Low Cord Blood Pneumococcal Antibody Concentrations Predict More Episodes of Otitis Media

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Objective: To determine if cord blood anticapsular polysaccharide pneumococcal IgG antibody concentration was related to the number of otitis media (OM) and acute OM episodes during the first year of life.

Design: Prospective study following infants from birth to 24 months.

Setting: Health maintenance organization.

Patients: The study population consisted of 415 infants whose mothers volunteered for the study during pregnancy. Cord blood samples were collected and infants were followed up for OM in the health maintenance organization. Ninety-seven percent of the infants were white, 49% male, 3% from households with annual incomes of less than $20000, and 30% from households with annual incomes of more than $60000.

Main Outcome Measure: Number of physician-diagnosed OM episodes, including both OM with effusion and acute OM, and acute OM episodes from birth to 12 months.

Results: With univariate analysis, low cord blood antibody concentrations against serotypes 3 and 19F predicted more acute OM episodes ($P = .04$ and $P = .05$, respectively), and low antibody concentrations against serotypes 19F and 23F predicted more OM episodes ($P = .04$ and $P = .05$, respectively) over the first year of life. With Poisson regression, which adjusted for variables related to the recurrence of OM and having low cord blood antibody concentrations, serotype 19F remained significantly related to the number of OM episodes (relative risk for lowest quartiles vs upper 3 quartiles 1.23; 95% confidence interval, 1.02-1.50; $P = .03$).

Conclusions: Low cord blood antibody concentrations to serotype 19F predicted more OM episodes over the first 12 months of life. These results suggest the potential benefit of maternal immunization to raise neonatal antipolysaccharide pneumococcal antibody concentration and delay the onset and reduce the number of OM episodes.


Otitis Media (OM) is the most frequent diagnosis in infants and children who visit physicians owing to illness and is responsible for more than 30% of all pediatric health care visits in the United States. It is estimated that $3 to $4 billion is spent annually in the United States on the medical and surgical treatment of OM.

Among the many factors contributing to the genesis of OM, infants with OM during the first 6 months of life are at a greater risk for recurrent OM and chronic OM with effusion (OME) than children of the same age with later onset of OM. This high-risk period for OM correlates with a period of relative immunodeficiency. The infant's immature immune system responds poorly to certain antigenic challenges and must rely on a declining concentration of maternally derived antibodies.

A previous study has shown that children with recurrent episodes of OM do not exhibit total IgG, IgM, or IgA deficiencies compared with healthy children. Other studies have demonstrated that low concentrations of pneumococcal antipolysaccharide (anti-PS) IgG antibodies correlate with increased susceptibility to recurrent OM. Further, infants with low cord blood antibody concentrations against Streptococcus pneumoniae serotypes 1-4 and 19F have significantly earlier onset of OM than those with higher levels. A study of 10 Swedish children with 6 or more episodes of acute OM (AOM) during a 12-month period demonstrated that they had lower cord blood antibody concentrations against S pneumoniae serotypes 6A.
SUBJECTS, MATERIALS, AND METHODS

POPULATION

The study population consisted of 592 infants born to women from separate but similar cohorts followed up by the same Minneapolis–St Paul health maintenance organization. Detailed recruitment and data collection methods are reported elsewhere. Briefly, one cohort of women, between the ages of 18 and 35 years, was enrolled during the third trimester of pregnancy. Women were excluded for conditions known to interfere with gestation or infant birth weight, a terminated pregnancy within 1 year, or a history of infertility. The second cohort of women was recruited from those 18 years or older who received obstetric care at the same health maintenance organization as those in the first cohort. The study population was limited to women from both cohorts whose children were born during the enrollment period and received care at the health maintenance organization clinics.

DATA COLLECTION

Women completed forms during the third trimester of pregnancy and monthly for 6 months after birth. The questionnaires were designed to measure demographic and environmental variables, such as maternal and paternal age, household income, ethnicity, maternal educational level, passive smoking exposure, day care attendance, and infant feeding methods. The questionnaires also addressed family history of OM (≥3 episodes of OM in a 12-month period, tympanostomy tubes, chronic otorrhea, or persistent middle ear effusion). Birth weight and gestational age were abstracted from the medical record.

Infants’ ears were examined by pneumatic otoscopy and tympanometry at scheduled 2-, 4-, and 6-month well-child visits, and with pneumatic otoscopy at 2 weeks and at 9- to 12-, 15-, and 24-month well-child visits and all illness visits through 24 months. At each visit an ear examination form was completed detailing symptoms, tympanic membrane position, color, mobility, appearance, and middle ear diagnosis. The examiners, who included pediatrics, pediatric nurse practitioners, and family practitioners, had no knowledge of pneumococcal antibody levels. Owing to the sample size and geographic variability, the use of validated otoscopists for each examination was infeasible. However, a validated otoscopist and an investigator (G.S.G.) performed interobserver testing with a sample of the examiners. Diagnostic consistency was also evaluated by comparing recorded signs and symptoms with a middle ear algorithm. Acute OM was defined as a middle ear effusion with a red or yellow tympanic membrane, an effusion with fever, irritability, otalgia, or by the presence of a tympanic membrane perforation and otorrhea. Otitis media with effusion was defined as an opaque, red or yellow, full to bulging tympanic membrane with abnormal mobility. Otitis media included both AOM and OME.

LABORATORY METHODS

A cord blood sample was collected at the time of birth from 415 infants. Samples were analyzed by enzyme-linked immunosorbent assay for pneumococcal anti-PS IgG antibody concentrations and recurrent AOM, whereas children with recurrent AOM and high cord blood pneumococcal antibody concentrations had no isolates of Streptococcus pneumoniae.

Without considering the causative agent, children with recurrent OM or chronic OM with effusion often have tympanostomy tubes placed. In a 1-year period, 30% of children younger than 24 months, followed up in a Cincinnati, Ohio, managed health care organization, had tubes placed. Another study demonstrated that an increased rate of tube placement mirrored the increase in recurrent OM. In US children younger than 5 years, recurrent OM increased from 19% to 26% between 1981 and 1988, and tube placement increased from 1.3% to 2.4% during the same period. An intervention that would decrease recurrent OM episodes could decrease the rate of tympanostomy tube placement and its associated costs.

A previous report demonstrated that low serotype-specific cord blood pneumococcal antibody concentration predicted earlier onset of OM. This study extended the period of observation of this cohort to determine the relationship between cord blood pneumococcal anti-PS IgG antibody concentrations and number of OM and AOM episodes during the first 12 months of life.

RESULTS

The study cohort was preponderantly white (97%) and 49% were male. Three percent of the subjects came from households with annual incomes of less than $20,000, and 30% came from households with annual incomes greater than $60,000. Birth weight ranged from 1.5 to 5.1 kg (mean birth weight, 3.3 kg). At the ages of 2 weeks and 6 months, 80% and 39%, respectively, were either fully or partially breastfed. By 6 months of age 48% of the children attended out-of-home day care. Physicians’ diagnoses, which were used for statistical analyses, agreed well with the previously described middle ear algorithm (κ = 0.92). Statistics comparing an investigator and a validated otoscopist with a sample of the clinical examiners were 0.54 and 0.65, respectively. Cord blood antipneumococcal serotype quartile distributions, geometric mean titers, and 95% confidence intervals, adjusted to 89-SF standard values, are given in Table 1. Other characteristics of the cohort have been described elsewhere.

Mean OM episodes for the 4 subsets of high-low antibody concentration and early-late onset did not differ significantly for serotype 14 (P = .31). Serotype 19F demonstrated an overall significant difference for these same four subsets (P = .02). The trend was for children in the low antibody group to have more OM episodes than those
serotypes 3, 4, 6B, 14, 18C, 19F, and 23F; levels were adjusted to Food and Drug Administration lot 89-SF reference values as previously described. Assays were performed after all infants were 6 months old.

STATISTICAL ANALYSIS

The number of physician-diagnosed OM and AOM episodes from 0 to 12 months were the outcome variables. In the following data analyses, the term OM encompasses episodes of both AOM and OME, whereas AOM refers to acute episodes only. A new OM episode was defined as either AOM or OME in either ear after a normal middle ear examination, or a new episode of AOM 21 days or more after a previous diagnosis of AOM or OME.

Infants were stratified into 2 groups on the basis of antibody concentration, as in the earlier article. The low antibody group included those with concentrations in the lowest quartile, and the high antibody group included those with concentrations in the upper 3 quartiles. Early onset was defined as the occurrence of an OM episode before the age of 6 months, and later onset was the occurrence of the first OM episode between the age of 6 and 12 months. To explore the influence of both OM onset and antibody concentration on number of OM episodes, 4 subsets were created separately for serotypes 14 and 19F: low antibody concentration and early onset, low antibody concentration and later onset, high antibody concentration and early onset, and high antibody concentration and later onset. These analyses included only serotypes 14 and 19F because they were both significantly associated with early OM onset, whereas other tested serotypes were not. The relationship between number of OM episodes and each subset was determined from 0 to 12 months for the early-onset groups, and from 6 to 18 months for later-onset groups. Further analyses combined both early- and both late-onset groups to determine the relationship between antibody concentration alone and number of OM episodes. Only those with OM onset by the age of 12 months were included in these analyses.

Since age at onset was not predictive of the number of OM episodes when considered jointly with antibody concentration, the following analyses included all infants irrespective of OM onset. Low and high antibody groups for serotypes 3, 4, 6B, 14, 19F, and 23F, responsible for 9%, 1%, 10%, 15%, 4%, 15%, and 13% of AOM episodes, respectively, were analyzed individually for number of OM and AOM episodes during the first 12 months of life. The t tests for independent means were used to test for significant differences in the number of episodes between high and low antibody groups of the previously mentioned serotypes. Those with P≤.1 for both AOM and OM episodes were further analyzed using Poisson regression to adjust for previously described variables related to both the recurrence of OM and low cord blood antibody concentrations. These variables include conjunctivitis in the first 6 months of life, birth in the fall, and having more than 1 sibling. Several models were explored, using each antibody that met the criteria with the confounding covariates. Groups of antibodies were also combined with covariates, and antibodies were removed if their associated P value was greater than .05. Risk ratios were calculated for each variable in the final model.

Table 1. Cord Blood Antipneumococcal Antipolysaccharide IgG Serotype Quartile Distributions, Geometric Mean Titers (GMT), and 95% Confidence Intervals (CI) Adjusted to 89-SF Standard Values

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Lowest Quartile, µg/mL</th>
<th>Middle 2 Quartiles, µg/mL</th>
<th>Highest Quartile, µg/mL</th>
<th>GMT</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>0.004-0.260</td>
<td>0.262-1.252</td>
<td>1.253-10.992</td>
<td>0.53</td>
<td>0.47-0.60</td>
</tr>
<tr>
<td>4</td>
<td>0.009-0.16</td>
<td>0.17-1.44</td>
<td>1.45-59.52</td>
<td>0.45</td>
<td>0.38-0.52</td>
</tr>
<tr>
<td>6B</td>
<td>0.02-0.52</td>
<td>0.53-4.65</td>
<td>4.66-157.09</td>
<td>1.47</td>
<td>1.26-1.72</td>
</tr>
<tr>
<td>14</td>
<td>0.05-0.56</td>
<td>0.57-6.83</td>
<td>6.84-135.62</td>
<td>1.80</td>
<td>1.52-2.10</td>
</tr>
<tr>
<td>18C</td>
<td>0.01-0.38</td>
<td>0.39-2.54</td>
<td>2.55-44.32</td>
<td>0.84</td>
<td>0.72-0.96</td>
</tr>
<tr>
<td>19F</td>
<td>0.03-0.69</td>
<td>0.70-5.02</td>
<td>5.03-132.77</td>
<td>1.73</td>
<td>1.48-2.01</td>
</tr>
<tr>
<td>23F</td>
<td>0.01-0.50</td>
<td>0.51-4.12</td>
<td>4.13-120.26</td>
<td>1.27</td>
<td>1.08-1.47</td>
</tr>
</tbody>
</table>

COMMENT

This study illustrates that low cord blood pneumococcal antibody concentrations against serotype 19F, inde-
life could be the result of exposure to and infection with type, the number of episodes in the first 12 months of depends on infection with a single organism or serotypes during the first year of life. Unlike the first OM episode, which is significantly lower concentrations of antibodies against 19F than 1 sibling predicts a greater number of OM episodes and Low Cord Blood Antibody Concentrations

Table 3. Poisson Regression Model Adjusting for Variables Related to Both the Recurrence of Otitis Media and Low Cord Blood Antibody Concentrations

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk Ratio</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotype 19F (lowest quartile)</td>
<td>1.23</td>
<td>1.02-1.50</td>
<td>.03*</td>
</tr>
<tr>
<td>Conjunctivitis in first 6 mo</td>
<td>1.16</td>
<td>0.95-1.42</td>
<td>.14</td>
</tr>
<tr>
<td>Birth in the fall</td>
<td>1.16</td>
<td>0.93-1.44</td>
<td>.18</td>
</tr>
<tr>
<td>≥1 Sibling</td>
<td>1.21</td>
<td>0.97-1.52</td>
<td>.10</td>
</tr>
</tbody>
</table>

*Statistically significant.

Although having a low antibody concentration against serotype 14 was associated with early-onset OM, it was not associated with number of OM episodes during the first year of life. Unlike the first OM episode, which depends on infection with a single organism or serotype, the number of episodes in the first 12 months of life could be the result of exposure to and infection with several different pneumococcal serotypes or organisms. Serotype 14 may be important in early-onset OM, but other organisms and serotypes may be the causative agents in later episodes, diminishing the relationship between serotype 14 cord blood antibody concentrations and the number of OM episodes. Although serotypes 14 and 19F are each responsible for 15% of pneumococcal OM in children younger than 6 years according to national data collected by the Centers for Disease Control and Prevention, Atlanta, Ga, it is difficult to know if these serotypes are responsible for the same proportion of OM in Minnesota children or, more specifically, in the study cohort.

Infants are poorly equipped to respond to pneumococcal PS. During the first 6 months of life, maternally acquired antibody declines while infant immune systems begin producing IgM followed by IgG. Serotypes 14 and 19F have been shown to be poor immunogens in infants vaccinated with pneumococcal polysaccharide vaccine. In one study, few infants 12 months or younger had prevaccination and postvaccination antibody concentrations presumed to be protective (>300 ng/mL) against serotypes 14 and 19F, but a higher proportion had protective levels against 14 than against 19F. This suggests that infants in the first year of life may be more prone to multiple infections of serotype 19F than of serotype 14 because they make less antibody to 19F.

The number of OM episodes experienced by a child results in part from having low concentrations of passively acquired and/or actively produced serotype-specific pneumococcal antibodies. Other important contributing factors include the exposure to other young children (eg, day care attendance, siblings), prevalence of serotypes to which the infant has low antibody concentrations (which affects the likelihood of exposure to those organisms), and other bacterial and host factors that affect the infectivity, pathogenicity, and immunogenicity of encountered organisms. Actively produced antibody is in short supply during the first year of life and passively acquired antibody is a reflection of maternal supply. Maternal antibody concentrations to specific pneumococcal serotypes probably result from cross-reactive antigens and previous exposures to specific pneumococcal serotypes carried by older children in day care centers. Carriage rates of specific serotypes have been shown to vary substantially among day care centers in the same community. Thus, given adequate maternal antibody production and transfer, cord blood antibody concentrations are likely to be elevated against serotypes to which the mother had been recently exposed. For example, children of women who were exposed mainly to serotype 19F may have fewer OM episodes due to 19F because they have high concentrations of passively transferred 19F antibody, whereas repeated exposure to a serotype that the infant’s mother had not encountered may result in more OM episodes due to low antibody concentrations to those serotypes. Therefore, developing an OM episode depends on low cord blood antibody concentration to a specific serotype and encountering a sufficient exposure to that same serotype.

Cord blood antibodies are a consequence of maternal production and placental transport. Low cord blood antibody concentrations may be a result of low maternal production due to a genetically compromised immune system,
a defect in maternal-fetal antibody transfer, or lack of recent maternal exposure to \textit{S pneumoniae}. A previous study documented that individuals with G2m(n), an allotype antigen of IgG2 heavy chains, had higher preimmunization and postimmunization antibody titers to PS antigens than individuals lacking G2m(n). Infants of G2m(n)-negative mothers would not only receive less maternal antibody due to poor production, but those inheriting maternal G2m(n)-negative status would be unable to respond as vigorously as G2m(n)-positive infants. Thus, their active response would be compromised and they would also have lower levels of maternally derived antibodies to respond to pneumococcal PS challenges. Other studies of OM-prone children have documented decreased responsiveness to pneumococcal vaccines. Pelton et al\textsuperscript{23} demonstrated that children with relatively lower preimmunization pneumococcal antibody concentrations had more episodes of OM during the following 24 months than other children. Another study has shown that OM-prone children respond more vigorously to pneumococcal conjugate vaccine than to the pneumococcal PS vaccine. Conversely, OM-free children respond equally well to both, suggesting a state of hyporesponsiveness to pneumococcal PS in OM-prone children.\textsuperscript{24}

Maternal-fetal transfer of IgG antibodies begins at 17 weeks of gestation and increases in proportion to gestational age.\textsuperscript{25} At term, the concentration of IgG in the infant is usually 10\% to 15\% higher than in the mother.\textsuperscript{25} The exception is children born to mothers with exceptionally high levels of IgG. In this case the placenta transfer mechanism acts as a limiting step and the infant will have relatively less than the mother.\textsuperscript{25} More specifically, correlation between maternal and infant serum concentrations of IgG1 against pneumococcal serotypes 1, 6A, 14, 19F, and 23F is strong.\textsuperscript{26,27} Thus it is unlikely that selective or defective maternal-fetal transfer is an adequate explanation.

In addition to providing passive immunity, maternal-fetal antibody transfer may also prime the immune system. Priming the immune system is thought to occur when anti-idiotypic antibodies, along with protective antibodies, cross the placenta and induce the synthesis of protective antibodies in the fetus.\textsuperscript{25} In an experimental system, maternal immunization with anti-idiotypic antibody fragments, which mimicked the conformation of the capsular antigen, protected neonatal mice against group B streptococcal infection.\textsuperscript{20} This may explain why infants with low concentrations of cord blood antibodies to specific serotypes have more episodes of OM, that is, infants who receive low concentrations of specific antibody may also receive low concentrations of anti-idiotypic antibodies. Thus, they would not only lack passive maternally derived antibody protection, they would also lack immune priming. Although anti-idiotypic immune priming has been documented in mice, little is known about the effects of anti-idiotypic antibodies in humans.\textsuperscript{23}

Many physicians and nurse practitioners examined infants, and OM may have been both underdiagnosed and overdiagnosed. However, \kappa \textsuperscript{values} for OM diagnosis comparing 20 clinicians, an investigator, and a validated otoscopy investigator demonstrated moderate to substantial agreement, and \kappa comparing physician diagnoses with the algorithm was 0.92.\textsuperscript{10} Since examiners did not have information about antibody concentrations, these findings could not have influenced their diagnostic decisions. Nondifferential misclassification of disease status (eg, unbiased misdiagnoses) results in a decreased rather than an increased estimate of the effect of the association between independent and dependent variables.\textsuperscript{30}

Infants with low cord blood antibody concentrations against serotype 19F have a greater number of OM episodes during the first 12 months of life than those with higher antibody concentrations when controlling for confounding factors in multivariate analysis. These results suggest the potential benefit of maternal immunization to delay the onset of OM and to also reduce the number of subsequent episodes up to the age of 12 months. Since this strategy has never been tested, it is impossible to estimate the effectiveness of maternal vaccination alone or in combination with infant pneumococcal vaccination in reducing OM in the first 6 months of life. Studies by Black et al\textsuperscript{24} and Eskola and Kilpi\textsuperscript{32} demonstrate that infant immunization with at least 3 doses of pneumococcal conjugate vaccine reduced OM by 6\% to 7\%, and frequent OM by 20\% after the third dose of vaccine. However, no data are available on OM reduction prior to the age of 6 months.\textsuperscript{31} Both maternal and infant immunization against pneumococcal disease are attractive prevention strategies for infants given the disturbing rise in antibiotic-resistant strains of \textit{S pneumoniae} over the past decade. Serotypes included in the conjugate vaccine match resistant serotypes involved in pediatric invasive pneumococcal infections.\textsuperscript{33} Ultimately, both maternal and infant immunization strategies have the potential to reduce infant OM in the first year of life, thus decreasing tympanostomy tube placement and the monetary costs and morbidity associated with recurrent OM.

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