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Low mannose-binding lectin (MBL) levels and MBL genetic polymorphisms associated with the risk of neonatal sepsis: An updated meta-analysis ☆

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ABSTRACT

Background: Relatively low serum mannose-binding lectin (MBL) levels and MBL genetic polymorphisms have been implicated as high risk factors for neonatal sepsis. However, different studies have reported conflicting findings and have generally been underpowered to exclude modest effect sizes.
Methods: Standard methodology of systematic reviews and meta-analyses was followed. PubMed, Embase, Cochrane, Web of Science, and Scopus databases were searched from January 1996 to December 2013. The eligible studies were collected and analyzed using Review Manager 5.2. Meta-Disc version 1.4 was used to describe and calculate sensitivity, specificity, summary receiver operator characteristic (SROC) curves and area under the curve. SROC curve analysis was used to summarize the overall performance. Funnel plots, Egger's test and Begg's test were used to investigate publication bias.
Results: Seven studies addressing low MBL levels and MBL genetic polymorphisms (structure variant A/O, A/B of Exon1) were analyzed for susceptibility to neonatal sepsis, respectively. All of these control studies were of reasonable methodological quality. The pooled unadjusted odds ratio showed that low MBL levels were significantly associated with neonatal sepsis ($P = 0.0002$; odds ratio = 4.94, 95% confidence interval = 2.16–11.29) and MBL genetic polymorphisms were also significantly associated with neonatal sepsis ($P = 0.03$; odds ratio = 1.41, 95% confidence interval = 1.03–1.94). In subgroup analysis based on gestational age, increased risk was found in the preterm infants in the dominant model (RR 2.33, 95%CI 1.06–5.13, $P = 0.03$). However, no association was observed for term infants in subgroup analysis. Additionally, the SROC curve of low MBL levels in the prediction of neonatal sepsis indicated a poor predictive ability. The area under curve was 0.80 (95% confidence interval = 0.74–0.86).
Conclusion: Currently available evidence shows that neonates with low serum MBL levels are more than four times more likely to have neonatal sepsis compared to those with higher serum MBL levels. Neonates with MBL genetic polymorphisms are also susceptible to developing neonatal sepsis. However, a low serum MBL level was only of moderate value in detecting neonatal sepsis.

1. Introduction

Despite recent advances in neonatal intensive care, neonatal sepsis remains an important cause of morbidity and mortality, particularly among preterm infants [1]. Neonatal sepsis causes poor neurodevelopmental outcomes in very preterm infants [2]. Although prematurity is the single most significant risk factor for sepsis, for which the risk increases in proportion to the decrease in birth weight and gestational age, neonatologists are actively searching for clinical or biomarkers to aid in an early diagnosis to treat neonatal sepsis. Nonetheless, an early diagnosis is difficult because the clinical signs and symptoms of neonatal sepsis are usually nonspecific. Thus, timely and accurate identification of sepsis is imperative to implement appropriate antibiotic treatment to reduce the risk of adverse outcomes.

The innate immune system is the host's primitive first-line response to invasive pathogens, and it interacts with other homeostatic patterns including inflammation and coagulation. Early activation of an immune response is mediated by soluble pattern recognition molecules that activate humoral and cellular effectors thereby identifying and neutralizing the invasive pathogens [3]. Mannose-binding lectin (MBL), a

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member of the collectin family, is produced by the liver as an acute phase protein which activates the lectin pathway of the complement system and subsequent inflammatory mechanisms [4,5]. The importance of MBL function during the first months of life, when the efficacy of innate immunity is crucial, has led some researchers to propose that MBL should be included in biomarker panels for the early detection of neonatal infections in low-resource settings [6].

In neonates, low MBL levels have not only been associated with the variant MBL2 genotype, but also with low gestational age [7,8]. Therefore, detection of MBL deficiency at birth should be based on actual MBL plasma levels rather than on the MBL2 genotype. Ozkan et al. [9] reported that low MBL levels and MBL genetic polymorphisms were important risk factors for developing both neonatal sepsis and pneumonia, especially in premature infants. Another study also showed that a low serum MBL level could be considered a sensitive and specific marker for predicting sepsis, septic shock, and clinical outcomes in newborn infants [10]. However, other studies have reported contrasting results [11–13], and in some cases low levels have even appeared to be a protective factor for neonatal sepsis, probably through reducing the inflammatory cytokine storm [14]. In view of this controversy, a more comprehensive review including the latest literature is needed to investigate the risk of neonatal sepsis in relation to both low MBL concentrations and MBL genetic polymorphisms.

According to the pathophysiology of innate immune development in neonates, we hypothesized that low MBL levels and MBL genetic polymorphisms were important risk factors for developing neonatal sepsis, especially in premature infants. We thus conducted a systematic review and meta-analysis to investigate low MBL levels and MBL genetic polymorphisms in association with the risk of sepsis in term and preterm infants.

2. Methods

2.1. Retrieval and selection of studies

The common approach to a computer-aided literature search was used to search PUBMED, EMBASE (http://www.embase.com/), the Cochrane Library (http://www.the-cochranelibrary.com/view/0/index.html), Web of Science, and Scopus for relevant citations from January 1996 to June 2013. The search items included "mannose-binding lectin," "MBL," "sepsis," "septicemia," "neonate," "newborn," "infant," "preterm," "premature," and mutual combinations. Online databases were also searched systematically to find studies that examined the relationship between MBL genetic polymorphisms and the risk of neonatal sepsis. The following keywords were used: "mannose-binding lectin," "MBL," "polymorphism," "variant," "sepsis," "septicemia," "neonate," "newborn," "infant," "preterm," "premature," and mutual combinations. We also examined the references of known articles.

The following criteria were applied to identify studies for inclusion in our meta-analysis: (1) original report (all study designs); (2) studies with MBL levels and MBL polymorphisms determined; and (3) confirmed sepsis as an outcome. Confirmed sepsis was defined as a positive microbial blood culture in the included studies. The selection of articles was performed independently by two investigators to ensure high accuracy.

2.2. Data extraction

Two reviewers independently extracted the information from all articles with regards the key study design and study group characteristics including ages of both cases and controls, method of MBL analysis, definition of MBL deficiency, definition of MBL genetic polymorphism, definition of outcome and risk factor analysis. Disagreements were either resolved in a consensus meeting or, if unresolved, after consultation with a third reviewer.

2.3. Quality assessment

The quality of the studies was independently assessed by two reviewers using the QUADAS tool, based on the recommended methods of the Cochrane handbook for diagnostic test accuracy reviews, with each item scored as 'low risk of bias', 'high risk of bias', or 'unclear' [15].

2.4. Statistical analysis

The statistical analysis was performed using Review Manager 5.2 and Meta-DiSc 1.4 software. Associations between the risk of developing neonatal sepsis as related to low MBL levels and MBL genetic polymorphisms were evaluated by combining the studies with an odds ratio (OR) or relative risk (RR). The pooled OR(RR) expressed much greater odds of having sepsis for neonates with MBL-deficiency than for neonates without MBL-deficiency and for neonates with MBL genetic polymorphisms than with a normal MBL gene [16]. Heterogeneity among the included studies was assessed by using the Cochran Q statistic and quantified with the I^2 lying between 0% and 100% [17]. In general, $I^2 > 50\%$ shows that heterogeneity among the studies produces some impact, whereas $I^2 < 50\%$ shows that homogeneity was good for the reliability of meta-analysis. When a significant I^2 (>50%) indicated heterogeneity across the studies, a random effects model was used for the meta-analysis; otherwise a fixed effects model was used. We investigated heterogeneity by subgroup analysis according to gestational age. Forest plots were used to illustrate the results of the meta-analysis. We also constructed summary receiver operator characteristic (SROC) curves, which showed the relationship between sensitivity and the proportion of false positives (1-specificity). Q^* values, defined by the point where the sensitivity equals the specificity, were calculated from the SROC curves. The area under the SROC curve (AUC) was also calculated to show the probability of correctly ranked diagnostic test values for a random pair of diseased and non-diseased subjects [18]. Funnel plots, Egger's and Begg's tests were used to investigate publication bias.

3. Results

3.1. Characteristics and quality of the included studies

Twenty-seven potentially relevant articles were identified, seven of which met our inclusion criteria. Fig. 1 shows the selection process. The detailed characteristics and data of each included study are presented in Table 1. To evaluate the association between MBL genetic polymorphisms and the risk of neonatal sepsis, seven studies with a total of 338 cases and 1066 controls were included (Table 2).

The methodology among the included studies was variable. The major limitations lay in the following categories: blinded reference standard results; explanation of withdrawals; acceptable delay between tests; reporting of un-interpretable results; and blinding of index test results. The strengths of the studies were related to: preclusion of sponsorship; acceptable reference standards; avoidance of partial or differential verification; representative spectrum; and avoidance of incorporation.

3.2. Association between low MBL levels and neonatal sepsis

Of the seven articles which met our inclusion criteria, the relationship between low MBL levels and neonatal sepsis, defined as culture-proven sepsis or confirmed sepsis in the first month after delivery, was estimated. Pooled unadjusted ORs showed that the risk of neonatal sepsis in the MBL-deficient group was significantly higher than that of the non-MBL-deficient group ($P = 0.0002$; OR = 4.94, 95% confidence interval (CI) = 2.16–11.29), and that heterogeneity was considered to be significant ($I^2 = 78\%$) (Fig. 2). The results suggested that infants