



## CLINICAL PRACTICE

## Complement component C6 deficiency and susceptibility to *Neisseria meningitidis* infections

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Meningococcal disease remains one of the most serious bacterial infections in both Western and developing countries. Despite recent advances in treatment the mortality rate remains at about 12%.<sup>1</sup> There is a group of South Africans who are particularly vulnerable to this disease. They are individuals with genetically determined deficiencies of individual terminal complement proteins, in particular of the sixth component of complement (C6).<sup>2</sup>

The human complement system forms part of the humeral immune system and consists of a series of proteins.<sup>3</sup> The interaction of antigen (such as components of bacterial outer membranes) and antibody leads to activation of the first component C1q, and consequent activation of part or all of the complement cascade. This has a number of biological effects including the formation on the membrane of the membrane attack complex (MAC) from components C5b, C6, C7, C8 and C9. The MAC is able to mediate lysis of some mammalian cells such as red blood cells, as well as lysis of bacteria and certain viruses. This action of complement has been recognised for many years as playing a major role in defence against infection.<sup>4</sup> In addition, MAC action is often sublytic on nucleated host cells, and this interaction can sometimes stimulate cellular biosynthesis and act in a pro-inflammatory manner.<sup>5</sup>

Many other complement proteins, and products of complement activation, also interact with the cellular immune system and the inflammatory system. If activation is caused by pathological processes such as ischaemia, complement can be an important contributor to host tissue necrosis.<sup>6</sup> The effects of complement activation are very complex and can be detrimental as well as beneficial.

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### Our patients

In the Western Cape we have been caring for patients with C6 deficiency (C6D) for a number of years.<sup>2,7</sup> These patients are susceptible to neisserial infections, particularly meningococcal disease.<sup>8</sup> However, despite complete absence of serum bactericidal activity, patients may be no more susceptible than normal individuals to infections not caused by encapsulated bacteria.

Approximately 45 individuals with C6 deficiency have been diagnosed in the Western Cape, and a few in Gauteng. The most common presentation is with recurrent meningococcal infections. Subjects are likely to have suffered their first infection after the pre-school years. Family studies have revealed some C6D siblings of index cases who have suffered no infections at all.

The diagnosis is made by first determining the patient's total haemolytic complement. Subjects with homozygous complete C6 deficiency lack all complement haemolytic function. Low haemolytic activity can be found in other diseases such as systemic lupus erythematosus and C1 esterase inhibitor deficiency, and it is therefore necessary to distinguish absent complement activity from low activity. Also, genetic deficiency of any of the terminal complement proteins presents in the same manner, so the specific diagnosis of C6 deficiency can only be made with an additional specific C6 haemolytic or antigenic assay.

Many individuals with C6 deficiency may not be diagnosed because individuals with only one episode of meningococcal infection are seldom investigated. However, in our patients the morbidity costs of repeated infections are high so steps need to be taken to protect these vulnerable individuals from further infections. The most common problems we have seen are deafness and mental retardation. It has been suggested that individuals with complement deficiency suffer milder meningococcal disease than normal individuals.<sup>4</sup> However, there is no convincing evidence that primary meningococcal infection is milder in complement-deficient individuals.

### What can be done

The problem is how to protect these individuals. The first step is education and counselling so that patients or their parents know the problem, and know that it is essential to obtain rapid



treatment should the signs and symptoms of meningococcal disease occur.

Patients lack serum bactericidal activity, and because antibodies require complement activity to mediate bacteriolysis, vaccination at best can only provide partial protection. Nevertheless, vaccination can enhance opsonophagocytosis, and vaccination with the tetravalent polysaccharide capsule vaccines A, C, Y and W135 is recommended for terminal complement-deficient individuals in Europe and other Western countries where meningococcal group B infections are rare.<sup>9</sup> However, group B was found to be the most common meningococcal strain isolated from Cape C6-deficient patients,<sup>10</sup> and it remains the most prevalent strain isolated in this country.<sup>11</sup> Until a satisfactory group B vaccine is available vaccination can only provide very partial protection and our patients have not been vaccinated.

Antibiotic prophylaxis, usually in the form of monthly bicillin injections, was used to protect the more vulnerable of the Cape patients. That study<sup>7</sup> was carried out over a 3-year period from 1984 to 1986 and showed that antibiotics did lessen the risk of recurrent infections. We are at present carrying out a further study to investigate the effectiveness of antibiotic prophylaxis over a much longer timespan.

## Long-term implications

What are the long-term implications of terminal complement component deficiency? The Western Cape cohort of C6-deficient subjects is large compared with cases reported from elsewhere, and we first examined many of these patients approximately 18 years ago. The cohort therefore provides an opportunity to investigate the long-term consequences of deficiency. However, the total number of patients is not large and although we have seen C6-deficient patients with tuberculosis and other diseases we cannot yet say whether C6-deficiency is a predisposing factor. An association between auto-immune disease and terminal complement deficiency is still speculative.<sup>12,13</sup>

Interactions between components of the complement system and the inflammatory system are known, and participation of complement in disease processes is now being recognised.<sup>6,14</sup> Some possible unwanted manifestations of complement activation only occur in diseases associated with ageing, such as atheroma formation, necrosis following myocardial infarction, arthritis, and central nervous system diseases such

as multiple sclerosis. It is therefore possible that there are beneficial effects of lacking terminal complement component activity.

Genetic defects responsible for C6 deficiency in the Cape were described in 1998.<sup>15</sup> Three defects were found among the Cape patients. One defect (879delG) has only been found in the Cape and the Netherlands, and the other (1195delC) has been observed in individuals of West African origin.<sup>16</sup> The third defect (1936delG) has also been observed in people of West African origin but only one instance of this gene was observed in the Cape.

Deficiency of C6 is an interesting genetic deficiency that may help us understand the role of complement in a number of disease processes. However, it is also a serious disease as it predisposes to life-threatening infections. These patients need to be diagnosed and then given appropriate care to try and prevent further recurrences of meningococcal infection.

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