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Meta analysis

Mannose binding lectin codon 54 polymorphism and susceptibility to recurrent respiratory tract infections in children: A meta-analysis

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ABSTRACT

Background: There have been studies focused on mannose binding lectin (MBL) polymorphism and susceptibility to recurrent respiratory tract infections (RRTI) with inconclusive results. This present study is a meta-analysis of possible MBL and RRTI association in children.

Methods: A literature search was performed using Medline and PubMed and abstracts were reviewed for relevance. Any study was considered to be eligible for inclusion if it met the following criteria: the MBL gene polymorphism at codon 54 was determined, the outcome was recurrent respiratory tract infection in children and there were at least two comparison groups. The odds ratios(OR) of the genetic MBL polymorphisms were combined and calculated, and the forest plots of the OR value distributions were drawn. Chi-squared testing of heterogeneity was done ($p < 0.001$).

Results: Five eligible studies were included in the study. There has been heterogeneity between the studies ($p = 0.001$). Our results did not show any association between MBL genotypes AA, BB, AB, alleles A and B and RRTI.

Conclusions: Our meta-analysis of accessible, published data has demonstrated no statistically significant association between MBL2 genotype and recurrent respiratory tract infection in children.

Summary of the article's main point

Here are discrepancies regarding the importance of MBL polymorphism and its impact on recurrent respiratory tract infections. Our meta analysis did not find statistically significant association between MBL codon 54 polymorphism and recurrent respiratory tract infection in children.

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1. Introduction

RRTI in children are one of the most common reasons for physician visits and hospitalizations. The recurrence of the respiratory tract infections constitute a demanding challenge for the pediatricians. While most children with RRTI have a normal

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immunity, it is still necessary to investigate the probable immunodeficiency [1]. Defective components of the cellular innate immune system that are responsible for recurrent respiratory tract infection are, natural killer cells with defective fc γIIIa, abnormal alveolar macrophages with defective removal of phagocytic cells, decreased neutrophil chemotaxis and pathologic phagocytosis [2,3]. On the humoral part of innate immune system, inflammation-related serum proteins such as complement, mannose binding lectin [4] and ficolins [5] take part. For innate immune system to function correctly, pathogen associated molecular patterns (PAMP) on microbes would need to be recognized by the receptors of the innate immune system which are; pattern-recognition receptors (PRR). PRR's are classified to five subgropus, one of which is the Toll-like receptor. A defective TLR-4, signal a defective response, and cause RRTI. Without functional IRAK (interleukin receptor associated kinase) [6], NF-κB cannot be activated. Alteration of cytokine levels (↑ IL-4, ↑IL-10, ↓IFN- γ,↓ IL-2) [11,12] and inflammatory mediators released from macrophages, mast cells and natural killer (NK) cells are the pathologies defined under humoral innate immune system pathologies for RRTI susceptibility. Mannose binding lectin is an important molecule in the innate immune system and acts as an acute phase reactant, mainly involved in killing microorganisms via activation of lectin complement pathway and opsonophagocytosis [7]. Even among individuals with identical allotypes, the concentration of MBL level in plasma vary considerably [8]. The cut off value defining the deficency for MBL ranges from 50 ng/ml to 1 μg/ml [9,10]. Mannose -binding lectin (MBL) binds on surfaces of variety of microorganisms and activates complement system. MBL production is controlled by the MBL2 gene, and polymorphisms of the structural regions of the gene or its promoter are associated with serum MBL deficiencies [11]. MBL2 exon 1 (codon 52, 54, 57) variants cause an increased risk of infection because of low protein levels [12]. There are a number of mechanisms that account for discrepancy between MBL levels and MBL2 genotypes and their associations with RRTI. Polymorphisms of the defined codon variants cause nearly 20% of normal MBL2 levels in heterozygotes and are found to be <2% or absent in homozygotes or compound heterozygotes. There are some discrepancies in the literature regarding the relative importance of polymorphisms of MBL2 gene and its impact on RRTI. As an attempt to discuss the association between RRTI and MBL gene codon 54 polymorphism which has been shown to be associated with low levels of serum MBL, we carried out a meta-analysis of selected studies from the literature.

2. Methods

2.1. Identification of studies

For the meta-analysis, we included all published studies that considered the association between recurrent respiratory tract infections and MBL polymorphisms. A literature search for the MeSH terms "respiratory tract infection" or "recurrent respiratory infection" or "MBL2 polymorphism" or "MBL polymorphism" was performed by the authors Ö.A., and F.Ö., screening Medline and PubMed and abstracts were reviewed for relevance. No language restrictions were applied to the search strategy. Any study was considered to be eligible for inclusion if it met the following criteria: the MBL gene polymorphism at codon 54 was determined, the outcome was recurrent respiratory tract infection in children and there were at least two comparison groups.

2.2. Data extraction

Data were extracted independently by two authors (Ö.A, and F.Ö) based on a customized database for data extraction. For each study, the following information was collected: first author, year and location of the study, average age, ethnicity, number of participants, number of cases and controls, and the frequency of the MBL2 genotypes in cases and controls (Table 1). The disagreements were resolved between the reviewers by concensus. For quality assessment six domains were assessed. Those were representativeness of classes, representativeness of the controls, ascertainment of recurrent respiratory tract infections, ascertainment of controls, genotypic examination and association assessment. The primary outcome considered in the meta-analysis was the association between recurrent respiratory tract infection and the presence of MBL polymorphisms. For the primary analysis and to allow appropriate comparison of all studies, cases and controls were classified based on codon 54 polymorphism, and wild type.

2.3. Statistical Analysis

The odds ratios (OR) with 95% confidence intervals, representativeness of the controls, ascertainment of recurrent respiratory tract infections, ascertainment of controls, genotypic examination and association assessments were done. The primary outcome considered in the meta-analysis was the association between recurrent respiratory tract infection and the presence of MBL polymorphisms. MedCalc Software (Acacialaan 22, 8400 Ostend, Belgium) was used to perform meta-analysis. The odds ratios (OR) of the genetic MBL polymorphisms were combined and calculated, and the forest plots of the OR value distributions were drawn. Chi-squared testing of heterogeneity was done ($P < 0.001$). Since the heterogeneity was significant between studies, a random effects model was applied to take into account between-study variation. Statistical heterogeneity across studies was quantified with the I^2 lying between 0% and 100%, where values less than 40% suggest that homogeneity is good for the reliability of meta-analysis.

3. Results

Our search yielded a total of 40 references. After screening the titles and abstracts, 35 studies were excluded, because they were not considered relevant to the study topic or because of duplication in databases, leaving 5 potentially eligible studies. Final inclusion yielded only five studies to be used for meta-analysis [13–17].

Characteristics of each case-control study included in our meta-analysis are summarized in Table 1. Two studies were conducted in Turkey, two in China and one in Belgium with a total of 721 children involved. All cases were diagnosed as recurrent respiratory tract infections (RRTI = 303) or healthy controls ($n = 418$). The definition of RRTI in all the studies followed similar guidelines which was considered appropriate and satisfactory for patient selection. Significant heterogeneity was observed between study groups (I^2 varied from 32% to 98%). Therefore, random effects model was employed for meta-analysis. All of the five studies included in our meta-analysis have reported association between MBL2 codon 54 polymorphism and RRI.

Forest plots were drawn for each compared group. The horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of the OR and 95% CI. In this analysis, a random-effects model was used.

Fig. 1 shows the ORs for RRTI comparing subjects with AA genotypes and those with AB and BB genotypes. Applying the random effects model yielded the pooled OR of 0.717 (95% CI 0.296–1.736 P for heterogeneity = 0.001, $I^2 = 84.667$).

Fig. 2 shows the ORs for RRTI comparing subjects with AB genotypes and those with AA and BB genotypes. Pooled OR for AB versus AA and BB was 1.187 (95% CI 0.114–0.81, P for heterogeneity = 0.001, $I^2 = 81.931$).