Invited Review

SOUTH AFRICAN PATIENTS WITH GENETIC DEFICIENCIES OF COMPLEMENT COMPONENTS C5 AND C6 SUFFER A MARKED INCREASE IN SUSCEPTIBILITY TO MENINGOCOCCAL DISEASE

A Orren1,2,3
A Thomas3
F Leisegang1,4
R Würzner5
EP Owen1
PC Potter2

1. Division of Chemical Pathology, Department of Clinical Laboratory Sciences, University of Cape Town, South Africa
2. Allergy Diagnostic and Clinical Research Unit, Department Medicine, University of Cape Town, South Africa
3. Division of Infection and Immunity, Cardiff University, United Kingdom
4. South African National Health Laboratory Services
5. Division of Hygiene and Medical Microbiology, Innsbruck Medical University, Austria

Email | orrena@cardiff.ac.uk

ABSTRACT
South African Black African and Cape Coloured patients who had suffered culture positive meningococcal disease (MD) were investigated for mutations in genes coding for the terminal complement pathway proteins C5 and C6. C5 mutations p.Q19X, p.R1476X and p.A252T are known to cause absent or very low serum C5 levels and thus increase susceptibility to meningococcal disease. In addition, four C6 deficiency genes are also responsible for increased susceptibility to the meningococcus and they too segregate in the Western Cape.

We tested admission samples from the 81 black patients and 84 coloured patients for the three C5 mutations and four C6 mutations responsible for the deficiencies. Among the 81 black MD patients we found six C5 deficient p.A252T homozygous individuals and 17 C6 deficient individuals. Thus 28% of black patients who had suffered MD were complement deficient and vulnerable to further MD infections. We found no homozygous C5 deficient coloured MD patients, however, 7 out of 84 (8%) coloured patients were C6 deficient. Thus the risk of recurrent MD infections is present for both groups but highest among black individuals. We strongly recommend antibiotic prophylaxis against further infections for terminal complement component deficient patients.

Keywords: Complement deficiency, meningococcal disease

ABBREVIATIONS
C5D - Complement C5 deficiency, C6D - Complement C6 deficiency, MD - Meningococcal disease, TCC - Terminal complement complex, MAC - Membrane attack complex

INTRODUCTION
The terminal complement pathway comprises the final five components of the complement cascade, C5 through to C9.1 Complement activation results in the splitting of C5 into the small (74 amino acids) C5a molecule, and the larger C5b molecule. C5a has an immunostimulatory role and also participates in pathological processes including the response to sepsis.2 C5b is the initial component of the complement system’s membrane attack complex (MAC). C6 is the second component of the MAC and C6 deficiency has been a problem in the Cape for many years.

The MAC has a major role in defending the host from...
Patients comprised 165 individuals who had presented with culture confirmed MD, either at the time or within the previous five years. Patients included were either Black African (predominantly Xhosa speaking) or Cape Coloured. The latter included individuals with ancestors from regions in the South Western areas of Southern Africa, Malaysia, Europe and a few Bantu speaking Africans. White South Africans were excluded because there was no evidence that they carried the pathological complement genes.

Patients diagnosed C5 or C6 complement deficient were asked to attend the Immunology Clinic. Immediate family members were also interviewed and tested for the three C5 mutations and four C6 mutations detailed above. C6 or C5 deficient patients identified were prescribed antibiotic prophylaxis. We used the collective data from all 165 patients for this study.

GENE FREQUENCIES OF C5 MUTATIONS

Among the 165 MD patients, we identified six independent cases of homozygous C5 deficiency (C5D). They were all Black affected p.A252T homozygous and required prophylaxis. One index case had died in hospital, however, he had a C5D homozygous sister who we investigated and treated in the study. She had not suffered any episodes of MD. The six C5D cases and one affected mother had very low serum C5 protein levels (0.1-4% of normal) and correspondingly low in vitro functional activity.

Allele frequencies of p.A252T in samples from control Black Africans and Cape Coloureds were 3% and 0.66% respectively. Results of genetic testing are presented in Table I.

DISCUSSION

Deficiencies of any of the components of the membrane attack complex are usually identified clinically after patients have presented with recurrent invasive *Neisseria meningitidis* infections. In South Africa, meningococcal disease is endemic with 1668 cases having been reported over a five year period (2008 to 2012).

Our earlier studies confirmed very strong associations between complement deficiencies and meningococcal disease. Molecular modelling has demonstrated the possible reason that p.A252T is pathological.

There are a number of factors that influence susceptibility to MD. At present, the ones we recognise are those important for the spread of the disease in complement sufficient individuals.

---

**TABLE I: RESULTS OF TESTING FOR C5 AND C6 GENETIC DEFECTS IN 165 SOUTH AFRICAN MENINGOCOCCAL DISEASE PATIENTS**

<table>
<thead>
<tr>
<th></th>
<th>BLACK</th>
<th>COLOURED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of MD patients</td>
<td>81</td>
<td>84</td>
</tr>
<tr>
<td>Number and percentage p.A252T homozygous C5D</td>
<td>6</td>
<td>7.4%</td>
</tr>
<tr>
<td>Number and percentage C6 deficiency (C6Q0)</td>
<td>17</td>
<td>21%</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>28.4%</td>
</tr>
</tbody>
</table>
However, there may be additional clinical factors that influence susceptibility in complement deficient individuals and we need to understand these in order to provide support for these patients. We have found that antibiotic prophylaxis is beneficial in preventing further infections. Hopefully vaccination will eventually be available for our patients.

The long term condition of complement deficient patients, particularly those who suffered recurrent MD episodes, can be very serious. Also we have seen families in the Cape with more than one sibling who is complement deficient but only one sibling has a history of MD. Recently C5 and C6 deficient patients have been ascertained through genetic screening and we hope that this can help reduce the incidence of recurrent disease. In any case, we have diagnosed patients as complement deficient at the age of twenty years or beyond who have no history of disease. It may be that there are additional immunological differences accountable for outcome. Many complement deficient patients have very serious sequelae from any episode of MD but long term pathology becomes more likely with more than one episode. We have followed up C6 deficient patients, some of them for many years, and the problems they have that result from the multiple infections can be very serious. In 2005 we recalled approximately 48 C6 deficient patients and assessed their clinical state. They were assessed as to how they were currently and we analysed the results according to their number of episodes of MD. We compared C6 deficient patients with “no or one episodes of MD” to those “who had suffered multiple (2 or more) episodes”. We assessed them as being “well” or suffering a “serious illness” by grouping them according to whether they could live normally. Those who could not were grouped as having a “serious illness”. As can be seen from Figure 1, there were a total of 22 patients who were in the group “Serious illness” and of these 19 had suffered more than one episode of MD. Medical support and the provision of prophylaxis is very important for these patients.

C5 deficiency was not found in any of the 84 coloured patients we tested, however, C6 deficiency is a problem among the Coloureds and Blacks. There are four C6Q0 defects segregating in the Cape and the particular C6 genetic defects differ somewhat between Coloureds and Blacks. It seems likely that different mutations arose in different areas of Africa. We sincerely hope that diagnosing and treating C5 and C6 mutations will be available in other parts of South Africa and beyond so that help can be provided to aid for these complement deficient patients.

There is also the question of whether boosting opsonophagocytosis could help the complement deficient children. Certainly we hope that meningococcal vaccination will be able to boost the production of antibodies that promote opsonophagocytosis. Hopefully meningococcal vaccines will eventually be provided by the Health Services in South Africa especially for vulnerable children.

ETHICS
The work was approved by the University of Cape Town Ethics Committee.

ACKNOWLEDGEMENTS
The work was funded by the South African Medical Research Council. The University of Cape Town provided space and facilities and helped with UCT Emergency funding when it was needed. Sr Sheila Baker provided excellent care and management and data collection for the patients. Prof David Marais provided laboratory facilities for DNA work. The NHLS provided space and facilities and support for staff.

REFERENCES