

Recurrent meningococcal meningitis

A case report

S. W. HARDCASTLE

Summary

A 17-year-old Coloured youth presented at Tygerberg Hospital on six occasions between 1978 and 1981. He was admitted three times for meningococcal meningitis and three times for a meningitic illness clinically suggestive thereof. He had been admitted twice before to the City Hospital, Cape Town, in 1966 and 1968, for presumed meningococcal meningitis. He was fully evaluated in the outpatient department and found to have no detectable total haemolytic complement activity. There was no evidence of classic or alternative pathway activation. He has been tentatively designated as having a deficiency in the C6 or C8 components of the terminal membrane attack mechanism of the complement cascade.

S Afr Med J 1984; 66: 345-346.

Recurrent neisserial infections have been described in association with various primary disturbances of the terminal components of the complement system, most commonly with C6 or C8 deficiency.¹⁻⁶ These primary defects result in an immune deficiency and increased frequency of recurrent meningococcal meningitis and gonococcal sepsis.¹⁻⁶

Case report

A 17-year-old Coloured youth was admitted to Tygerberg Hospital in August 1981 with a typical history and clinical picture of meningococcal meningitis. Cerebrospinal fluid (CSF) and blood culture were both positive for *Neisseria meningitidis* and there were signs of disseminated intravascular coagulation on clotting screening. The patient was referred to the City Hospital, Cape Town, where he was treated with penicillin and chloramphenicol with good clinical response. He returned to Tygerberg Hospital for a follow-up visit.

Analysis of his medical records revealed a remarkable history of recurrent meningitis since 2 years of age (Table I). He had been admitted to hospital eight times for meningitis and the cause of the most recent admissions, between 1978 and 1981, had proved to be *N. meningitidis*. There was no history of recurrent viral, pyogenic or mucocutaneous infections, but one sibling had died of meningococcal meningitis at 2 years of age. Clinical examination of the youth in the outpatient department revealed no abnormalities. Chest radiographs were normal and blood examination revealed no neutropenia or lymphopenia. Throat swabs taken from the patient and members of his family were

TABLE I. MEDICAL HISTORY

Date	Diagnosis	Comment/clinical notes
1966	Meningitis	History from mother; presumed meningococcal; treated at City Hospital
1968	Meningitis	As above
March '78	Meningitis	Purpura; culture negative; abnormal CSF in keeping with bacterial infection
May '78	Meningitis	Vomiting; purpura; culture negative; abnormal CSF
Oct. '78	Meningococcal meningitis	Culture positive
Dec. '78	Meningococcal meningitis	Culture positive; protein electrophoresis normal; C3 68 mg/dl, C4 21 mg/dl; total < 1:2
July '79	Meningitic illness	Purpura; culture negative; T and B cells normal; IgA decreased; IgG and IgM normal
Oct. '80	Mono-arthritis (right knee)	Exudate
July '81	Meningococcal meningitis	Culture positive

negative. Biochemical findings, including protein electrophoresis, were normal. Immuno-electrophoresis revealed a decreased serum IgA level on two occasions with values of 0,64 g/l and 0,48 g/l (normal 1,56 - 4,17 g/l) and a third value of 2,77 g/l. There were normal numbers of T and B cells and neutrophil function was within the accepted normal range for our laboratory. The serum complement profile, however, revealed a striking finding: the C3 and C4 values were normal, but the total serum complement value was less than 1:2 (normal 1:16 - 1:64). Total haemolytic complement activity (CH₅₀) was also absent on repeated testing. Radiographs of the skull and a computed tomographic scan were normal.

Discussion

Persistent, recurrent, severe or unusual infection is the principal manifestation of both primary and secondary immunodeficiency, and the type of infection often gives important clues as to the specific immune defect.⁷ Recurrent bacterial infection suggests antibody deficiency and B-cell defects, phagocytic defect (neutrophil and splenic dysfunction), or complement deficiency. Initial screening should include assessment of total serum immunoglobulin levels (IgG, IgM, IgA and IgE), serum complement, and peripheral blood lymphocyte and neutrophil counts.⁸

Measurement of the serum total CH₅₀ activity will adequately screen for an isolated complement deficiency syndrome,¹ and will also provide an overall measure of the integrity of the complement pathway. Individual complement components must be determined by assay. The typical pattern of terminal complement component deficiency is absent or markedly reduced

CH₅₀ without evidence of classic or alternate pathway activation.¹ A reduction in serum complement may be due to one or more of the following: complement consumption by *in vivo* formation of antigen-antibody complexes, decreased or absent production of complement, increased catabolism, formation of an inhibitor, and improper handling of samples. Decreased or absent production is seen in hereditary complement factor deficiency syndromes and in severe liver disease.⁶ This results in a typical serum complement profile. Complement profiles and their association with disease are shown in Table II.⁶

TABLE II. COMPLEMENT PROFILES AND THEIR ASSOCIATION WITH DISEASE

Profile	Pathway activated	Disease association
1. Decreased CH ₅₀ , C3 and C4	Classic	Active SLE; chronic active hepatitis; immune complex disease; subacute bacterial endocarditis; serum sickness
2. Decreased CH ₅₀ and C3; normal C4	Alternate	Acute poststreptococcal glomerulonephritis; immune-complex disease; congenital C3 deficiency
3. Decreased CH ₅₀ and C4; normal C3	Classic (mild)	C1-inhibitor deficiency; C4 deficiency; mixed cryoglobulinaemia
4. Decreased CH ₅₀ ; normal C3 and C4		Hereditary complement component deficiency; cryoglobulinaemia; immune complex disease; coagulation-associated abnormality

SLE = systemic lupus erythematosus.

Our patient's complement profile of normal C3 and C4 levels and absence of CH₅₀ activity is consistent with group 4 in Table II. Care was taken to ensure proper handling of the serum, and the results were reproducible. The clinical picture of recurrent neisserial infection suggested a hereditary complement component deficiency. Unfortunately, specific assays for C6 and C8 were not available.

The clinical pictures resulting from primary complement component deficiencies fall into two broad groups: (i) immune deficiency; and (ii) immunological disease resembling systemic lupus erythematosus (SLE). Clinical associations have been described in the literature for all the components of the classic and terminal pathways except C9^{4,5} (Table III⁵).

It is now well recognized that inherited deficiencies of the terminal complement components C6 and C8 are associated with a high frequency of recurrent or chronic neisserial infections.¹⁻⁶ The terminal portion of the complement cascade is termed the membrane attack system and is responsible for cell lysis. Susceptibility to haematogenous neisserial infection due to deficiency in the terminal complement components suggests that direct serum bacteriolysis may play a prophylactic role in meningococcal infection.⁹ It is interesting to note, however, that in none of the 17 patients with terminal complement component deficiency described in the literature has the outcome been fatal.^{3,10}

Management and prophylaxis

Once it has been determined that the patient has a complement deficiency, especially of C6 or C8, it is important to isolate the strain of the organism responsible. The patient should be immunized with meningococcal vaccine and informed of the

TABLE III. COMPLEMENT COMPONENT DEFICIENCY IN MAN AND ITS CLINICAL ASSOCIATIONS⁵

Component	Clinical associations
C1 _q	Hypogammaglobulinaemia
C1 _r	Infection — SLE-like syndrome
C1 _s	SLE
C4	SLE (atypical)
C2	Immune complex diseases including SLE, polymyositis, glomerulonephritis, Henoch-Schönlein purpura
C3	Severe immune deficiency, fever, arthralgia
C5	SLE
C6	Gonococcal sepsis, recurrent meningococcal meningitis
C7	Raynaud's disease, rheumatoid arthritis
C8	Gonococcal sepsis, recurrent meningococcal meningitis

inherent dangers of venereal disease, especially gonorrhoea, which may result in a disseminated infection, including gonorrhoeal meningitis. Rheumatic fever prophylaxis should also be recommended and the family should be screened for complement deficiencies and carrier status. Fresh-frozen plasma may be used during acute infection, but may lead to the formation of C8 antibodies. The infections are otherwise treated by conventional antimicrobial therapy.

Conclusion

Specific component assay could not be performed in our patient, but the clinical picture and complement profile are consistent with a primary deficiency in the terminal complement components. To date he has suffered one further episode of meningitis. He was admitted to a country hospital and his clinical course was uncomplicated.

The physiological role of complement in the maintenance of a normal state of health is dramatically illustrated by the predisposition to disease and susceptibility to infection which characterize primary deficiency of complement components. The clinical features are those of recurrent neisserial or pyogenic infections and of immunological disease resembling SLE.

I wish to thank Professor J. R. Joubert of the Department of Medicine, Tygerberg Hospital, for his most useful comments, and Professor A. R. Rabson of the Department of Immunology, University of the Witwatersrand, for his suggestions on management and prophylaxis.

REFERENCES

- Charlesworth JA, Pussell BA. Complement deficiency and disease. *Aust NZ J Med* 1982; **12**: 649-655.
- Lim D, Gewurz A, Lint TF, Ghaze M, Sepheri B, Gewurz H. Absence of the sixth component of complement in a patient with repeated episodes of meningococcal meningitis. *J Pediatr* 1976; **89**: 42-47.
- Ellis-Pegler RB, McKay EJ, Laurell AB, Sjöholm AG. Deficiency of the eighth component of complement and recurrent meningococcal disease. *Aust NZ J Med* 1982; **12**: 638-641.
- Agnello GV. Complement deficiency states. *Medicine (Baltimore)* 1978; **57**: 1-23.
- Lachman PJ. Clinical effects of complement deficiency. *Advanced Medicine* 12. Kent: Pitman Medical Publishing, 1976: 43-55.
- Coffey RL, Zile MR, Luskin AT. Immunologic tests of value in diagnosis: Part 2. Complement. *Postgrad Med* 1981; **70**: 183-187.
- Meuwissen HJ. Evaluating patients with suspected immunodeficiency. *Postgrad Med* 1979; **66**: 116-131.
- Reeves WG. Investigation of immunological disorders. *Medicine SA* 1978; **2**: 39-43.
- Fudenberg HH, Stites DP, Caldwell JL, Wells JV. *Basic and Clinical Immunology*. 3rd ed. California: Lange Medical Publications, 1980: 83-95, 607-609.
- Peterson BH, Lee TJ, Snyderman R, Brooks GF. *Neisseria meningitidis* and *Neisseria gonorrhoea* bacteraemia associated with C6, C7 and C8 deficiency. *Ann Intern Med* 1979; **90**: 917-920.