Assessment of Complement Deficiency in Patients with Meningococcal Disease in the Netherlands

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The frequency of complement deficiency in 176 of 7,732 patients with meningococcal disease in the Netherlands from 1959 through 1992 was assessed. Complement deficiency was found in six patients (3%): 3 (7%) of the patients with *Neisseria meningitidis* serogroup C disease, 1 (2%) of the patients with *N. meningitidis* serogroup A disease, and 2 (33%) of the patients with infections due to uncommon serogroups and nongroupable strains of *N. meningitidis*. Of 91 additional patients with meningococcal infections due to uncommon serogroups, 33% also had complement deficiency. Thirty-four of the 36 complement-deficient patients with meningococcal disease who were from 33 families were 5 years of age or older. Twenty-six additional complement-deficient relatives were found. Screening individuals with meningococcal disease due to uncommon serogroups who were 5 years of age or older identified 30 of the 33 complement-deficient families. Only 27% of the complement-deficient relatives had had meningococcal disease. This risk was lower for relatives with properdin deficiency (18%) than for those deficient in the late component of complement (38%). Therefore, pedigree studies are warranted for identifying those complement-deficient persons who require vaccination for meningococcal disease.

Complement-deficient individuals have a high risk of developing meningococcal disease [1–3]. Properdin deficiency (X-linked inherited) is associated with nonrecurrent meningococcal disease [3]. The frequency of autoimmune diseases and infections due to various bacterial species, including meningococci, is high among persons with autosomal inherited deficiencies of C1, C2, C4, C3, factor H, or factor I [1]. Late complement component (C5, C6, C7, C8, or C9) deficiency (LCCD; autosomally inherited) is associated with recurrent meningococcal disease [1, 2].

Under the assumption that persons with complement deficiency are capable of developing immunity to meningococci, vaccination with the available vaccine for *Neisseria meningitidis* infection has been recommended [1, 3]. The question is how to identify complement-deficient persons being considered for vaccination. Population screening for the various inherited complement deficiencies is not feasible, since the estimated frequency of all complement deficiencies together in the general population is only 0.03% [1]. The annual rate of meningococcal disease in western Europe and the United States is 2 to 10 cases per 100,000 population [4]. Therefore, if all patients with meningococcal disease were to be tested for complement deficiency, a huge effort would have to be made.

Microbiological data on and clinical characteristics of complement deficiency associated meningococcal disease are derived from studies including selected groups of patients [1–3, 5–7]. Complement-deficient individuals have meningococcal disease at an older age than do the general population, and the serogroups causing their diseases are relatively uncommon in the general population [5, 7, 8]. Meningococcal disease in properdin-deficient patients is associated with a high risk of death [3], whereas recurrent episodes in patients with LCCD are often mild [1, 9].

We reviewed data from the archives of the Netherlands Reference Laboratory for Bacterial Meningitis (Amsterdam) to determine the frequency of complement deficiencies in patients with meningococcal disease. These data allowed us to retrospectively trace the survivors of meningococcal disease in the period from 1959 through 1992. Since it has been demonstrated that the outcome of meningococcal disease is directly related to the clinical manifestations of the disease (meningitis, meningococcal septicemia, or meningococcal septic shock) [10], we compared the clinical course of meningococcal disease in complement-deficient patients with that in complement-sufficient patients. Because data on the frequency, microbiological characteristics, and clinical course of meningococcal disease in nonselected groups of patients with complement deficiencies are scarcely known, we also per-

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Table 1. Summary of data for patients with *Neisseria meningitidis* disease in the Netherlands during the period from 1959 through 1992 according to serogroup and complement function.

Period	Mean annual rate of *N. meningitidis* disease*	No. of patients with infection due to indicated meningococcal serogroup who were studied for complement function/total no. of infected patients									
		A	B	C	W135	X	Y	Z	29E	NG	Total/total
1959–1964	1.35	3/29	2/292	3/83	0	0/2	3/9	0	0	0/1	11/416
1965–1969	2.2	5/60	3/788	8/98	0	1/2	1/4	0	0	0	18/952
1970–1974	1.7	5/165	1/665	4/154	17/53	0	1/9	0	0	1/4	29/1,050
1975–1979	0.99	2/173	3/480	6/135	16/39	1/2	3/8	0	0	3/5	34/842
1980–1984	1.68	15/146	5/578	9/226	8/14	3/4	3/6	1/1	1/1	1/3	46/979
1985–1989	2.54	14/48	45/1,410	15/344	11/18	4/6	9/17	0/3	1/1	1/1	100/1,848
1990–1992	3.6	1/19	20/1,242	1/363	2/11	0/1	3/6	0/1	0	2/2	29/1,645
1959–1992	2.0	45/640	79/5,455	46/1,403	54/135	9/17	23/59	1/5	2/2	8/16	267/7,732

NOTE. NG = nongroupable.
* Per 100,000 population.

formed studies involving the relatives of complement-deficient probands.

Study Population and Methods

Patients with Meningococcal Disease Selected for Complement Function Study

The archives of the Netherlands Reference Laboratory for Bacterial Meningitis have data on and CSF and blood isolates from 7,732 patients (table 1) with meningococcal disease that were collected from 1959 through 1992. The isolates were serogrouped by means of Ouchterlony gel diffusion with use of rabbit antisera to the capsular polysaccharides of serogroups A, B, C, 29E, H, I, K, L, W135, X, Y, and Z [6, 11, 12].

For each year in the period from 1959 through 1992, four patients each with meningococcal disease due to serogroups A, B, and C were selected. Two of them were younger than 5 years of age and two were 5 years of age or older at the time that they contracted the disease. Since the frequency of meningococcal disease due to the uncommon serogroups W135, X, Y, Z, and 29E and to nongroupable meningococci is low (table 1), three patients for each 10-year interval were selected. In the years 1989 through 1992, the incidence of *N. meningitidis* serogroup B disease increased twofold. Therefore, 55 additional patients with meningococcal disease due to serogroup B in this period were included.

The first study group included 460 (6%) of the 7,732 patients on the basis of age and infecting meningococcal serogroup. One hundred seventy-six patients (38%) were traceable and willing to participate in the study. The second study group included 91 of the other 225 patients with meningococcal disease due to uncommon serogroups in the period 1959 through 1992 who were traced and willing to participate in the study (table 1).

Pedigree Studies of Patients with Complement Deficiency

Pedigree studies were performed for patients with inherited complement deficiencies. In properdin-deficient families, presumed female carriers and their male offspring were requested to take part in the study. In families with other deficiencies, brothers, sisters, and parents of each proband were requested to participate in the study. Household members as well as other relatives of the patients were asked by questionnaire whether they had had meningococcal disease; if their answers reflected a history of meningococcal disease, then a search in the archives of the Netherlands Reference Laboratory for Bacterial Meningitis was done to collect clinical and/or bacteriologic data. If their data were not present, the medical records of the general practitioner or the hospital to which they had been admitted were studied. If the medical history of a relative suggested that meningococcal disease had occurred, the sibship of that relative was studied for complement deficiency. None of the complement-deficient patients or relatives had been vaccinated for meningococcal disease before or during the study period.

Course of Meningococcal Disease

Standard criteria were used to ascertain the clinical diagnosis of meningococcal disease in patients and relatives [10, 13]. Meningococcal disease was classified as meningitis, septicemia, meningitis with septicemia, and septic shock. Meningitis was defined by a CSF culture positive for *N. meningitidis* or, in the case of a negative culture, by the presence of gram-negative diplococci in CSF sediment. In cases in which results of CSF culture or staining were not available, meningitis was defined on the basis of presence of symptoms and signs such as fever, headache, vomiting, and nuchal rigidity as well as an increased number of polymorphonuclear neutrophils, an increased protein concentration, and a decreased glucose concentration in the CSF. Meningococcal septice-

mia was defined by a culture of a blood or skin lesion (petechiae, purpura, or macular rash) sample that was positive for meningococci or by the presence of such lesions. Meningococcal septic shock was defined as septicemia associated with hypotension requiring supportive treatment with inotropic and/or vasopressor medication.

Data for the patients were obtained from the archives of the Netherlands Reference Laboratory for Bacterial Meningitis and from the general practitioners and medical specialists in the hospitals to which the patients had been admitted. In a previous study, data on 429 cases of meningococcal disease, which occurred from 1989 through 1990, were collected and analyzed similarly to those for complement-deficient individuals [14].

Assays for Complement Determination

All selected patients who were traced were visited by one of us for collection of blood samples for complement studies. Serum samples were flash frozen and stored at −70°C. In cases in which a complement deficiency was assessed, blood samples from relatives were also collected for complement studies. Hemolytic screening for the alternative, classic, and terminal pathways of complement activation was performed, both in gel according to Truedsson et al. [15] and in free suspension according to Nilsson and Nilsson [16]. Tests were done in duplicate. Control sera with a deficiency in the alternative pathway (factor B; C-0535, Sigma, St. Louis) or the classic pathway (C1q; 0410, Sigma) were always included.

If hemolytic screening showed a defect in one of the pathways, the deficient component was identified by using quantitative assays. ELISA was used for properdin, C8, and C9, and double radial immune diffusion assays were used for C3, factor H, and factor B. Hemolytic assays were used for C3, C5, C6, C7, factor D, and C3 nephritic factor (C3 NeF) [17, 18]. C8β deficiency was confirmed by western blotting [19]. Serum samples from the probands were studied for all factors within the affected pathway. Serum samples from relatives were quantitatively investigated for the particular complement component deficient in their proband.

Statistical Analyses

The χ^2 test or Fisher's exact test was used to determine whether the difference between the frequency of complement deficiency in patients with meningococcal disease who were 5 years of age or older and younger than 5 years of age; the frequency of distinct clinical presentations of meningococcal disease in patients with properdin deficiency, patients with LCCD, and complement-normal persons; and the frequency of meningococcal disease in complement-deficient and complement-normal relatives was significant. The proband method of Weinberg was used to assess the frequency of meningococcal disease in the complement-deficient families [20].

Results

Frequency of Complement Deficiency in Patients with Meningococcal Disease

Between 1959 and 1992, 7,732 meningococcal isolates collected at the Netherlands Reference Laboratory for Bacterial Meningitis were characterized. Serogroups A, B, and C accounted for 8%, 71%, and 18% of all strains, respectively. Nongroupable meningococci and uncommon serogroups (W135, X, Y, and Z) represented 3% of all patient isolates.

In the first study group, 176 (38%) of the 460 patients took part in the study. Of these 176 patients, six (3%) had a complement deficiency (table 2). One (2%) of the 45 patients with serogroup A disease and three (7%) of the 46 patients with serogroup C disease had a complement deficiency. Complement deficiencies were not found in the 79 patients with meningococcal disease due to serogroup B. A complement deficiency was found in two (33%) of the six patients with meningococcal disease due to the uncommon serogroups W135, X, Y, Z, and 29E and nongroupable meningococci. In the second study group of an additional 91 patients with disease due to uncommon serogroups, 30 (33%) had a complement deficiency.

Of all 267 patients in both study groups, 92 (34%) were younger than 5 years of age at the time of their disease. A complement deficiency was present in only two (2%) of these patients, while 34 (19%) of the 175 persons 5 years of age or older at the time of their disease were complement-deficient ($\chi^2 = 15.79$; $P = .0001$). The age distribution for the 32 complement-deficient patients with meningococcal disease due to uncommon serogroups showed that only one (3%) was younger than 5 years of age (figure 1). In contrast, 29 (45%) of the 65 complement-sufficient persons with meningococcal disease due to uncommon serogroups were younger than 5 years of age. Three of the four complement-deficient persons with meningococcal disease due to serogroups A and C were also 5 years of age or older.

Type of Complement Deficiency

Properdin deficiency was the single most common complement deficiency; it was detected in 13 patients (36%) (table 2), of whom two had dysfunctional properdin. Properdin deficiency was identified only in patients with meningococcal disease due to uncommon serogroups (table 2). The mean age for these patients at the time of their disease was 12 years (range, 1–21 years). C3 deficiency syndrome was present in six patients (17%) (mean age, 21 years; range, 10–48 years), of whom three had an acquired complement deficiency due to C3 NeF. One patient had factor H deficiency, and two patients had inherited C3 deficiency. LCCD (C5 through C8) was present in 17 patients (47%) (mean age, 16 years; range, 4–36 years) during the first episode of meningococcal disease. Patients with C3 deficiency syndrome and LCCD were found within all serogroups.

Table 2. Summary of data for patients with meningococcal disease who were studied for complement deficiency and the specific complement deficiencies found according to meningococcal serogroup.

Meningococcal serogroup	No. of patients with indicated complement deficiency										No. of patients with complement deficiency/total no. studied (%)
		C3 deficiency syndrome				LCCD					
	Properdin	Total	Factor H	C3	C3 NeF	Total	C5	C6	C7	C8	
A	0	0	0	0	0	1	0	0	0	1	1/45 (2)
B	0	0	0	0	0	0	0	0	0	0	0/79
C	0	1	0	1	0	2	0	0	0	2	3/46 (7)
W135	9*	2	0	0	2	5	2	0	1	2	16/54 (30)
X	0	1	1	0	0	2	1	0	1	0	3/9 (33)
Y	4	2	0	1	1	5	1	1	2	1	11/23 (48)
Z	0	0	0	0	0	0	0	0	0	0	0/1
29E	0	0	0	0	0	0	0	0	0	0	0/2
NG	0	0	0	0	0	2	0	0	1	1	2/8 (25)
Total	13	6	1	2	3	17	4	1	5	7	36/267 (13)

NOTE. C3 NeF = C3 nephritic factor; LCCD = late complement component deficiency; NG = nongroupable.
* Including two patients with dysfunctional properdin deficiency.

Pedigree Studies

Studies involving 216 relatives of 27 families were done. There were 36 complement-deficient patients with meningococcal disease from 33 families. One patient with functional properdin deficiency, one patient with complete properdin deficiency, and one C8β-deficient patient belonged to families who were identified twice. Six families of six patients did not participate in the study. Of the 216 relatives studied, 26 (12%) had a complement deficiency (table 3).

The nine families of the probands with complete properdin deficiency included 84 relatives, 34 of whom were males (17 were descendants of obligate female carriers). Of these 17 males, 11 (65%) were properdin-deficient (table 3). None of the 21 relatives of the factor H–deficient proband was factor H–deficient (table 3). Two C3-deficient relatives were found in one of two families. In the 15 families of patients with LCCD, 97 relatives (including 44 brothers and sisters of the probands) were studied. In nine (20%) of these 44 close relatives, a deficiency was detected.

Frequency of Meningococcal Disease in Relatives

Seven (27%) of the 26 complement-deficient relatives had had one or more episodes of meningococcal disease (table 3), while two of 190 complement-sufficient relatives had had meningococcal disease ($P < .01$, Fisher's exact test). Meningococcal disease occurred in two (18%) of 11 relatives with complete properdin deficiency at the ages of 1 year and 2 years,

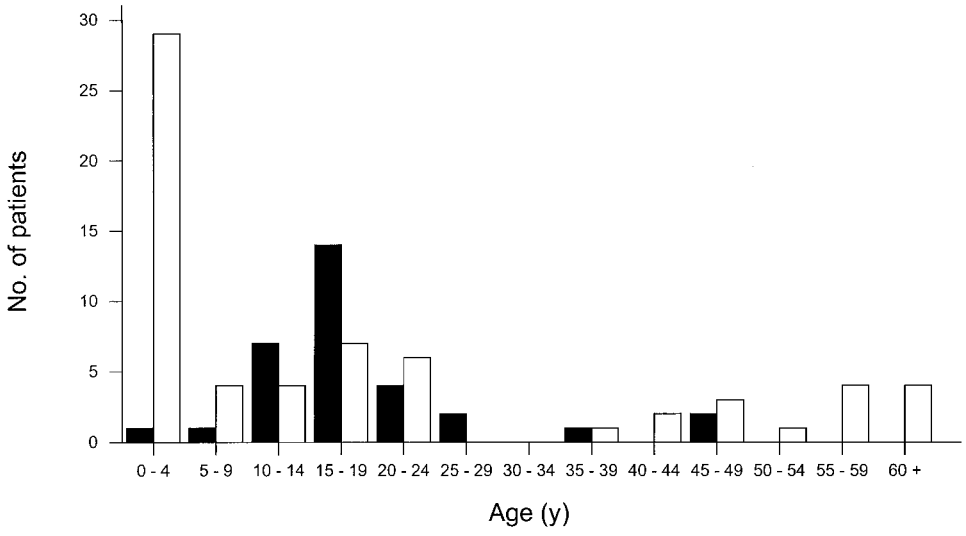

Figure 1. Age distribution for and complement status of patients with meningococcal disease due to serogroups W135, X, Y, Z, and 29E and nongroupable meningococci at the time of their disease. ■ = complement-deficient patients (n = 32); □ = complement-sufficient patients (n = 65).

Table 3. Summary of data for families and relatives of complement-deficient patients with meningococcal disease (probands).

Complement deficiency	Probands	Relatives studied	Informative relatives*	Relatives with complement deficiency	Relatives with complement deficiency and meningococcal disease
Properdin	9	84	17	11	2
C3 deficiency syndrome					
Factor H	1	21	4	0	0
C3	2	14	10	2	0
LCCD					
C5	3	23	11	2	1
C6	1	6	3	0	0
C7	5	16	9	1	0
C8	6	52	26	10†	4
Total	27	216	80	26	7

NOTE. Data are no. of persons. LCCD = late complement component deficiency.

* Male offspring of female obligate carriers of properdin deficiency (X-linked inherited) and brothers and sisters of probands with all other deficiencies (autosomal inherited).

† Includes two additional generations in one of the C8-deficient families.

respectively (table 4). The mean age for nine relatives with properdin deficiency and no previous meningococcal disease was 34 years (range, 22–60 years).

Five (38%) of the 13 relatives with LCCD had had meningococcal disease (table 3); one had C5 deficiency, and four had C8β deficiency. In these latter four patients (all of whom belonged to one family), eight episodes of meningococcal disease occurred (table 4) in the period between 1938 and 1990. The mean age at the first episode of meningococcal disease in the five patients with LCCD was 13 years (range, 6–25 years). The mean age for the eight relatives with LCCD who did not have meningococcal disease was 38 years (range, 27–55 years) at the end of the study period.

Episodes of Recurrent Meningococcal Disease in Probands and Relatives

Properdin-deficient persons and individuals with factor H or C3 NeF deficiency had no recurrences of meningococcal disease. The two probands with inherited C3 deficiency had one recurrence of meningococcal disease due to serogroups B and C, respectively. In total, 17 recurrences of meningococcal disease occurred in nine of the 16 probands with LCCD and three of the five relatives with LCCD. Twelve (57%) of the 21 patients with LCCD had two episodes of meningococcal disease; of these 12 patients, four (33%) had a third episode and of these four, one (25%) had a fourth episode of meningococcal disease. Of the 16 probands with LCCD, nine (56%)

Table 4. Characteristics of the seven relatives of complement-deficient patients with meningococcal disease who also had complement deficiencies and meningococcal disease.

Patient no./sex	Complement deficiency	No. of episodes	Clinical diagnosis	Meningococcal isolate	Age(s) in y/ year(s) of episode(s)	Other disease(s)
1/M	Properdin	1	Meningitis and septicemia	Serogroup C	2/1973	Recurrent otitis
2/M	Properdin	1	Meningitis	Serogroup Y	1/1961	
3/F	C5	1	Meningitis and septicemia	*Neisseria meningitidis*	18/1980	Bronchopneumonia, ear-throat infections
4/F	C8	2	Meningitis, meningitis	ND, ND	16/1938, 25/1947	Bronchitis, urinary tract infections
5/M	C8	3	Meningitis, meningitis and septicemia, meningitis	ND, ND, ND	6/1947, 20/1961, 21/1962	
6/M	C8	2	Meningitis, meningitis	ND, serogroup C	10/1953, 21/1964	Throat infections, hypertension, myocardial infarction
7/M	C8	1	Meningitis and septicemia	NG	17/1990	

NOTE. ND = not determined; NG = nongroupable.

Table 5. Clinical entities of meningococcal disease in the general patient population, patients with LCCD, and properdin-deficient patients.

Patient type	No. studied	No. of meningococcal episodes	No. (%) of episodes of indicated meningococcal disease			
			Meningitis	Septicemia	Meningitis and septicemia	Septic shock
General patient population	429	429	98 (23)	65 (15)	217 (51)	49 (11)
Patients with LCCD	17	22	6 (27)	4 (18)	7 (32)	5 (23)*
Properdin-deficient patients	11	11	2 (18)	1 (9)	5 (46)	3 (27)*

NOTE. LCCD = late complement component deficiency.
* $P = .04$, in comparison with septic shock in the general population.

had had 13 recurrences. These recurrent episodes of meningococcal disease were caused by serogroup B in 1 case, serogroup C in 3 cases, and serogroup Z in 1 case. Seven isolates were not serogrouped, and in one case, recurrence of meningitis was caused by the *Neisseria*-related *Moraxella osloensis* [11]. Of the five relatives with LCCD and meningococcal disease, three had had four recurrent episodes of meningococcal disease (table 4).

Course of Meningococcal Disease

The clinical entities of meningococcal disease in 11 properdin-deficient individuals (10 probands and one relative) were compared with those in 17 persons with LCCD (14 probands and three relatives) and with those in 429 patients from the general population (table 5). Meningococcal septic shock developed in three properdin-deficient patients (27%); septic shock was caused by serogroup W135 in two patients and serogroup Y in one. Meningococcal septic shock developed in five patients with LCCD (23%); it was caused by serogroup B in 1 patient, serogroup C in 2 patients, and serogroup W135 in 2 patients. No difference was found in the clinical course of meningococcal disease in patients with LCCD and in the first and recurrent episodes. Forty-nine (11%) of 429 episodes of meningococcal disease were septic shock, either with or without meningitis, in the 429 patients in the general population, which was significantly lower ($P = .04$) than eight (24%) of 33 episodes in both the properdin-deficient individuals and the patients with LCCD. Serogroup B was the predominant (75%) serogroup for the 429 patients, of whom 41% were younger than 5 years of age at the time of disease.

Estimated Mortality Rate Associated with Meningococcal Disease in Complement-Deficient Probands and Relatives

Probands and their relatives were interviewed by questionnaire to assess the number of relatives who died of complement deficiency–related meningococcal disease. We obtained information from 140 subjects, encompassing three to four generations, from the families of nine properdin-deficient probands. Within one family, three relatives were found who had had meningococcal meningitis. Two of them proved to be properdin-deficient. The third relative, the brother of an obligate female carrier who was presumed to be properdin-deficient, died of bacterial meningitis. The estimated mortality rate among properdin-deficient patients with meningococcal disease, including the nine probands, was 8% (one of 12).

We collected information from 180 subjects, encompassing three to four generations, from the families of 15 patients with LCCD. Six relatives were found who had had meningococcal meningitis, of whom five were complement-deficient. One female relative died of meningococcal disease due to serogroup A at the age of 39 years, but her complement status was unknown. If she were complement-deficient, the estimated mortality rate among patients with LCCD and meningococcal disease, including the 15 probands, would be 5% (one of 21).

Discussion

A complement deficiency was found in six (3%) of 176 patients with meningococcal disease who were selected for the study on the basis of age and infecting serogroup (first study group). The number of patients with disease due to serogroup B was underrepresented with regard to the frequency of disease due to this serogroup in the general population. None of our patients with disease due to serogroup B had a complement deficiency, but two of the 10 recurrences of meningococcal disease in complement-deficient patients were due to serogroup B. This finding is in agreement with previous reports that serogroup B is rarely associated with complement deficiency [21–23]. A complement deficiency was found in 7% of patients with meningococcal disease due to serogroup C and in 2% of patients with disease due to serogroup A. The distribution of complement deficiencies in the endemic situation of meningococcal disease due to serogroups A, B, and C, often causing outbreaks and epidemics, has not yet been reported. Of 91 patients with meningococcal disease due to the uncommon serogroups W135, X, Y, and Z (second study group), 30 (33%) had a complement deficiency. In three studies reporting the frequency of complement deficiency in patients infected with uncommon serogroups [5, 7, 8], this rate varied from 26% to 50%.

The results of our study also confirm that the age at which meningococcal disease is contracted is another important criterion for the decision to perform complement studies [5, 8]. In the Netherlands, 41%–52% of patients with meningococcal disease are younger than 5 years of age [11, 24]. In our study, 31 (46%) of the 67 patients older than 5 years of age who had meningococcal disease had a complement deficiency, whereas only one (3%) of the 30 patients younger than 5 years of age at the time of disease due to uncommon serogroups had a complement deficiency. Our findings indicate that, in the general population, protection against disease due to uncommon serogroups is present at the age of 5 years, while the risk for the disease due to these serogroups remains in complement-deficient persons.

Of the 36 complement-deficient persons, complete properdin deficiency was present in 11 patients (30%); dysfunctional properdin deficiency, in 2 related persons (6%); C3 deficiency syndrome, in 6 patients (17%); and LCCD, in 17 patients (47%). Remarkably, no deficiency of a component of the classic pathway of complement activation was found, although homozygous C2 deficiency is supposed to be the most commonly inherited defect of the complement cascade (occurring in 0.009% to 0.01% of the normal Caucasian population) [1].

In our study, we were able to estimate by questionnaire that 8% of properdin-deficient persons and 5% of individuals with LCCD died of their meningococcal disease. The case-fatality rate for meningococcal disease in the general population is 5.2%–7.7% [14, 24]. When the surviving probands were excluded, the mortality rate among properdin-deficient relatives with meningococcal disease was 33% (one of three) and that among relatives with LCCD and meningococcal disease was 17% (one of six). These high mortality rates among the small number of complement-deficient relatives were associated with a rather high frequency of meningococcal septic shock. However, it should be emphasized that only survivors underwent complement screening. Therefore, the mortality rates associated with various complement deficiencies that have been reported may be negatively biased.

The risk of contracting meningococcal disease in persons with the various types of complement deficiency differs considerably and is significantly higher than that in the general population. The families of the nine probands with total properdin deficiency included 84 relatives, 34 of whom were male (17 were descendants of obligate female carriers); of these 17 males, 65% had a properdin deficiency, which is close to the expected rate of 50% for an X-linked trait. Meningococcal disease occurred in only two (18%) of 11 relatives with complete properdin deficiency, but when the probands were included, 57% of properdin-deficient relatives had had meningococcal disease. The latter rate is as high as the assumed frequency of 45% to 53%, which is based on a review of all cases of properdin-deficient persons [3]. In families with dysfunctional properdin deficiency, both the risk for meningococcal disease and the mortality rate are greater [3, 25]. The families of the patients with LCCD included 97 relatives; 20% of the brothers and sisters of the probands were complement-deficient (this rate is in agreement with the expected rate of 25% for an autosomal recessive trait). Of the 13 relatives with LCCD, five (38%) developed meningococcal disease; when the probands were included, the frequency of meningococcal disease increased to 71%, which is higher than the previously estimated risk of 57% [1].

During the 33-year study period, the mean annual incidence of meningococcal disease in the general population was ~2 cases per 100,000 persons (table 1). The incidence for the properdin-deficient individuals and those with LCCD was 500 and 1,200 cases per 100,000 persons, respectively. Consequently, the risk of contracting meningococcal disease in properdin-deficient persons and persons with LCCD is 250 and 600 times higher than that in the general population, respectively. However, it cannot be excluded that in certain complement-deficient families additional risk factors for meningitis are present, as indicated by the finding that two complement-normal relatives of one family with LCCD developed meningococcal disease. It may be that the IgG Fcγ receptor phenotype FcγRIIa R131R131/IIIb NA2NA2 comprises such a factor, since an association between this phenotype and meningococcal disease has been recently reported [26, 27].

The identification of complement deficiency by testing for complement function in patients with meningococcal disease due to uncommon serogroups or nongroupable strains who were 5 years of age or older resulted in the recognition of 30 (91%) of 33 complement-deficient families. In addition, two C3-deficient relatives, 11 relatives with complete properdin deficiency, and 13 relatives with LCCD were identified by pedigree studies. Nine (82%) of 11 properdin-deficient relatives and eight (62%) of 13 relatives with LCCD had not developed meningococcal disease. These relatives were all older than 20 years of age, at which time it is assumed that 95% of the general population has had carriage of meningococci [28, 29]. The median age at which the probands and relatives developed meningococcal disease was 16 years. As a consequence of the usual approach of assessing complement deficiency in patients with meningococcal disease, a relevant number of complement-deficient individuals will not be detected. Therefore, pedigree studies are necessary to identify those complement-deficient individuals who are candidates for vaccination for meningococcal disease.

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