Deficiency of the seventh component of complement

A case report

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Summary

Deficiency of the 7th component of the complement cascade was diagnosed in a white male with recurrent meningococcal infections. This deficiency has not previously been reported in South Africa.

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Homozygous deficiencies of the terminal components of the complement cascade (C5, C6, C7, C8 and C9), are associated with recurrent *Neisseria meningitidis* infections.[1,2] We have recently identified and reported 41 individuals with homozygous C6 deficiency, 39 of whom reside in the western Cape.[3,4] All but 1 of these patients presented to hospital with recurrent meningococcal meningitis and none had the associated C7 deficiency reported by others.[5] C7 deficiency is a rare genetic disorder.[6] It is important to identify such patients because it is likely that they would also benefit from a programme of long-term penicillin prophylaxis, which we have found beneficial in our patients with C6 deficiency.[4] The first case of homozygous C7 deficiency in South Africa is reported here.

Case report

The index patient is an 18-year-old white male medical student who was admitted to the H.F. Verwoerd Hospital, Pretoria, with a diagnosis of meningococcal septicaemia. He was treated with 2 g cefotaxime 8-hourly and 500 mg cloxacillin intravenously 6-hourly for 5 days and thereafter with intravenous penicillin 4 million units 6-hourly for 5 days and after a full recovery was discharged from hospital.

One month later the patient presented to Universitas Hospital, Bloemfontein, with fever, headache and neck stiffness; *N. meningitidis* was isolated from his cerebrospinal fluid. He responded well to intravenous penicillin given for 7 days and his subsequent course was uneventful. The past medical history was non-contributory; the only past illness being bilateral otitis media as a toddler. The patient has had no unusual susceptibility to any other infections. The family history was also non-contributory. In particular, neither the parents nor 2 siblings have any history of meningococcal or other recurrent infections. The patient has been treated with prophylactic benzathine penicillin G 2,4 mega-units monthly since discharge from hospital and has had no further episodes of meningococcal infection.

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Investigations

The proband and his family were investigated for complement deficiencies. Total haemolytic complement and alternative pathway levels were measured by radio-immunodiffusion haemolytic assay. C3 and C4 levels were measured immunochemically by laser nephelometry. C1, C2, C5, C6, C7, C8, C9, factor B and factor H were measured by immunodiffusion technique (Ouchterlony). C6 and C7 antigenic levels were measured by rocket immuno-electrophoresis (Laurell). Functional C6 and functional C7 haemolytic activity were measured as previously described.[7]

Results

Investigations performed on the patient, his parents and his brother and sister are shown in Table I. The patient had no total haemolytic complement activity and no C7 was detected either by antigenic or functional assays. Normal levels of Clq, Cls, C2, C3, C4, C5, C6, C8, C9 and factor B were present. The father and sister each had C7 levels of 77%, the mother and brother 68% and 59%, respectively. These levels are below the normal range of 80 - 100%. The father and sister also had reduced total haemolytic complement activity (51% and 63%, respectively — normal 80 - 100%).

TABLE I. TOTAL HAEMOLYTIC COMPLEMENT, ANTIGENIC C7 ACTIVITY AND FUNCTIONAL C7 ACTIVITY IN THE INDEX PATIENT AND 4 IMMEDIATE FAMILY MEMBERS

	Total haemolytic complement (%)	Antigenic C7 (%)*	Functional C7†
Patient	**0**	**0**	—
Father	**51**	**77**	+
Mother	**105**	**59**	+
Brother	**98**	**68**	+
Sister	**63**	**77**	+

* By rocket electrophoresis.
† Using agarose indicator gels.

Discussion

The presentation of patients with homozygous C7 deficiency is usually with recurrent *N. meningitidis* infections. In a review by Ross and Densen[1] in 1984 of the 22 cases published worldwide, 10 patients presented with meningitis or *N. meningitidis* infection. All the patients were over the age of 8 years. The patient described here is not only the first patient with homo-

zygous C7 deficiency reported in South Africa but is also to our knowledge the first white patient who has been shown to have a terminal component complement pathway deficiency in South Africa. All the patients who have presented with C6 deficiency to date are of coloured or Xhosa extraction.

The inheritance of C7 deficiency is believed to be autosomal co-dominant and in this patient would be homozygous for the C7 deficiency null genes. Results of the haemolytic assays for C7 in Table I suggest that his parents may be heterozygotes for C7 deficiency but this would have to be confirmed by C7 allotyping. Combined C6 and C7 deficiency has previously been reported in 3 kindreds[8] but was not present in this patient.

Since the review of Ross and Densen,[1] a further 15 cases of C7 deficiency have been reported world-wide. Although the recent reported cases presented with neisserial infections, 1 patient with C7 deficiency presented with *Haemophilus parainfluenzae* meningitis.[9]

Recently Zimran *et al.*[10] in a study of survivors of meningococcal disease have reported a high prevalence of C7 and C8 deficiency in Sephardic (Moroccan) Jews; there were no cases in the Ashkenazi subjects studied. C7 deficiency has also been reported[11] in association with C4b deficiency in an adult with meningogoccal disease and several cases have had associated auto-immune diseases.[1,12–14]

There are at least 7 polymorphic forms of C7.[13,14] The complete primary structure of C7 has been determined from the cDNA sequence of clones isolated from a human liver library.[17] C7 is a mosaic protein that consists of 821 amino acids and its amino terminal has 23 - 30% homology with the complement components C8 and C9. C7 plays a major role in bringing about the hydrophilic-amphiphilic transition during the formation of the membrane attack complex and also, it seems, as a membrane anchor for the C5b-7 complex.

We consider the identification of this first case of C7 deficiency in South Africa important because we now know that the gene for C7 deficiency, unlike C6 deficiency, is present in the Afrikaner population and thus white patients presenting with recurrent *N. meningitidis* infection should be screened for the possibility of the deficiency. We have put our patient on a monthly benzathine penicillin G prophylactic regimen, which we have successfully used in our C6 deficiency patients to prevent subsequent neisserial infections. Since penicillin-resistant *N. meningitidis* organisms have been reported in South Africa,[18] it will be important in the future to monitor the sensitivity of the organisms in areas where patients are receiving penicillin prophylaxis.

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