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Association of Human FcγRIIa (CD32) Polymorphism with Susceptibility to and Severity of Meningococcal Disease

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Phagocytosis of bacteria constitutes an important defense mechanism against invasive bacterial diseases. Efficacy of phagocytosis by polymorphonuclear neutrophils is known to vary between allotypes of FcγRIIa (a class of Fc receptors for immunoglobulins that is constitutively expressed on neutrophils). We compared the distribution of FcγRIIa-R131 and FcγRIIa-H131 allotypes in 98 Slavic complement-sufficient patients with meningococcal disease with that of the allotypes in 107 healthy controls. A strong association was found between the IIa-R/R131 allotype and the development of meningococcal disease after the age of 5 years, compared with IIa-R/H131 and IIa-H/H131 allotypes ($P < .03$; odds ratio [OR], 2.9). A severe course of meningococcal disease was observed in 21 (68%) of 31 episodes in patients with IIa-R/R131 genotype and in 22 (54%) of 41 episodes in patients with IIa-R/H131 genotype, in contrast to eight (31%) of 26 episodes in patients with IIa-H/H131 genotype ($P < .02$; OR, 4.7). Our data show that individuals older than 5 years of age who have the IIa-H/H131 allotype are less susceptible to severe meningococcal disease than are individuals with the IIa-R/R131 or IIa-R/H131 genotype.

Meningococcal disease is an infectious disease associated with a high rate of mortality that affects otherwise healthy individuals and causes severe neurological sequelae. The annual incidence of meningococcal disease in western Europe and in Russia fluctuates around one to six cases per 100,000 individuals [1]. Most cases of meningococcal disease occur in the first 4 years of life, but the occurrence peaks again during the teenage years [1]. The rates of mortality (5%–20%) and of morbidity and sequelae (5%–30%) due to meningococcal disease depend on both bacterial virulence factors and host immune defense mechanisms, such as the complement system, antibody production, cytokine production, and phagocytic killing [2–7].

The effectiveness of phagocytosis depends significantly on the Fc receptors (FcRs) for immunoglobulins that are found on phagocytes [4, 8, 9, 10]. Three major classes of leukocyte FcRs for IgG exist in humans: FcγRI (CD64), FcγRII (CD32), and FcγRIII (CD16) [11]. The latter two classes are constitutively expressed on neutrophils as FcγRIIa and FcγRIIIb and exhibit structural and functional polymorphisms. Both receptors can bind to human IgG1 and IgG3 subclasses, but FcγRIIa represents the sole leukocyte FcR capable of binding to IgG2 [12]. Two allotypic forms of FcγRIIa are known (FcγRIIa-R131 and FcγRIIa-H131) because of the presence of arginine or histidine at position 131 in the extracellular domain of the receptor, respectively [12].

The IgG2 isotype dominates in the immune response to encapsulated bacteria, such as meningococci [13, 14]. In vitro, neutrophils with the IIa-H/H131 allotype optimally phagocytose IgG2-opsonized *Haemophilus influenzae* type b, *Staphylococcus aureus, Neisseria meningitidis* group B, and group B streptococcus type III [4, 8, 9]. Neutrophils with the IIa-R/R131 allotype are less effective than neutrophils with the IIa-H/H131 allotype, and neutrophils with a heterozygous allotype exhibit intermediate levels of phagocytosis [4, 8, 9]. On the basis of these in vitro data, we hypothesized that individuals with IIa-R/R131 allotypes are more susceptible to meningococcal disease than are individuals with IIa-H/H131 and IIa-R/H131 allotypes. A prospective study was designed to collect DNA samples from patients with meningococcal disease who were admitted to the Second Moscow Hospital of Infectious Diseases; the FcγRIIa allotypes were analyzed by using a recently developed molecular biological approach.

Patients and Methods

Patients. Ninety-eight patients admitted consecutively to the Second Moscow Hospital of Infectious Diseases because of a diagnosis of systemic meningococcal disease (see below)

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were enrolled in the study. Criteria for inclusion were Slavic origin, intact hemolytic activity of the classic and alternative complement pathways, and normal levels of complement components. All patients included in the study were Caucasian, had Slavic surnames, used Russian as their native language, and considered themselves as Russians. The age and sex distribution corresponded to that observed for patients admitted previously to the hospital because of meningococcal disease in Moscow; 62 patients (63%) were male, and the median age of the patients was 5 years (range, 1 month to 59 years). The controls consisted of 107 healthy Slavic adult (age range, 18–40 years) blood donors from Moscow.

Diagnosis of meningococcal disease. Analyses of the patients' clinical diagnoses and severity of disease were performed retrospectively; these analyses were based on information obtained by the treating physicians that was documented on standard case records and discharge letters. The diagnosis of meningococcal disease was made on the basis of the following: bacterial culture yielding *N. meningitidis* (group A, 13 organisms; group B, 9; group C, 3; group W135, 1; and nongroupable, 2), 28 cases; PCR analysis specific for meningococci [15, 16], 28 cases; positive CSF test for meningococcal antigen, 20 cases; direct microscopy revealing diplococci on a gram-stained preparation of CSF or a methylene blue–stained preparation of blood, 14 cases; and typical clinical picture only, 8 cases. Results of laboratory tests for other bacterial pathogens causing meningitis, including a modified PCR method based on the 16S rRNA of *H. influenzae* and *Streptococcus pneumoniae,* were negative for all patients [17].

Criteria for estimation of the severity of meningococcal disease. Two previously described grades of severity were used to classify episodes of meningococcal disease in the patients included in this study [7]: severe—coma; shock, defined and graded according to Martin and Silverman [18] (including tachypnea, tachycardia, and inadequate organ perfusion with hypoxemia, oliguria, acute alteration of mental status, and/or hypotension; refractory septic shock was defined when hypotension and oliguria persisted for >2 hours despite adequate volume resuscitation and treatment with dopamine and vasopressors); necrotic skin lesions requiring surgery; focal neurological signs; and/or complications and neurological sequelae; and moderately severe—all other cases of systemic meningococcal disease that were not graded as severe.

Blood samples and DNA extraction. Blood specimens (1 mL) were collected by venipuncture into EDTA-containing tubes for DNA analysis. In addition, serum samples were obtained and flash-frozen at −70°C for investigation of the complement system. DNA was isolated and extracted by the method of Boom et al. [19]. Purified DNA was stored in distilled water with sodium acetate (0.3 m*M*) and isopropanol (50%) at −20°C until testing was performed. The hemolytic activities of the classic and alternative complement pathways and the individual complement components C1–C5, C7, and C8 were measured as described previously [7].

Determination of FcγRIIa-R131 and FcγRIIa-H131 genotypes. Genomic DNA derived from peripheral blood leukocytes was used to determine FcγRIIa allotypes by means of allele-specific oligonucleotide hybridization with FcγRIIa-R131- and FcγRIIa-H131-specific oligonucleotides [20].

Statistical analysis. All statistical analyses and tests were performed by using SPSS version 6.0 (SPSS, Chicago). Numerical variables were compared by means of the Mann-Whitney pairs test for nonparametric data. The χ^2 test was used to compare the distribution between discrete variables [21].

Results

Meningococcal disease and FcγRIIa polymorphism. The distribution of the FcγRIIa allotypes in various subgroups of patients is provided in table 1. More of the 98 patients with systemic meningococcal disease had the IIa-R/R131 allotype than did the 107 healthy Slavic blood donors (32% vs. 18%, respectively; $P < .06$). The median age at the time of disease was 18 years for 31 patients with the IIa-R/R131 allotype, 7 years for 41 patients with the IIa-R/H131 allotype, and only 3.5 years for 26 patients with the IIa-H/H131 allotype. Patients with the IIa-R/R131 allotype developed meningococcal disease at a relatively older age compared with patients with the IIa-R/H131 or IIa-H/H131 allotype (table 1 and figure 1). When the relative risk of developing meningococcal disease at an age of 5 years or older was assessed, patients with the IIa-R/R131 allotype were 1.5 times more susceptible than patients with the IIa-H/H131 allotype (95% CI, 0.9–2.6) and 1.2 times more susceptible than patients with the IIa-R/H131 allotype (95% CI, 0.8–1.8).

FcγRIIa allotypes and severity of meningococcal disease. Next, the association of FcγRIIa allotypes with different clinical entities of meningococcal disease was evaluated. The distribution of FcγRIIa allotypes in patients with moderate or severe infection at all ages is presented in table 1. A moderately severe course of meningococcal disease was observed in 18 (69%) of 26 episodes in patients with the IIa-H/H131 allotype, in contrast to severe disease in 21 (68%) of 31 episodes in patients with the IIa-R/R131 allotype ($P < .02$). This correlation was found in both age groups (table 1 and figure 1). The association for patients with the IIa-R/H131 allotype was intermediate.

Severe complications of meningococcal disease were found in 18 (58%) of 31 episodes in patients with the IIa-R/R131 allotype: 4 patients developed meningococcal septic shock (including one case of refractory septic shock), 10 had coma and signs of brain edema, 1 had meningoencephalitis, 2 developed arthritis, and 1 had severe focal neurological impairment. Complications were found in 15 (37%) of 41 episodes of meningococcal disease in patients with the IIa-R/H131 genotype: 5 patients had septic shock, 8 had coma, 1 had arthritis, and 1 had focal neurological impairment. Complications developed in 5 (19%) of 26 episodes in patients with a homozygous IIa-H/H131 genotype (χ^2 distribution = 12; $P < .05$ for significance of difference between other subgroups): 4 patients had

Table 1. Distribution of FcγRIIa allotypes in subgroups of Slavic patients with SMD and a control group of healthy Slavic blood donors.

Group or subgroup of patients (no. of patients)	Frequency (%) of allotype (no. of patients)			χ^2 distribution; *P* value*; OR (95% CI)†
	IIa-R/R131	IIa-R/H131	IIa-H/H131	
Controls, healthy Slavic blood donors (107)	18 (19)	54 (58)	28 (30)	
All patients with SMD (98)	32 (31)	41 (41)	27 (26)	In comparison with controls: 5.7; <.06; 1.9 (0.9–4.1)
Patients with SMD at 5 y of age or younger (45)	24 (11)	41 (19)	33 (15)	In comparison with controls: 1.9; .38; 1.2 (0.4–3.0)
Patients with SMD at older than 5 y of age (53)	38 (20)	42 (22)	20 (11)	In comparison with controls: 7.7; <.03; 2.9 (1.1–7.3); in comparison with patients with SMD at 5 years of age or younger: 2.8; .24; 2.5 (0.9–7.3)
Patients with moderate SMD (47)	21 (10)	40 (19)	39 (18)	In comparison with controls: 2.6; .28; 0.9 (0.3–2.3)
Patients with severe SMD (51)	41 (21)	43 (22)	16 (8)	In comparison with controls: 10; <.01; 4.1 (1.5–11); in comparison with patients with severe SMD: 7.8; <.02; 4.7 (1.5–14.5)
Patients with moderate SMD at 5 y of age or younger (24)	21 (5)	29 (7)	50 (12)	In comparison with controls: 5.5; .06; 0.7 (0.2–2.2)
Patients with severe SMD at 5 y of age or younger (21)	29 (6)	57 (12)	14 (3)	In comparison with controls: 2.4; .3; 3.2 (0.7–14); in comparison with patients with moderate SMD at 5 y of age or younger: 6.6; <.05; 4.8 (0.9–27)
Patients with moderate SMD at older than 5 y of age (23)	22 (5)	52 (12)	26 (6)	In comparison with controls: 0.2; .9
Patients with severe SMD at older than 5 y of age (30)	50 (15)	33 (10)	17 (5)	In comparison with controls: 12; <.003; 4.8 (1.5–15); in comparison with patients with moderate SMD at older than 5 y of age: 4.5; <.1; 3.6 (0.76–17)

NOTE. SMD = systemic meningococcal disease.

* Significance of difference between controls or comparison subgroup was determined according to Pearson's correlation coefficients.

† OR of >1 means that the ratio of the frequency of IIa-R/R131 allotypes to the frequency of IIa-H/H131 allotypes in this subgroup was greater than that in the comparison subgroup. Nonsignificant ORs were omitted.

coma, and one had arthritis. The duration of hospitalization for patients with the IIa-H/H131 allotype (18 ± 6 days) was significantly shorter than that for patients with the IIa-R/H131 allotype (20 ± 6 days) or patients with the IIa-R/R131 allotype (21 ± 7 days) ($P < .05$; Mann-Whitney pairs test).

Another factor associated with patient's age was the serogroup of the infecting strain. Eleven of 13 infections caused by group A meningococci occurred in patients older than 5 years of age, in contrast to three of 13 cases caused by group B or C meningococci (χ^2 distribution = 10; $P < .01$). This association was statistically independent of the influence of FcγRIIa allotypes.

Discussion

Host defense against meningococcal disease is exerted as mucosal immunity, antibacterial immunity, and phagocytosis [6]. After entry into the intravascular compartment, the invading meningococcus is recognized by complement, circulating antibodies, and phagocytes. Antibody-independent lysis of meningococci by the alternative pathway of complement activation is considered a crucial element of innate resistance. Individuals lacking a complement component from the alternative pathway are highly susceptible to meningococcal infections [22–24]. Lysis of meningococci via both classic and alternative pathways is absent in patients with deficiencies of late complement components; therefore, they are also highly susceptible to meningococcal infections even at older ages [7, 22, 23]. In these latter patients, antibody-mediated phagocytic activity may constitute an important defense mechanism against meningococcal disease, and allotypes of FcγRIIa affect the susceptibility to meningococcal disease considerably [24, 25].

The results of the present study show that FcγRIIa allotypes also constitute an important element in the immune defense against meningococcal disease in patients with an intact complement system. The distribution of FcγRIIa allotypes in 98 Russian patients with meningococcal disease differed from that of these allotypes in a control group of 107 healthy blood donors. The IIa-R/R131 allotype was significantly overrepresented in patients with meningococcal disease who were older than 5 years of age, whereas individuals with the IIa-H/H131 allotype were affected mainly at 5 years of age or younger. This observation fits well in our hypothesis that FcγRIIa polymorphisms affect the age at which meningococcal disease develops. The incidence of meningococcal disease is highest in early childhood (6 months to 2 years; after the disappearance of maternally acquired antibodies) and decreases gradually until the age of 5 to 10 years (when protective antibodies to meningococci develop) [5, 6]. A still unexplained second peak

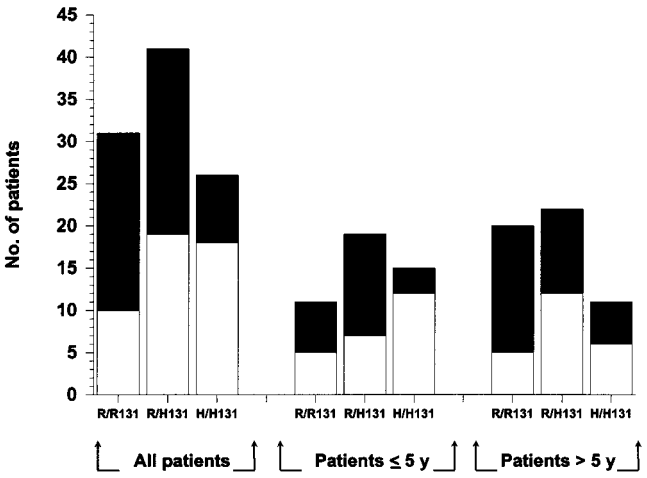

Figure 1. Severity of meningococcal disease in relation to the patient's age and FcγRIIa allotype. White bars = cases of moderately severe disease; black bars = cases of severe disease. The proportion of moderate cases vs. severe cases among patients with IIa-R/R131, IIa-R/H131, and IIa-H/H131 allotypes was 32% vs. 68%, 46% vs. 68%, and 69% vs. 31%, respectively. Among patients 5 years of age or younger, this proportion was 45% vs. 55%, 37% vs. 63%, and 80% vs. 20%, respectively, and among patients older than 5 years of age, the proportion was 25% vs. 75%, 55% vs. 45%, and 55% vs. 45%, respectively.

of meningococcal disease is observed between the ages of 15 and 20 years [1]. Our observations reveal that individuals with the IIa-R/R131 allotype are not able to use protective antibodies to meningococci as efficiently as individuals with the IIa-H/H131 allotype.

Furthermore, our results indicate that, irrespective of the patient's age, the severity of meningococcal disease is associated with the IIa-R/R131 allotype. Unfortunately, samples from nonsurvivors were not available for determination of FcγRIIa allotypes. Assuming that all six nonsurvivors (three patients younger than 5 years of age and three patients older than 5 years of age) had the H/H131 allotype, the odds ratio for patients with the R/R131 allotype to develop severe meningococcal disease after the age of 5 years decreases from 4.8 to 2.9 but remains >1. Our findings are also in agreement with the previous observations of Bredius et al. [4] who found that 11 (44%) of 25 children (younger than 15 years of age) with fulminant meningococcal septic shock who were admitted to an intensive care unit had the IIa-R/R131 allotype as a predisposing factor. The relevance of this clinical observation was supported by experiments demonstrating that the phagocytosis of IgG2-opsonized meningococci by neutrophils with the IIa-R/R131 allotype was less effective than that by neutrophils with the IIa-H/H131 allotype [10].

Early antibiotic treatment of bacterial meningitis resulted in a high percentage (70%) of culture-negative episodes of meningococcal meningitis, and laboratory methods based on antigen detection and PCR were used to diagnose meningococcal disease in 49% of all cases. In Russia, severe complications of meningococcal disease are observed in ~40% of the episodes [7]. The case-fatality rate is 11% among patients with septicemia and 3% among patients without septicemia [1, 7]. The case-fatality rate and the development of severe complications of meningococcal disease are associated with the concentration of bacterial lipopolysaccharides and cytokines in the blood and CSF [2, 3]. Complications of meningococcal disease, such as endotoxic shock, brain edema, coma, and neurological and inflammatory sequelae, were more frequently observed in patients with the IIa-R/R131 allotype. We speculate that these patients may have less efficient FcγRIIa-dependent phagocytosis, thus resulting in extensive multiplication of meningococci and subsequent release of meningococcal endotoxin [3].

Since FcRs are involved in clearance of immune complexes, secretion of reactive oxygen intermediates, and enhancement of antigen presentation, other FcR-mediated pathways may also influence the severity and clinical outcome of meningococcal disease [11, 26]. We did not investigate the role of genetic influences on cytokine production. Genetic influences on cytokine production may contribute to a severe or fatal outcome of meningococcal disease, but the currently available data are contradictory. In one study [27], death associated with meningococcal disease was related to a TNF-α gene promoter polymorphism (namely, with the possession of the TNF-2 allele), thus resulting in a presumably high level of TNF production. In another study [28], the outcome of meningococcal disease associated with a low level of TNF production and a high level of IL-10 production ex vivo was poor, and TNF-α gene promoter polymorphism was not found in first-degree relatives of patients with fatal meningococcal infections. In future studies, the simultaneous measurement of specific meningococcal antibodies, FcγRIIa allotypes, levels of endotoxin and cytokines, and the number of living meningococci in the blood and CSF of patients should be determined to further substantiate the validity of our hypothesis.

Our results reveal that FcγRIIa-dependent IgG2-mediated phagocytosis of meningococci constitutes a vital element of host defense against meningococcal disease. This observation may have implications for vaccination against meningococcal disease. We are currently investigating the FcγRIIa allotype and the subclasses of IgG antibodies to meningococci in individuals who developed meningococcal disease despite vaccination with meningococcal capsular polysaccharides. If our hypothesis is correct that FcγRIIa allotypes are associated with vaccination failures, combined vaccines with polysaccharides and proteins should be used to induce specific antibodies of different IgG subclasses.

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