently low anti-pneumococcal antibodies (7).

It can therefore be argued that deficiency of C2 leads to impaired activation of C3 via the classical pathway (15), resulting in failure of T cell-dependent class switching and generation of IgG antibody responses (9). Appropriate vaccination may prevent or reduce the number of episodes of infection in C2-deficient individuals, although this has not been shown. If excessive delay in the maturation of antibody responses is indeed causally related to complement deficiency, then immunization of C2-deficient individuals might be enhanced by co-administering normal serum containing the missing complement component (15). One might also expect at least some individuals deficient in C2 to become less prone to recurrent infection as they get older; thus, the critical period during which they would require protection from infection would be during the first years of life.

References
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Received Oct. 18, 1999; revision received March 23, 2000; accepted March 24, 2000