The Fcγ Receptor IIA-R/R131 Genotype Is Associated with Severe Sepsis in Community-Acquired Pneumonia

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Community-acquired pneumonia (CAP) can be caused by a variety of microorganisms but is most frequently associated with Streptococcus pneumoniae and gram-negative bacteria like Haemophilus influenzae. Encapsulated bacteria are able to escape phagocytosis, unless they are bound by immunoglobulin G2 subclass antibodies. These antibodies interact with Fcγ receptor IIa (Fcγ-RIIa), thereby facilitating opsonophagocytosis of the encapsulated bacteria. We studied the relationship between the Fcγ-RIIa-R/R131 polymorphism and the clinical course of CAP and pathogen-specific susceptibility. Regarding methodology, the Fcγ-RIIa genotype R/H131 was determined in 200 patients with CAP and in 313 healthy controls and was correlated with the clinical course, laboratory parameters, and causative microorganism. The Fcγ-RIIa-R/R131 genotype was found more frequently in patients with severe sepsis (odds ratio [OR], 2.55; 95% confidence interval [CI], 1.30 to 5.00; P < 0.01). The majority of patients in this group suffered from invasive pneumococcal disease. The duration of hospital stay was longer for patients with the Fcγ-RIIa-R/R131 genotype. Fcγ-RIIa genotypes were not associated with an increased risk of CAP in general; however, the Fcγ-RIIa-R/R131 genotype was found more frequently in patients with CAP caused by H. influenzae than in controls (OR, 3.03; CI, 1.04 to 9.09; P < 0.05). In conclusion, the Fcγ-RIIa-R/R131 genotype is associated with severity of CAP and is more frequent in CAP caused by H. influenzae.

Despite advances in diagnostic methods and antibiotic therapy, community-acquired pneumonia (CAP) is still a major cause of morbidity and mortality worldwide. Pneumonia accounts for approximately 10% of the total mortality in The Netherlands. Streptococcus pneumoniae, Haemophilus influenzae, Legionella pneumophila, and Mycoplasma pneumoniae are the pathogens most frequently identified in CAP. The encapsulated bacteria are surrounded by a polysaccharide capsule that protects the bacteria from phagocytosis. However, if immunoglobulin G2 subclass antibodies recognize and bind capsular polysaccharide antigens, opsonophagocytosis can take place. The only receptor to interact efficiently with IgG2 antibodies is Fcγ receptor IIa (Fcγ-RIIa; CD32). This receptor is expressed in a variety of cells of the immune system, including lymphocytes, macrophages, and polymorphonuclear leukocytes (PMNs). The binding of immune complexes by Fcγ-RIIa of PMNs can induce degranulation and phagocytosis.

Due to a single nucleotide polymorphism (guanine [G] into adenine [A]), two codominant Fcγ-RIIa allotypes exist with different binding capacities for IgG2. The G-to-A point polymorphism at base 494 results in the replacement of arginine (R) with histidine (H) at residue 131 of the protein. Fcγ-RIIa-H131 has a high affinity for IgG2, whereas Fcγ-RIIa-R131 displays a low affinity for IgG2 (12, 13, 17, 18). As a result, phagocytosis of IgG2-opsonized bacteria by homozygous Fcγ-RIIa-R/R131 PMNs is less efficient than phagocytosis by homozygous Fcγ-RIIa-H/H131 PMNs. Heterozygous Fcγ-RIIa-H/R131 receptors show intermediate phagocytic capacity.

Several studies have reported an association between the Fcγ-RIIa polymorphism and meningococcal disease and periodontitis. The association between the Fcγ-RIIa genotype and pneumococcal disease has been examined, however, with conflicting results. The association between Fcγ-RIIa and CAP caused by microorganisms other than S. pneumoniae has not yet been documented. We have investigated the severity of CAP and the causative microorganisms in relation to the Fcγ-RIIa genotype.

MATERIALS AND METHODS

Patients and controls. Patients diagnosed with CAP in the emergency department of the St. Antonius Hospital Nieuwegein during a 22-month period (October 2004 to August 2006) were included in this study. A patient was defined as having CAP by an infiltrate on chest X rays, with at least one of the following conditions: cough, sputum production, a temperature of >38°C or <35°C, auscultatory findings consistent with pneumonia, a C-reactive protein level of >15 mg/liter, or a white blood cell count of >10 × 10⁹ cells/liter or <4 × 10⁹ cells/liter. Exclusion criteria consisted of defined immunodeficiency (congenital or acquired immunodeficiency), chemotherapy in the previous 6 weeks, corticosteroid administration less than 6 weeks prior, prednisone equivalent of >20 mg.

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TABLE 1. Characteristics of 201 hospitalized patients with CAP

| Characteristics | No. (%) of patients |
|-----------------|---------------------|
| Mean age (yr) ± SD | 63 ± 17 |
| Sex, male | 124 (62) |
| PSIs | |
| I (low) | 30 (15) |
| II (low) | 34 (17) |
| III (low) | 53 (26) |
| IV (moderate) | 56 (28) |
| V (high) | 26 (14) |
| Clinical outcomes | |
| Severe sepsis | 54 (27) |
| Admission to ICU | 21 (10) |
| Death | 10 (5) |
| Median length of hospital stay, days (IQR) | 11 (8) |
| Causative microorganisms | |
| S. pneumoniae | 60 (30) |
| H. influenzae | 14 (7) |
| L. pneumophila | 9 (5) |
| M. pneumoniae | 9 (5) |
| Other pathogens | 36 (18) |
| Unknown | 73 (36) |

a Data are presented as the number (percentage) of patients, unless otherwise indicated.
b IQR, interquartile range.

daily for more than 3 days), and hematological malignancies. The following data were collected at admission: social demographic data, comorbidities, and pre-hospital treatment. On the day of admission, the pneumonia severity index (PSI) score was calculated (9). During hospitalization, patients were closely monitored. The endpoints of the clinical outcome were defined as length of hospital stay, intensive care unit (ICU) admission, and occurrence of severe sepsis and death during the hospital stay. In the presence of a documented infection, severe sepsis was defined as systemic inflammatory response syndrome in combination with organ failure (1). The controls consisted of healthy Caucasian unrelated individuals with the same geographical background. The study protocol was approved by the Institutional Medical Ethical Committee, and written informed consent was obtained from all patients.

Receptor genotyping. Blood was taken from all patients and collected in 10-ml containers. DNA was extracted from a 200-μl whole-blood sample with MagNA Pure LC DNA Isolation Kit I (Roche Diagnostics). After extraction, DNA was genotyped on a TaqMan 7500 fast real-time PCR machine from Applied Biosystems. The custom primers and reporters necessary for genotyping of the Fc-RIIa-131 polymorphism (rs1801274) were obtained from Applied Biosystems. The sequences of the primers used were GCTTGTTGGAGTGGAGA AGGT and CTGGTCAAGGTCACATTCTTCCA. Probes were coded as CTC CCGTTTGAGATCC and TTCTCCCATTTGGATCC (underlining indicates polymorphism). After 10 min of incubation at 95°C, 40 cycles of 15 s at 95°C and 1 min at 60°C followed. After a run, the samples were cooled. Confirmation of genotypes was done by sequencing.

Pathogen identification. Pathogens were identified by cultures of sputum and blood; urine antigen testing for S. pneumoniae and L. pneumophila; PCR assay of sputum for Chlamydia pneumoniae/psittaci, L. pneumophila, and M. pneumoniae; and viral culture of the pharynx and serologic testing for respiratory viruses, L. pneumophila, M. pneumoniae, and Coxiella burnetii.

Statistical analysis. Descriptive statistics were performed for all variables. After calculation of the Hardy-Weinberg equilibrium, two-by-two χ² tests were used to determine differences in the frequencies of the different Fc-RIIa genotypes between patients and controls and between clinical outcomes within patients. In the case of statistically significant results, logistic regression analysis was performed with the significant variable in combination with the PSI score. Continuous parameters were investigated with independent-sample t tests or Mann-Whitney U tests, depending on the distribution of the data. Ninety-five percent confidence intervals (CIs) are reported. Statistical analyses were performed with SPSS 14.0 for Windows (Chicago, IL). The significance level was set at P < 0.05 unless reported otherwise.

RESULTS

Demographics. A total of 201 patients were included in this study. Demographic and clinical characteristics are shown in Table 1. The mean age was 63 (standard deviation, 17) years, and 124 (62%) subjects were male. In 128 (64%) cases, a causative agent could be identified. In 60 (30%) patients, S. pneumoniae was identified as the causative pathogen of the CAP. H. influenzae was isolated from 14 patients, while L. pneumophila and M. pneumoniae were both isolated from 9 patients. During their hospital stays, 21 (10%) patients were admitted to the ICU and 10 (5%) patients died. Control subjects consisted of 314 (118 males) healthy unrelated Caucasians from the same geographical area as the patients.

Fc-RIIa genotype and outcome of CAP. In one patient and one control subject, Fc-RIIa receptor genotyping failed. The data from the remaining 200 patients and 313 control subjects were used for further analysis. Frequencies of the genotypes were in Hardy-Weinberg equilibrium (P > 0.2). In patients with the Fc-RIIa-R/R131 genotype, the frequency of severe sepsis (42%) was significantly higher than in patients with the Fc-RIIa-R/H131 and Fc-RIIa-H/H131 genotypes (22%) (odds ratio [OR], 2.55; CI, 1.30 to 5.00; P < 0.01) (Table 2). Logistic regression analysis showed that this finding was independent of the PSI score. The majority of the patients with severe sepsis suffered from CAP caused by an unidentified microorganism (35%), followed by S. pneumoniae (33%). In patients with bacteremias (all due to S. pneumoniae), the Fc-RIIa R/R131 genotype was present more frequently, though not significantly so. The frequency of Fc-RIIa-R/R131 was nonsignificantly higher in patients who had been admitted to

TABLE 2. Distribution of Fc-RIIa genotypes among patients with or without clinical endpoints of CAP

| Fc-RIIa genotype | Severe sepsisb | Admission to ICUb | Mortalityb | Hospital stay durationb |
|------------------|----------------|------------------|------------|------------------------|
|                  | Positive | Negative | Positive | Negative | Died | Survived |             |
| RR (CC)          | 22 (41)† | 31 (21)  | 7 (33)   | 46 (26)  | 3 (30) | 50 (26)  | 11 (5–153)†|
| RH (CT)          | 18 (33)† | 73 (50)  | 10 (48)  | 81 (45)  | 4 (40) | 87 (46)  | 11 (3–69)†|
| HH (TT)          | 14 (26)† | 42 (29)  | 4 (19)   | 52 (29)  | 3 (30) | 53 (28)  | 10 (4–42)†|

a Data are presented as numbers (percentages) of patients, unless otherwise indicated.
b Data are presented as the median (range) number of days.
c Chi-square test result (RR versus non-RR): OR, 2.55 (CI, 1.30 to 5.00; P < 0.01).
d Mann-Whitney test result (RR versus non-RR): P < 0.05.
the ICU during their hospital stay than in those who had not. In patients with the Fcγ-RIIa-R/R131 genotype, the duration of their hospital stay was longer than that of patients with the Fcγ-RIIa-H/H131 genotype (P < 0.05). This, however, was not independent of the PSI score. Patients with the Fcγ-RIIa-R/R131 genotype, the genotype with lower binding affinity for IgG2, are at risk for a more severe clinical course, which is reflected by a higher risk of severe sepsis and a longer stay in the hospital.

**Fcγ-RIIa genotype and risk of CAP.** Table 3 shows the distribution of the Fcγ-RIIa genotypes in patients with CAP and controls. There was no association between the Fcγ-RIIa-R/R131 genotype and susceptibility to CAP in general, nor was there an association with CAP severity at presentation (Fine class IV and/or V). In order to study the association of the Fcγ-RIIa genotype in patients with CAP caused by specific microorganisms, we tested the frequencies of genotypes in patients with the microorganisms that most commonly cause CAP: *S. pneumoniae*, *H. influenzae*, *L. pneumophila*, and *M. pneumoniae*. The results are also shown in Table 3. The frequency of the Fcγ-RIIa-R/R131 genotype was significantly higher in patients with CAP caused by *H. influenzae* (OR, 3.03; CI, 1.04 to 9.09; P < 0.05). There was no association between the Fcγ-RIIa genotypes and CAP caused by *S. pneumoniae*. In the small group of 21 patients with atypical pneumonia, the frequency of the R/R131 genotype was lower in nine patients with CAP caused by *M. pneumoniae* (R/R131, 0%; R/H131, 33%; H/H131, 66%) than in controls (OR, 0.16; CI, 0.04 to 0.65; P < 0.01). For the nine patients with *Legionella pneumonia*, the distribution of the Fcγ-RIIa genotypes was similar to that in the controls (R/R131, 22%; R/H131, 44%; H/H131, 33%).

**DISCUSSION**

We have shown that the Fcγ-RIIa-R/R131 genotype is associated with a more severe clinical course (severe sepsis, longer hospital stay) in patients hospitalized for CAP. The Fcγ-RIIa-R/R131 genotype was more frequently found in patients with CAP caused by *H. influenzae*.

The genetic polymorphism of Fcγ-RIIa has functional implications for the efficacy of phagocytosis of encapsulated bacteria. In vitro research has shown that the uptake of opsonized streptococci (15), staphylococci, *H. influenzae* type b (2), and *Neisseria* species (3) by PMNs from subjects homozygous for Fcγ-RIIa R/R131 is less than the uptake by PMNs from subjects homozygous for Fcγ-RIIa H/H131. More recent studies have focused on the in vivo effects of this polymorphism (12, 20, 21). It is thought that bacterial clearance in Fcγ-RIIa R/R131 homozygous patients is less effective, thus allowing pathogens to replicate and translocate from the site of inflammation to the bloodstream. Although such a mechanism is still speculative, our results support this hypothesis. In our study, pneumococcal bacteremia was nonsignificantly more common in patients with the Fcγ-RIIa R/R131 genotype, a finding that has been reported before for patients with pneumococcal pneumonia (20). The incidence of severe sepsis, and to a lesser extent bacteremia, was increased in the group of patients with the Fcγ-RIIa R/R131 genotype. Bacteremia was solely caused by *S. pneumoniae*, which was also the most frequently identified causative microorganism in cases of severe sepsis. We further demonstrated that the duration of the hospital stay was associated with the Fcγ-RIIa genotype, being the lowest in HH homozygous patients, intermediate in RH heterozygous patients, and highest in RR homozygous patients (Table 2). In conclusion, patients with the Fcγ-RIIa R/R131 genotype may have a more severe clinical course of CAP, possibly due to a higher bacterial load as a result of diminished bacterial clearance (of *S. pneumoniae*). The role of the Fcγ-RIIa genotype in susceptibility to pneumococcal bacteremia has been studied previously; however, the published results are inconsistent. The Fcγ-RIIa-R/R131 genotype was found more commonly in children with pneumococcal bacteremia than in healthy adult controls (21). Yee et al. found similar results in patients with bacteremic pneumococcal pneumonia, who were more likely to be homozygous for Fcγ-RIIa-R/R131 than patients with nonbacteremic pneumococcal pneumonia or controls (20). However, Moens et al. reported that the frequencies of the Fcγ-RIIa genotypes in patients with invasive pneumococcal disease (pneumococcal bacteremia, meningitis, and arthritis) and controls were similar in an adult population. In 74% of the cases, pneumonia was the focus of infection (12). In accordance with the latter study, we did not find an association between the Fcγ-RIIa genotypes and pneumococcal CAP in general but did find a possible association between pneumococcal invasive disease and the Fcγ-RIIa-R/R131 genotype.

In a small group of patients with CAP caused by *H. influenzae*, we did find a possible association between the Fcγ-RIIa-R/R131 genotype and CAP, which has not been reported before. If true, it is remarkable that the risk of CAP caused by *H. influenzae* is influenced by the Fcγ-RIIa genotype, whereas the risk of CAP caused by *S. pneumoniae* is independent of the Fcγ-RIIa genotype. The reasons for this discrepancy are unknown, but there are several possibilities that might explain these findings. The IgG2 antibody binding to nonpolysaccharide surface components such as lipopolysaccharide may differ. Also, the host defense against gram-negative bacteria might be more dependent upon Fcγ-RIIa-mediated opsonophagocytosis than the host defense against gram-positive bacteria such as *S. pneumoniae*. Clearance of encapsulated bacteria can be established through Fcγ-RIIa-mediated opsonophagocytosis, but the impact of this process on the development of the infection is highly uncertain and may also depend on the specific pathogen in question. For example, in cystic fibrosis patients, the R allele of Fcγ-RIIa has been associated with an increased risk of acquiring chronic *Pseudomonas aeruginosa* infection (4).
is in agreement with the hypothesis that clearance of gram-negative bacteria is dependent upon FcγRIIa-mediated opsonophagocytosis with IgG2. A comparison between these findings and those of our study is hampered by differences in the study populations with respect to age, ethnicity, and morbidity.

In contrast to the findings on CAP caused by *H. influenzae*, the frequency of the FcγRIIa H/H131 genotypes was higher in patients with CAP caused by *M. pneumoniae*. Although the number of patients in this group is too small to support conclusions, it is surprising that none of the patients had the R/R131 genotype. *M. pneumoniae*, like *L. pneumophila*, is an intracellularly living pathogen and so might benefit from receptors that facilitate phagocytosis, thereby escaping other parts of the immune system. It is clear that the role of the FcγRIIa genotype in susceptibility for CAP caused by specific microorganisms should be a topic for further research.

The expected FcγRIIa genotype distribution ratio of FcγRIIa-R/R131 to FcγIIa-H/H131 to FcγIIa-H/H131 in Cauca-
sians is 1:2:1 (16), which is similar to the genotype distribution in our study population. This allows direct comparison with other studies and/or populations. The strength of this study is the relatively large study population compared to those of previous studies, although the numbers of patients with specific pathogens (especially *M. pneumoniae*) and a severe clinical course (death or ICU admission) are still too small to support definite conclusions.

In conclusion, we have demonstrated an association between the FcγRIIa-R/R131 genotype and severe sepsis and a longer hospital stay for CAP, in general, and a genetic predisposition for CAP caused by *H. influenzae*.

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