

Systemic meningococcal infections in patients with acquired complement deficiency

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Congenital deficiency of the late components of the complement may predispose the individual to systemic meningococcal infection. Assuming that patients with acquired complement deficiencies may also have an increased risk of contracting meningococcal infections, a retrospective and prospective study to assess this association was conducted. Over 20 years (1970-1989), 30 patients with meningococemia or meningococcal meningitis, proven by blood or CSF culture, were treated at the Beilinson Medical Center. Only one patient died of the infection. Risk factors were found in three patients (10%). One had a congenital deficiency of C7, and two had acquired complement deficiency due to systemic lupus erythematosus (SLE) and membranoproliferative glomerulonephritis (MPGN). These latter two patients had low serum concentration of C3 and C4 and reduced complement hemolytic activity before onset of the infection. Since the incidence of culture-proven systemic meningococcal infection in the Jewish population in central Israel is 1/100,000, and the prevalence of SLE and MPGN is, at most, 250/100,000, the finding of two patients with meningococcal infection and these rare disorders is over 100 times the expected incidence. We conclude that patients with acquired complement deficiency are at significant risk of meningococcal infection.

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Systemic meningococcal infections are serious, often life threatening diseases. Several conditions may predispose individuals to these infections, including congenital deficiency of the late components of complement (1, 2), low serum immunoglobulins (3), deficiency of a single subclass of IgG such as IgG₂ (4), and lack of specific IgM antibodies (5).

It is well known that individuals with congenital deficiency of the late components of complement (C5-C9) are at increased risk of systemic neisserial infections (1, 2, 6, 7). It was estimated that this risk is about 100 times that of the general population (8). One may assume that patients with acquired complement deficiencies may also run a similar risk. This theory is supported by the study of Ellison et al. (9) who reported the occurrence of meningococcal infections in patients with complement-depleting underlying illness. We therefore

performed a retrospective and prospective study of all cases of meningococemia and meningococcal meningitis seen at the Beilinson Medical Center over 20 years to examine the hypothesis that patients with acquired complement deficiency be at increased risk of systemic meningococcal infection.

Methods

The medical charts of all patients with culture-proven meningococemia or meningococcal meningitis seen in the Beilinson Medical Center from 1970 to 1989 were examined. Special attention was paid to previous medical history, concomitant diseases or occurrence of severe infections in the proband and his family, or unexplained death of a family member. The patients were invited after recovery for interview and blood tests, including

C3 and C4, components of complement, complement hemolytic activity (CH_{50}), and immunoglobulins.

Results

Thirty patients (21 men and 9 women) with meningococemia or meningococcal meningitis proven by blood or CSF culture had been treated at the Beilinson Medical Center during the study period. Age range was from 2 months to 62 years (mean, 8.2 years); 26 were in the pediatric age (14 years or younger). One patient died during the acute disease. In three patients risk factors for systemic neisserial infection were found: one girl had congenital deficiency of C7 and a family history of meningococcal infections, and two patients (6.6%) had acquired complement deficiencies at the time of the meningococcal infection. None of the other patients had reported infections or diseases other than the exanthemic diseases of childhood, and there were no remarkable family histories. Immunologic work-up including C3 and C4, component of complement, complement hemolytic activity (CH_{50}) and immunoglobulins, was normal in another 17 patients.

These tests were not performed in the remaining nine patients who did not respond to our request or refused to be tested and in the patient who died during the acute disease. However, without a history of background medical disorders, it is unlikely that these patients had acquired complement deficiency, although congenital complement deficiency cannot be ruled out completely.

Case reports: patients with acquired complement deficiency

Patient 1 – SLE was diagnosed in a 10-year-old, previously healthy girl, who presented with malar rash, lymphadenopathy, arthritis, pericarditis and nephritis. Laboratory tests showed normal WBC, platelets and blood chemistry (SMA-18). Hemoglobin was 9.6 g/dl, ANA was 1/1280, anti DNA – 96% (normal 0–20%). Urinalysis showed 3–6 WBC and 5–8 RBC per field. Urine protein excretion was 0.5–1.0 g per 24 hours. IgG was 1890 mg/dl, IgA 284 mg/dl, IgM 122 mg/dl. C3 component of the complement was in the range: 20–32 mg/dl (normal, 80–180 mg/dl), C4 was 3–5 mg/dl (normal, 8–24 mg/dl) and CH_{50} was 0–21% (normal, 50–200%). Skin biopsy showed deposits of IgM, IgG, and C1q in the dermis-epidermis junction and deposits of IgM and IgG around the blood vessels.

Three weeks after the diagnosis of SLE, while the patient was under treatment with prednisone 60 mg/day, fever, chills and macular eruption on

the chest developed. The following day headache, vomiting, and signs of meningeal irritation appeared. The eruption spread to the limbs and became purpuric. Cerebrospinal fluid examination showed 385 leukocytes/mm³ (95% of them polymorphonuclear), protein 84 mg/dl, and glucose 80 mg/dl. Despite treatment with penicillin, chloramphenicol and methylprednisolone, the patient sank into a stuporous state and developed adult respiratory distress syndrome. Meningococcus group B grew from the CSF and blood cultures.

Normalization of the temperature was observed on the third day of treatment, and after 12 days, the antibiotics were discontinued. The recovery was without apparent sequelae. On follow-up of five years, she was well on a maintenance dose of prednisone, 10 mg every other day.

Patient 2 – MPGN was diagnosed in a 12-year-old boy. There was no family history of immune deficiency, autoimmune disease, recurrent infections or unexplained death of children. After an episode of streptococcal pharyngitis, routine urinalysis showed numerous erythrocytes and granular casts. Blood pressure was normal, and there was no edema. Complete blood count, blood chemistry (SMA-18), ANA, HbsAg, cryoglobulins and circulating immune complexes were normal. The erythrocyte sedimentation rate was 35 mm/hour. IgG was 1020 mg/dl; IgA – 220 mg/dl; IgM – 180 mg/dl. Twenty-four-hour urine collection showed excretion of 1.3 g protein.

Repeated tests for serum complement over two years, showed the following ranges: C3, 0–22 mg/dl (normal, 80–180 mg/dl), C4, 8–24 mg/dl (normal, 8–26 mg/dl); CH_{50} , 0–20% (normal, 50–200%). The diagnosis of MPGN was established by renal biopsy, which also showed granular deposition of C3, IgG and fibrinogen along the basement membrane and in the mesangium. The child was treated with prednisone, 2 mg/kg/day, without apparent effect on the urinalysis or the complement levels. The dosage of prednisone was gradually reduced to 0.5 mg/kg/day every second day.

At the age of 14 years, while his serum complement tests (C3, C4 and CH_{50}) were still very low, the patient contracted meningococcal meningitis. Following several hours of fever and headache, purpuric eruption, vomiting, and signs of meningeal irritation appeared. Cerebrospinal fluid examination showed 5400 leukocytes/mm³, of which 95% were polymorphonuclear, protein 254 mg/dl, and glucose 21 mg/dl. Meningococcus group B grew in blood and CSF cultures. The patient was treated with penicillin and chloramphenicol for two days and afterwards with penicillin only. Normalization of temperature was observed on the

fourth day, and the treatment was discontinued one week later. The child recovered without any apparent sequelae, and has been clinically stable during follow-up of three years.

Discussion

The defense against *Neisseria meningitidis* is mediated principally by such humoral immunity factors as immunoglobulins and complement (3). Therefore, one may assume that patients with immunoglobulin or complement deficiency, either congenital or acquired, will be at increased risk of meningococcal infections.

The results of our study showed that two of 30 patients with systemic meningococcal infection had acquired complement deficiency. One had SLE, a disease with complement depletion, and the other had hypocomplementemic MPGN. The association does not seem coincidental in view of the relative rarity of systemic meningococcal infection in the population. The incidence of culture-proven systemic meningococcal infection in the Jewish population in central Israel is 1/100,000 (10) [while in California it is 0.85 cases per 100,000 persons (11) and in Colorado 0.36 cases per 100,000 persons (9)]. The prevalence of SLE and of MPGN is, at most, 250/100,000 (12, 13). Therefore the finding of two patients, one with SLE and the other with MPGN, among 30 patients, is over 100 times the expected incidence.

A possible association between acquired complement deficiency and meningococcal infections was found in the study of Ellison et al. (9), who reported that three of 20 patients with meningococcal infections had acquired complement deficiency. In that study, the rate of acquired complement deficiency and congenital complement deficiency was 15% each. In our hospital the rate of occurrence of meningococcal infections in patients with acquired complement deficiency is similar (6.6% of all cases), and one of our patients had congenital deficiency of C7. It is possible that some cases of congenital complement deficiency were overlooked in the present study, since the complement was tested only in two-thirds of the patients. However, there was no personal or family history of recurrent infections in the untested patients.

Infections are known to be a major cause of morbidity and mortality in patients with SLE (14, 15). At least 10 cases of meningococcal infections in SLE patients have been reported (9, 16–20). Three of 125 children with SLE developed this infection, and it was estimated that this was 3000 times higher than the expected incidence of meningococcal infection (16). However, it was unclear whether the infection was associated with

acquired complement deficiency, since only one of the three had borderline low C3 and C4. All three patients were infected with *Neisseria meningitidis* serotype Y which is commonly carried in the nasopharynx, but is rarely a cause of disease in normal individuals (21). Ellison et al. (9) reported three patients with SLE and meningococcal infections, two with low serum complement and one with apparently normal complement. In addition, four other sporadic cases of meningococcal infection in patients with SLE have been reported (17–20).

MPGN is often associated with low complement activity due to circulating C3 nephritic factor which causes acquired complement deficiency and partial lipodystrophy (22). It is a relatively uncommon kidney disease, and the association between MPGN and meningococcal infection in one of our patients and in several patients in the medical literature (22–25) indicates the propensity of this acquired complement deficiency condition to meningococcal infection.

One of our 30 patients with systemic meningococcal disease had congenital C7 deficiency (3.3%). No complement deficiencies were found by Merino et al. (26) in a group of 71 patients who were tested after the first episode of meningococcal infection, while a prevalence of 30% was discovered in patients with recurrent meningococcal infections. In a survey of congenital complement deficiencies in Israel, 111 patients with meningococcal infection were investigated and it was found that 9% had congenital complement deficiency (19). This deficiency was described to be common in North African (Sephardi) Jews (18% of the individuals of this ethnic group with a history of meningococcal infection had congenital complement deficiency) and especially in the subgroup of Jews of Moroccan origin (40% of the individuals with a history of meningococcal infections had congenital deficiency). There were no cases of congenital complement deficiency among Ashkenazi Jews (although such a case was reported in the USA). These ethnic differences in the occurrence of congenital complement deficiencies in Israel, which are similar to the finding of an increase in the incidence of congenital complement deficiencies among blacks in the USA, may explain the finding of a single patient with congenital deficiency of the complement in our survey. Twenty-seven of our patients were Jews of Ashkenazi origin but only three were of North-African origin. These were among the 20 who were tested, and one of them was found to have C7 deficiency.

It is important to consider individuals with acquired complement deficiency as having an increased risk of meningococcal infections. Quadrivalent meningococcal vaccine for individuals with

congenital late complement deficiencies has been recommended (27, 28), but the vaccine has not always been protective. Prophylactic penicillin treatment was found to be effective in a group of C6 deficient patients (29), but it is still unknown whether it is effective in other cases of complement deficiency. Therefore, awareness, early diagnostic work-up, and early introduction of antibiotic treatment are indicated.

Abbreviations:

SLE – systemic lupus erythematosus
 MPGN – membranoproliferative glomerulonephritis
 ANA – anti-nuclear antibody
 DNA – deoxyribonucleic acid
 WBC – white blood cells
 RBC – red blood cells
 HbsAg – hepatitis B surface antigen.

References

- PETER G, WEIGERT MB, BISSEL AR, GOLD R, KREUTZER D, McLEAN RH. Meningococcal meningitis in familial deficiency of the fifth component of the complement. *Pediatrics* 1981; 67: 882–6.
- PETERSEN BH, LEE TJ, SNYDERMAN R, BROOKS GF. Neisseria meningitidis and Neisseria gonorrhoeae bacteremia associated with C6, C7, or C8 deficiency. *Ann Int Med* 1979; 90: 917–20.
- CASTAGLIUOLO PP, NISINI R, QUINTI I, FATTOROSI A, D'AMELIO R. Immunoglobulin deficiencies and meningococcal disease. *Ann Allergy* 1986; 57: 68–70.
- BASS JL, NUSS R, MEHTA KA, MORGANELLI P, BENNETT L. Recurrent meningococcemia associated with IgG₂ subclass deficiency. *N Engl J Med* 1983; 309: 430.
- HOBBS JR. Genetic predisposition to meningococcal meningitis. *Lancet* 1986; 1: 501.
- AGNELLO V. Complement deficiency states. *Medicine* 1978; 57: 1–23.
- ELLIS-PEGLER RB, McKAY EJ, LAWRELL AB, SJOHOLM AG. Deficiency of the eight component of the complement and recurrent meningococcal disease: a case and family study. *Aust NZ J Med* 1982; 2: 638–41.
- ROSS SC, DENSEN P. Complement deficiency states and infections Epidemiology pathogenesis and consequences of Neisserial and other infections in an immune deficiency. *Medicine* 1984; 63: 243–73.
- ELLISON RT, KOHLER PF, CURD JG, JUDSON FN, RELLER LB. Prevalence of congenital or acquired complement deficiency in patients with sporadic meningococcal disease. *N Engl J Med* 1983; 308: 913–16.
- State of Israel – Ministry of Health – Monthly epidemiological bulletin, 1986; 21: 4–19.
- JUELS C, MORRISON FR, OVERTURF GD, ROBERTO RR, CHIN J. Meningococcal disease in California. *West J Med* 1978; 128: 195–202.
- SCHUR PH. Clinical features of SLE. In: KELLY, HARRIS, RUDDY, SLEDGE, eds. *Textbook of rheumatology*. Philadelphia: Saunders, 1989: 1101.
- SIMON P, ROMEE MP, ANG KS, CAM G. Variations of primary glomerulonephritis incidence in a rural area of 400,000 inhabitants in the last decade. *Nephron* 1987; 45: 171.
- STAPLES PJ, GERDING DN, DECKER JL, GORDON RS. Incidence of infection in systemic lupus erythematosus. *Arthritis Rheum* 1974; 17: 1–10.
- WALRAVENS PA, CHASE HP. The prognosis of childhood systemic lupus erythematosus. *Am J Dis Child* 1976; 130: 929–33.
- LEHMAN TJA, BERSTEIN B, HANSON V, KORNREICH H, KING K. Meningococcal infection complicating systemic lupus erythematosus. *J Pediatr* 1981; 99: 94–6.
- VACHTENHEIM J. Meningococcal meningitis with symptoms of Waterhouse Friderichsen syndrome in a patient with familial occurrence of systemic lupus erythematosus. *Cas Lek Cesk* 1971; 110: 1128–37.
- SCHUR PH, FLAX MH. Sudden death of a woman with systemic lupus erythematosus. Case report of the Massachusetts General Hospital. *N Engl J Med* 1967; 276: 684–692.
- ZIMRAN A, RUDENSKY B, KRAMER MR, et al. Hereditary complement deficiency in survivors of meningococcal disease: high prevalence of C7/C8 deficiency in Sephardic (Moroccan) Jews. *Q J Med* 1987; 63: 349–58.
- KIMBERLY RP, LOCKSHIN MD, SHERMAN RL, MOURADIAN J, SAAL S. Reversible “end stage” lupus nephritis. Analysis of patients able to discontinue dialysis. *Am J Med* 1983; 74: 361–9.
- COHEN MS, STEERE AC, BALTIMORE R, et al. Possible nosocomial transmission of group Y *Neisseria meningitidis* among oncology patients. *Ann Intern Med* 1979; 91: 7–12.
- THOMPSON RA, YAP PL, BRETTLE RB, DUNMOW RE, CHAPEL H. Meningococcal meningitis associated with persistent hypocomplementemia due to circulating C3 nephrotic factor. *Clin Exp Immunol* 1983; 52: 153–6.
- SISSONS JGP, WEST RJ, FALLOWS J, WILLIAMS DG, BOUCHER BJ, AMOS N, PETERS DK. The complement abnormalities of lipodystrophy. *N Engl J Med* 1976; 294: 461–5.
- REICHEL W, KOBBERLING J, FISCHBACH H, SCHELER F. Membranoproliferative glomerulonephritis with partial lipodystrophy. *Klin Wschr* 1986; 54: 75–81.
- SCHIFFERLI JA, BLANC E. Partial lipodystrophy meningococcal meningitis and nephritis. *Dermatologica* 1986; 173: 9–12.
- MERINO J, RODRIGUEZ-VALVERDE V, LAMELAS JA, RUESTRA LL, CASANUEVA B. Prevalence of deficits of complement components in patients with recurrent meningococcal infections. *J Infect Dis* 1983; 148: 331.
- Meningococcal vaccines. *MMWR* 1985; 34: 225–229.
- Center of Dis Control. Bacterial meningitis and meningococcemia, United States, 1978 *MMWR* 1979; 28: 277–279.
- POTTER PC, FRASCH CE, VAN DER SANDE WJM, COOPER RC, PATEL Y, ORREN A. Prophylaxis against Neisseria meningitidis infections and antibody responses in patients with deficiency of the sixth component of complement. *J Infect Dis* 1990; 161: 932–937.