Original Contribution

Genetic Susceptibility to Severe Infection in Families with Invasive Pneumococcal Disease

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Received for publication June 30, 2007; accepted for publication December 3, 2007.

Severe infections may be influenced by genetic constitution. The authors examined familial aggregation of invasive infections, using invasive pneumococcal disease (IPD) as the index condition to ascertain families at risk. From Danish national registers, they identified relatives of persons with IPD from 1977 through 2005. Risks of IPD, bacterial meningitis, septicemia, and any invasive infection were analyzed for relatives of IPD cases in a prospective cohort study (23 million person-years). In total, 43,134 persons were found to have an IPD case in the family. The authors observed an increased risk of invasive infections in relatives of IPD cases most likely sharing the same household (parents, offspring, siblings, half-siblings), but only regarding those events within 1 year of the index IPD diagnosis (rate ratio \( = 7.4 \), 95% confidence interval: 2.4, 23.0). After 1 year, there were no increased risks of severe infections, including IPD, in close relatives. For other relatives, no increased risks of severe infections were observed at any time. No aggregation of invasive infections in IPD relatives was found, other than for close events among relatives who most likely shared the same household. Thus, at the population level, genetic constitution appears of little importance in the development of IPD and other severe infections.


Streptococcus pneumoniae is an important pathogen causing substantial morbidity and mortality, especially in young children and in immunocompromised patients and elderly persons who suffer from chronic diseases (1). A number of genetic and environmental risk factors for invasive pneumococcal disease (IPD) have been reported. Among the genetic factors, host susceptibility to IPD and other invasive infections has been reported to be associated with polymorphisms of the human leukocyte antigens, mannose-binding lectin, interleukin 10, and the FcyRIIA receptor (2–11). Twin studies also report a genetic component of infectious disease susceptibility (12, 13). However, these studies have been of limited size with possible ascertainment bias. Furthermore, because persons share the same household, it is difficult to exclude environmental factors when familial aggregation is observed (14, 15). In sum, the contribution of genetic susceptibility to the overall risk of IPD and other invasive infections is not well established.

To our knowledge, no population-based studies have been performed to address this question. In the present study, we used population-based data to examine the risk of invasive infections in first-, second-, and third-degree relatives of index cases. Rates were compared with rates seen in the general public. As index cases, we used persons diagnosed...
with IPD. As outcomes, we sought second cases of IPD, bacterial meningitis, septicemia, and any major invasive infections, reasoning that these conditions could represent both specific genetic risk factors that affect responses to \( S.\ pneumoniae \) and more general risk factors that lead to severe infection, such as lack of immunologic control.

**MATERIALS AND METHODS**

For this study, we used information from three Danish nationwide registries: the Danish Civil Registration System (16), The Pneumococcus Database (17), and The Danish National Patient Registry (18). Based on information from the Danish Civil Registration System, a cohort was established consisting of all persons born in Denmark during the period January 1, 1977, through May 1, 2005. The Danish Civil Registration System registry, established April 1, 1968, contains daily updated demographic information on all residents of Denmark (16). For individuals born since the early 1950s, information was available linking parents and offspring. On the basis of such information, we developed a multigenerational database, the Danish Family Relations Database, allowing identification of first-, second-, and third-degree relatives. Persons born since 1977 and who had no registered relatives (\( n = 1,114 \)) were excluded from the cohort.

**Identification of IPD relatives**

IPD was defined as the isolation of \( S.\ pneumoniae \) from a normally sterile site (i.e., blood, cerebrospinal fluid, peritoneal fluid, synovial fluid). IPD cases were identified in The Pneumococcus Database, which was established as part of a national surveillance program of IPD among patients hospitalized in Denmark since 1938 (17). For all individuals in the cohort, relatives were identified in the multigenerational database. An individual was defined as having an IPD relative if one or more relatives were registered in The Pneumococcus Database. IPD relatives were defined as follows: first-degree relatives were siblings or parents; second-degree relatives were half-siblings, grandparents, uncles/aunts, or nephews/nieces; and third-degree relatives were cousins. Parents, offspring, siblings, and half-siblings were categorized as “household” relatives on the assumption that they probably lived together, but residence was not verified. Other types of relatives were considered “nonhousehold.”

**Identification of invasive infections**

Information on hospital contact with invasive infectious disease was obtained from The Danish National Patient Registry, a register containing information on all admissions, treatment, and discharge diagnoses for all patients treated in Danish hospitals, including outpatient and emergency-room visits, since January 1, 1977 (18). Therefore, only persons born since January 1, 1977, were included in our cohort to ensure complete registry information on infectious diseases from The Danish National Patient Registry. Diagnosis coding in The Danish National Patient Registry used the International Classification of Diseases, Eighth Revision (ICD-8) during 1977–1993 and the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) during 1994–2005. We included the following categories of invasive infections in our study: bacterial meningitis (including pneumococcal meningitis) (ICD-8 codes 32000–32099, 04500–04599, 01300, 013010, 03609, 05201, 05302, 05403, 05501, 05601, 07501; ICD-10 codes DG00–DG039, DA87–DA879, DA022C, DA170A, DA229C, DA321, DA390, DA514B, DA548D, DB003, DB010, DB021, DB051, DB060B, DB261, DB451A); septicemia (including pneumococcal septicemia) (ICD-8 codes 03800–03899, 03610–03619, or 67003, 67008, 67009; ICD-10 codes DA40–DA419, DA392–DA394, DP36–DP369 or DA021, DA427, DA327, DA419B, DB377, DJ950A, DO080S-U, DO859, DT802D-F, DT814D, DT880A); invasive infections (including bacterial meningitis and septicemia) (ICD-8 codes 03200–032400, 04200–044200, 051000–051099, 051300–051399, 056700–056799, 071000–071999, 072000–072099, 067000–067099, 071000–072099; ICD-10 codes DG00–DG07, DI30, DI32, DI33, DI38, DI85–DJ86, DK65, DK67, DM00–DM01, DM86, DP35–DP39). Cases of IPD were ascertained from The Pneumococcus Database.

**Statistical analysis**

Familial aggregation of invasive infections in relatives was investigated by comparing the rate of invasive infection among persons with IPD-affected relatives with the rate among individuals without IPD-affected relatives. Rate ratios for invasive infections in the family, according to type of relative, were estimated for both the first year following diagnosis of the IPD relative and later, using general population rates as the expected incidence. Persons in the cohort contributed person-time to follow-up from birth until first hospital contact for any of the identified infectious diseases, death, disappearance or emigration, or end of follow-up (May 1, 2005), whichever occurred first. Incidence rates for infectious disease hospitalization were modeled by a log-linear Poisson regression model (19), producing estimates of incidence rate ratios according to history of having an IPD relative. Having a specific type of IPD relative was a time-varying variable changing at the time of the first diagnosis of IPD in a relative of the specific type. All rate ratios were adjusted for age (1-year intervals), sex, and calendar period (1-year intervals). Analyses were conducted by using the SAS procedure GENMOD (SAS Institute, Inc., Cary, North Carolina).

**RESULTS**

Among the 1,758,253 persons included in our cohort, 43,134 relatives of 10,597 IPD probands were identified. Among persons in the cohort, we identified 1,773 cases of IPD, 7,055 cases of any bacterial meningitis, 26,798 cases of any septicemia, and 46,376 cases of any major invasive infections during approximately 23 million person-years of follow-up. The incidence rate of IPD in 2003 (per 100,000 individuals) among persons aged 0–<2 years was
52, among those aged 2–17 years was 6, among persons aged 18–64 years was 14, and among those aged ≥65 years was 72.

Invasive infection in relatives <1 year from the IPD proband’s date of diagnosis

Five relatives had IPD within 1 year of the proband’s IPD diagnosis date. Compared with persons without IPD in the family, household relatives were at increased risk of IPD within 1 year after the proband’s diagnosis (rate ratio = 7.4, 95 percent confidence interval: 2.4, 23.0). For other infections, household relatives of an IPD proband had rate ratios of bacterial meningitis of 5.0 (95 percent confidence interval: 2.2, 11.0), septicemia of 4.0 (95 percent confidence interval: 2.6, 6.3), and any major invasive infection of 3.5 (95 percent confidence interval: 2.5, 5.0). The estimates for household relatives were largely based on the risk for first-degree relatives, but an increased risk among half-siblings, who are second-degree relatives, also contributed to the increased risk. Relatives who most likely did not share the household with the proband were not at increased risk of any of the invasive infectious disease outcomes. Figure 1 illustrates the modifying effect of the time elapsing since the IPD event in the proband.

Invasive infection in relatives ≥1 year from the IPD proband’s date of diagnosis

In table 1, we present the rate ratios for categories of invasive infectious diseases occurring more than 1 year after the diagnosis of an IPD case in the family, according to type of relative. Having parents who had IPD more than 1 year earlier was associated with an increased risk of any invasive infections, compared with the risk for persons without an IPD case in the family (rate ratio = 1.4, 95 percent confidence interval: 1.0, 1.8). Siblings of IPD probands were not at increased risk of invasive infections. In second-degree relatives, the risk of invasive infections was increased in half-siblings (considered household relatives) (rate ratio = 1.9, 95 percent confidence interval: 0.3, 13.3) but not in grandparents. A 20–40 percent increased relative risk of invasive infections was observed for all household relatives, whereas nonhousehold relatives were not at increased risk compared with the risk for persons without IPD in the family. Overall, the risks of IPD and other severe invasive infections were not increased for any relative of IPD probands.

DISCUSSION

Using a large, nationwide, population-based cohort, we studied familial aggregation of invasive infections within first-, second-, and third-degree relatives of IPD cases. After excluding cases diagnosed within the first year of an index case, we found no indication that families affected by IPD were more susceptible to developing IPD or other severe invasive infections than families without a case of IPD. This lack of risk suggests that the genetic contribution to aggregation of invasive infections in families with a case of IPD is at best marginal. However, our data showed an increased risk of invasive infection for household relatives of an IPD case within the first year, suggesting that they shared environmental risk factors within the household for acquiring infections during a common time period. Examples of such factors might include the presence of underlying conditions such as influenza in the household at that time or a particularly virulent bacterial strain in the index case. Since the time from acquisition of S. pneumoniae to development of disease is measured in days or weeks (20), the use of a 1-year lag period effectively excludes risk factors for directly transmitted infection in studies of long-term risk.

The few investigations of familial aggregation of invasive infectious diseases have shown conflicting results. One study reported a fivefold increased risk of dying from an infectious disease for adopted children if a biologic parent had died prematurely of infection, whereas no increased risk was observed if the adopting parent died from infection (21). The investigators suggested that genetic factors might be important determinants of infectious disease. However, in later and updated reanalyses of data from the same study, the authors were unable to confirm their initial results (22, 23). Another study based on 443 cases of Neisseria meningitidis meningitis reported an eightfold increased sibling recurrence risk ratio more than 1 year after the event in the index case, suggesting that susceptibility to N. meningitidis meningitis might have a genetic component (24). However, the study was based on questionnaire data and could have been subject to selection and recall biases.
TABLE 1. Rate ratios* for invasive infections in relatives more than 1 year after a case of invasive pneumococcal disease in the family, according to type of relative, Denmark, 1977–2005

<table>
<thead>
<tr>
<th>Type of relative ‡</th>
<th>Invasive pneumococcal disease</th>
<th>Bacterial meningitis</th>
<th>Septicemia</th>
<th>Any major invasive infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>RR‡</td>
<td>95% CI‡</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Genetic relationship</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twins</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-degree relatives</td>
<td>3</td>
<td>1.2</td>
<td>0.4, 3.6</td>
<td>10</td>
</tr>
<tr>
<td>Siblings</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parents</td>
<td>3</td>
<td>1.9</td>
<td>0.6, 6.0</td>
<td>7</td>
</tr>
<tr>
<td>Second-degree relatives</td>
<td>13</td>
<td>1.1</td>
<td>0.6, 1.9</td>
<td>27</td>
</tr>
<tr>
<td>Half-siblings</td>
<td>1</td>
<td>1.9</td>
<td>0.3, 13.3</td>
<td>2</td>
</tr>
<tr>
<td>Uncles/aunts</td>
<td>2</td>
<td>0.7</td>
<td>0.2, 2.7</td>
<td>7</td>
</tr>
<tr>
<td>Grandparents</td>
<td>10</td>
<td>1.2</td>
<td>0.6, 2.2</td>
<td>17</td>
</tr>
<tr>
<td>Third-degree relatives §</td>
<td>3</td>
<td>0.8</td>
<td>0.3, 2.6</td>
<td>10</td>
</tr>
<tr>
<td>Environmental relationship</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household relatives ¶</td>
<td>4</td>
<td>1.3</td>
<td>0.5, 3.4</td>
<td>12</td>
</tr>
<tr>
<td>Nonhousehold relatives ¶</td>
<td>15</td>
<td>1.0</td>
<td>0.6, 1.6</td>
<td>35</td>
</tr>
<tr>
<td>Any relative</td>
<td>18</td>
<td>1.0</td>
<td>0.6, 1.6</td>
<td>47</td>
</tr>
</tbody>
</table>

* All rate ratios was adjusted for age, sex, and calendar period.
† Separate estimates for offspring and nephews are not shown because of low numbers of such relatives. Offspring was included in first-degree relatives, "household" relatives, and any relative. Nephews/nieces were included in second-degree relatives, "nonhousehold" relatives, and any relative.
‡ RR, rate ratio; CI, confidence interval.
§ Defined as cousins.
¶ Household relatives: parents, offspring, siblings, and half-siblings; nonhousehold relatives: other types.

Disparities in IPD rates have been reported for different ethnic groups. For example, Australian aborigines, Greenland Inuits, and North American Amerindians appear to be at higher risk of IPD (25–27). However, it is difficult to adjust for great differences in the socioeconomic status between these populations and the local comparison populations. Although it is possible that genetics could contribute to the higher risks observed in these isolated groups, the large geographic and historical separations between Australia and North American/Greenlandic indigenous peoples would make a related genetic problem seem unlikely. Since the current study included only the largely homogeneous population of Denmark (excluding Greenland), differences in risk between populations could not be addressed.

Numerous candidate genes related to innate immunity have been associated with susceptibility to invasive infections (2–11). However, the genetic effects from individual genetic variants are usually modest, and the frequency of the disease-modifying variant was often unknown (28). Furthermore, previous studies may have been subject to ascertainment bias because of small sample sizes. Our study was based on a large cohort encompassing the entire Danish population. Although we cannot exclude the possibility that there might be families with increased susceptibility to invasive infections within our large sample, our results strongly indicate that environmental factors dominate in the risk of these infections.

Transmission of pathogens between family members may increase the risk of disease and contribute to near-term increases in risk for household contacts. Transmission of \textit{S. pneumoniae} from persons with symptomatic pneumococcal disease, or the more common asymptomatic infections, to other family members has been reported (29–31). However, the rate at which secondary \textit{S. pneumoniae} infections occur in household contacts is not known. Factors such as crowding and poor air quality have been associated with outbreaks of \textit{S. pneumoniae} disease in jails and nursing homes (32, 33), and these factors may also be shared within households. We observed a highly increased risk of invasive infections in household relatives within 1 year after an IPD event in the proband, but the increased risk occurred among only those relatives likely to share a household and not among more distant relatives. Increased awareness in the family after a case of IPD may bias results. However, because persons with invasive infections most likely require treatment in a hospital setting, the risk of bias is limited.

The lack of familial aggregation in the period beyond 1 year after the proband’s diagnosis cannot be ascribed to misclassification. The present study was registry based and therefore was not subject to recall bias. Notification of IPD to The Pneumococcus Database (17) required a positive culture of \textit{S. pneumoniae} from a normally sterile site. In a validation study of the database, 15 percent of the cases of IPD were unreported (34), and other cases of disease would likely have been missed because they were not cultured. However, IPD is a rare disease, and persons whose invasive infections were missed would have no measurable impact on the results.
This study highlights the lack of familial aggregation of invasive infections in families with IPD patients, other than a short-term aggregation among household relatives. While an ineonsequential contribution from genetic susceptibility could still be present, there is no significant impact of genetic factors on the development of invasive infections when risk is measured in a total population. Transmission of *S. pneumoniae* within the household is an important risk factor for IPD, outweighing any contribution from genetic susceptibility. Administration of prophylactic antibiotics is not currently recommended to IPD household contacts. We did observe an excess risk in household relatives; although the relative risk was high, the absolute risk remained small because the background expected rates were very low. Whether preventive measures, such as antibiotic prophylaxis in IPD household contacts, are warranted seems dubious, but counseling might be appropriate. The long-term risk of invasive infections in relatives of affected IPD cases is not increased.

**ACKNOWLEDGMENTS**

Financial support was obtained from the Danish Graduate School in Public Health Science, the Lundbeck Foundation, and the Danish Lung Association. The funding organizations did not participate in the design and conduct of the study; the collection, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

Conflict of interest: none declared.

**REFERENCES**


