SHORT COMMUNICATION

Development of antibodies against the putative proteinase maturation protein A in relation to pneumococcal carriage and otitis media

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Abstract
The putative pneumococcal proteinase maturation protein A is a potential pneumococcal vaccine candidate. We examined serum antipneumococcal proteinase maturation protein A antibodies at 6, 12, 18 and 24 months of age, and showed that the age-related development of antipneumococcal proteinase maturation protein A antibodies is associated with pneumococcal contacts. A higher antipneumococcal proteinase maturation protein A antibody concentration at 18 months of age tends to predict for a lower risk of pneumococcal acute otitis media in the following 6 months (relative risk: 0.84, 95% confidence interval: 0.62–1.13).

Streptococcus pneumoniae is worldwide an important cause of life-threatening infections such as meningitis and sepsis, and of respiratory tract infections such as pneumonia and acute otitis media (AOM) (ACIP, 1997). The vaccines currently available are the 23-valent polysaccharide vaccine Pneumovax® and the 7-valent conjugate vaccine Prevnar®. The latter is highly immunogenic and protective against invasive disease in children (Black et al., 2000). However, the efficacy of this vaccine against respiratory tract infections such as otitis media is small, and due to the limited number of pneumococcal serotypes included in the vaccine, replacement of vaccine serotypes by nonvaccine serotypes has already been observed (Eskola et al., 2001; Veenhoven et al., 2003). A potential solution for these drawbacks could be a protein-based vaccine, representing a combination of immunogenic surface-associated proteins (Bogeart et al., 2004). Such a vaccine might potentially cover the whole spectrum of pneumococcal serotypes and genotypes.

The surface-associated pneumococcal protein putative proteinase maturation protein A (PpmA) is one of the proteins considered to be involved in virulence of S. pneumoniae. In addition, anti-PpmA antibodies induce opsonophagocytosis in vitro (Overweg et al., 2000). Therefore, it is thought to be a potential candidate for future protein-based pneumococcal vaccines. Recently, we have studied the immunogenicity of this protein in a large cohort of Finnish children with acute otitis media (AOM) during the first 2 years of life (Adrian et al., 2004). From this study, we concluded that PpmA is an immunogenic protein that elicits antibody responses early in life. However, we were not able to show a correlation between antibody concentrations and pneumococcal carriage or disease (Adrian et al., 2004).

In this study, we examined the development of anti-PpmA antibodies in relation to age and pneumococcal contacts in 50 healthy Finnish children, who participated in the Finnish Otitis Media Cohort Study. As described previously, pneumococcal contacts by means of colonization (10 nasopharyngeal swabs) and AOM (cultures of middle ear fluids) were determined during a follow-up period of 24 months (Rapola et al., 2000; Kilpi et al., 2001). Immunoglobulin G anti-PpmA antibodies were measured in sera of these children obtained at 6, 12, 18 and 24 months, and in sera from 129 mothers. The
association between PpmA antibody concentration and the risk of developing AOM during the following 6 months was calculated for the periods 12–18 months (256 samples with 48 AOM episodes) and 18–24 months (234 samples with 27 AOM episodes) in a total of 290 children.

We showed that children as young as 6 months have anti-PpmA antibodies in serum, and that the antibody concentrations increase significantly between 6 and 24 months of age. However, they do not reach adult concentrations (Fig. 1a). We further analyzed the data with respect to previous pneumococcal contacts (Fig. 1b). The number of children in the group with previous pneumococcal contacts increased with age as more children come in contact with pneumococci. Simultaneously, the number of children in the group without previous pneumococcal contacts declined. The anti-PpmA antibody concentrations increased only in children with previous pneumococcal contacts, but not in children without a history of pneumococcal contacts (Fig. 1b). These data suggest that pneumococcal contacts induce the development of the anti-PpmA antibodies.

In addition, we evaluated whether the presence of anti-PpmA antibodies was associated with the development of AOM caused by *S. pneumoniae* (PncAOM). We performed univariate and multivariate logistic regression analyses, including anti-PpmA antibody concentrations and previous pneumococcal colonization, previous PncAOM or previous pneumococcal contacts in general defined as pneumococcal colonization or infection. A higher concentration of serum anti-PpmA antibodies at 18 months of age is correlated with a lower relative risk of PncAOM during the following 6 months (not statistically significant). We did not observe this association at the age of 12 months (Table 1). In the multivariate analyses we included the previous pneumococcal exposure as an explanatory variable. Previous pneumococcal carriage decreased the risk of PncAOM during the following 6 months, both at 12 months (relative risk: 0.40, 95% confidence intervals: 0.19–0.84) and 18 months of age (relative risk: 0.42, 95% confidence intervals: 0.18–0.98), but did not influence the association of anti-PpmA antibodies and the risk of PncAOM. Previous PncAOM increased the risk of a new PncAOM in the following 6 months both at 12 months

Table 1. Relative risk (RR) of pneumococcal AOM with 95% confidence intervals (95% CI) in univariate and multivariate models as determined by anti-PpmA antibodies and pneumococcal history in 6-month intervals

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Anti-PpmA RR (95% CI)</th>
<th>Any pneumococcal contact RR (95% CI)</th>
<th>Pneumococcal carriage RR (95% CI)</th>
<th>Pneumococcal AOM RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12–18</td>
<td>0.98 (0.76–1.25)</td>
<td>–</td>
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<td>–</td>
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<tr>
<td></td>
<td>1.02 (0.80–1.31)</td>
<td>0.7 (0.39–1.27)</td>
<td>–</td>
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<tr>
<td></td>
<td>1.03 (0.81–1.32)</td>
<td>–</td>
<td>0.4 (0.19–0.84)</td>
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</tr>
<tr>
<td></td>
<td>0.95 (0.74–1.22)</td>
<td>–</td>
<td>–</td>
<td>1.69 (0.91–3.14)</td>
</tr>
<tr>
<td>18–24</td>
<td>0.84 (0.62–1.13)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>0.79 (0.57–1.08)</td>
<td>1.84 (0.67–5.03)</td>
<td>–</td>
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</tr>
<tr>
<td></td>
<td>0.89 (0.66–1.20)</td>
<td>–</td>
<td>0.42 (0.18–0.98)</td>
<td>–</td>
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<tr>
<td></td>
<td>0.79 (0.58–1.07)</td>
<td>–</td>
<td>–</td>
<td>3.49 (1.63–7.46)</td>
</tr>
</tbody>
</table>

Any pneumococcal contact, pneumococci cultured from the nasopharynx or from middle ear fluid (MEF); pneumococcal carriage, pneumococci cultured from the nasopharynx, but not from MEF sample; pneumococcal AOM, pneumococci cultured from MEF sample. Significant data in italics.
(relative risk: 1.69, 95% confidence intervals: 0.91–3.14) and 18 months of age (relative risk: 3.49, 95% confidence intervals: 1.63–7.46), although only the latter analysis was statistically significant (Table 1). Including both variables in a multivariate analysis showed that both previous PncAOM and anti-PpmA antibody concentrations are independently correlated with the risk of a new AOM (Table 1). Whether there is a direct association between the presence of PpmA antibodies and protection against PncAOM remains unclear.

We conclude that the development of anti-PpmA antibodies occurs early in life and is associated with previous pneumococcal contacts. Furthermore, higher anti-PpmA antibody concentrations may be associated with a decreased risk to develop pneumococcal AOM. These findings are in line with recent observations made by Rapola et al. (2003). They made comparable observations for the development of natural antibodies against pneumococcal surface adhesin A (PsaA). Both studies suggest that the proteins investigated could be serious vaccine candidates with a potential protective effect against pneumococcal disease. Since PpmA is a conserved protein in S. pneumoniae, use of PpmA as vaccine component could induce protective immunity against a broad range of pneumococcal sero- and genotypes (Overweg et al., 2000).

References


