Immunological Status in the Aetiology of Recurrent Otitis Media with Effusion: Serum Immunoglobulin Levels, Functional Mannose-Binding Lectin and Fc Receptor Polymorphisms for IgG

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The objective was to study the role of serum immunoglobulin levels, mannose-binding lectin (MBL), and Fc gamma receptor (FcγR) polymorphisms on the development of recurrent otitis media with effusion (OME). Children aged between two and seven years with persisting OME received bilateral tympanostomy tubes and immunological parameters were investigated in relation with OME recurrence within six months after tube extrusion. No statistically significant differences in serum immunoglobulin levels were present between children with and without OME recurrence. In children with bilateral recurrence (n = 56), median levels of MBL were 1.39 mg/L compared to 2.48 mg/L in children with OME recurrence (n = 17) (p = 0.29). In addition, 34% of the children with bilateral recurrence were homozygous for the genotype FcγRIIa-R/R131, whereas less than 20% of the children with unilateral recurrence or those without recurrence were homozygous for this Fcγ receptor (p = 0.26). Serum mannose-binding lectin and FcγRIIa-R/R131 polymorphism may play a role in the aetio-pathogenesis of recurrent OME.

KEY WORDS: Otitis media with effusion; recurrence; immunoglobulins; mannose-binding lectin; Fc gamma receptors.

INTRODUCTION

Otitis media with effusion (OME) is a highly prevalent ear disorder in young children; at least 80% of children experience one or more episodes of OME by the age of four years (1, 2). OME is characterized by a high rate of spontaneous recovery, but also by a high rate of recurrence (3). As adverse effects of OME mainly occur in the group of children with a history of recurrent or chronic OME, it is necessary to distinguish these children from the total group of OME children early in the course of the disease to focus intervention measures, such as tympanostomy tubes, on this particular group (4–8). Predisposing factors for the recurrence of OME are believed to be related to its aetiology. OME is a multifactorial-generated condition in which the inflammatory response to respiratory pathogens, both bacterial and viral, seems to be a crucial element (9). In order to distinguish children with transient OME from those with recurrent OME, we studied three aspects of the immune response to respiratory tract pathogens in a group of children with chronic OME. These children were referred for bilateral tympanostomy tube insertion. Serum immunoglobulin levels, functional

Abbreviations used: OME, otitis media with effusion; MBL, mannose-binding lectin; NA, neutrophil antigen; GP, general practitioner; SAS, Statistical Analysis Systems; AOM, acute otitis media.
mannose-binding lectin (MBL) serum levels, and Fcγ receptor polymorphisms were assessed.

Low serum immunoglobulin levels, despite infections or chronic inflammatory processes, may be indicative for a subtle immunodeficiency (10, 11). This phenomenon was the basis of our first hypothesis: children with low IgA, IgG (and subclasses), or IgM levels early in the course of the disease are more likely to develop recurrent OME (12–14).

Independent of antibodies, MBL is able to initiate the complement pathway by directly opsonizing pathogens by binding to specific oligosaccharides (15, 16). Increased susceptibility to bacterial and viral respiratory infections in early childhood is associated with low or absent serum MBL levels (17, 18). This phenomenon led us to the second hypothesis: children who have lower functional MBL serum levels early in the course of OME are more likely to develop recurrent disease.

Leukocyte antibody receptors for IgG (FcγR) play an important role in IgG-facilitated phagocytosis of bacteria. Genetically determined functional polymorphisms for three classes of human FcγR have been described (19, 20). In FcγRIIA, the biallelic polymorphism consists of the presence of either arginine (R) or histidine (H) at position 131. Only the H131-allotype is capable of binding IgG2 opsonized bacteria, such as Streptococcus pneumoniae. In FcγRIIIA, the allotype with phenylalanine (F) at position 158 has been shown to bind complexed IgG1, IgG3, and IgG4 less avidly than the Valine (V) allotype. FcγRIIIb bears the neutrophil antigen (NA) polymorphism. NA1 homozygotes have a higher phagocytic capacity for IgG1 and IgG3 opsonized bacteria than NA2 homozygotes. Recently, it has become evident that some of these genetically determined functional polymorphisms may contribute to susceptibility to infections (21–25). Thus our third hypothesis was: children with recurrent OME are more likely to be homozygous for the Fcγ receptors with the lower binding affinity for IgG subclasses IgG1, IgG2, and IgG3 (FcγRIIa-R/R131) and IgG1 and IgG3 (FcγRIIIb-NA2/NA2).

To test these three hypotheses, we conducted a cohort study on a group of children with their first clinical episode of OME. Follow-up of these children enabled us to study the role of immunological status on the subsequent probability of developing recurrent OME.

METHODS

Patients and Study Design

In The Netherlands, health insurance companies require formal referral by a general practitioner (GP) before refunding specialist care. Therefore, nearly all patients with OME are initially seen by their general practitioners (GP). According to the guidelines of the Dutch College of General Practitioners, children with chronic OME should only be referred to an otologist after repeated observations of middle ear effusion over a period of at least three months. Children were eligible for the study if they were aged between two and seven years, their first clinical episode of bilateral OME had persisted for at least three months as documented by their GP and they had been referred for the first time to the Departments of Otorhinolaryngology of one of the three participating hospitals in Nijmegen or Winterswijk (The Netherlands) between December 1999 and March 2002. Children with Down’s syndrome, cleft palate, or daily treatment with inhalation or topical corticosteroids for at least one month per year were excluded, as were children with proven immunodeficiency or previous adenoidectomy. The Medical Ethical Committees of the participating hospitals approved the study protocol. Signed informed consent was obtained from the parents or legal guardians. At study entry, all the children received bilateral tympanostomy tubes for OME under general anesthesia. Blood samples were collected during this surgical intervention. Serum and DNA were isolated and stored at −20°C until required for analysis.

To monitor OME recurrence, an otologist examined the ear status of each child once every three months until six months after documentation of spontaneous tube extrusion. The date of tube extrusion was taken as the date of the first check-up during which extrusion had been observed (per ear).

Definition of OME Recurrence

OME was defined in accordance with an algorithm, which is primarily based on tympanometry (26). Tympanograms were classified in accordance with Jerger (27). OME was considered to be present when tympanometry resulted in a type B tympanogram or a type C2 tympanogram with otoscopic findings that suggested the presence of effusion in the middle ear and the absence of an acute ear infection (26). If tympanometry (Rexton Danplex TYMP 87 A/S Copenhagen, Denmark) could not be performed, otoscopic findings that suggested effusion in the middle ear were considered to diagnose OME. Children were categorized into those who developed bilateral OME (biOME), children with unilateral OME recurrence (uni_rOME), and children who did not develop OME in the follow-up period (no_rOME).

Immunological Tests

Total serum immunoglobulin concentrations of IgA, IgM, and IgG as well as IgG1–IgG4 subclass