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ORIGINAL ARTICLE

Interleukin-33 in children with asthma: A systematic review and meta-analysis

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Abstract
Background: Previous studies have shown that serum interleukin 33 serving as an ''alarmin'' is increased in children with asthma. The objective of this study was to assess the validity of serum IL33 test for early diagnosis of childhood asthma.
Methods: A literature search was performed in June 2016 using PubMed, Embase, the Cochrane Library and other Chinese Medical Databases to identify studies. The search terms used were ''cytokine'', ''interleukin-33'', ''asthma'' and ''children''. The meta-analysis was performed using Review Manager 5.3 software. Random-effects model was used to estimate the standardized mean differences (SMDs) with 95% confidence intervals (CIs).
Results: A total of eight studies were included into this meta-analysis, involving 330 asthmatic children and 248 healthy children. The meta-analysis results revealed that the serum IL33 level was higher in asthmatic children compared to that in healthy children (SMD = 1.29, 95%CI = 0.53–2.05, $P = 0.0009$), with significant heterogeneity across studies ($I^2 = 94\%$ and $P < 0.00001$).
Conclusions: The meta-analysis showed that serum IL33 is a helpful biomarker for early diagnosis of childhood asthma. However, owing to lack of enough data, the increased serum concentration of IL33 cannot be an indicator for the asthma severity.

Introduction

Asthma is a chronic inflammatory disorder of the airways, characterized by periodic attacks of wheezing, shortness of breath, chest tightness, and coughing.[1] The prevalence

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of asthma is increasing in most countries, especially among children.[2] Childhood asthma is more common in boys than in girls and may persist throughout life. Because asthma symptoms are heterogeneous in children, persistent wheezing and respiratory symptoms in children may indicate other diagnostic considerations. Unnecessary investigations can delay the diagnosis of childhood asthma. In some cases, uncontrolled asthma without proper treatment can be fatal.[3]

IL33 is IL-1 family constitutively expressed by many cell types included bronchial and epithelial cells, endothelial cells, macrophages and dendritic cells.[4,5] Recent studies emphasize IL-33 possibly serving as a danger signal (''alarmin'') to activate the immune system following cell aggression and damage.[6,7] After genome-wide association studies, strong associations between single nucleotide polymorphisms (SNPs) flanking IL33 gene and asthma have been approved.[8,9] However, the association between the level of serum IL33 and childhood asthma is unknown. Although some studies reported significant elevations in serum IL33 levels in childhood asthma compared with health controls,[10–15] these were not confirmed in similar studies.[16,17] Moreover, it is unknown whether the level of serum IL33 can be an indicator for childhood asthma symptom severity.

Thus, the purpose of this meta-analysis was to analyze the level of serum IL33 in childhood asthma, which may be a marker of the disease severity and potential clinical diagnosis targets.

Methods

Literature search and selection of studies

A literature search was performed in June 2016 using PubMed, Embase, the Cochrane Library and other Chinese Medical Databases to identify studies. The search terms included ''(IL33 OR Interleukin-33)'' AND ''(asthma)'' AND ''(children and infant)''. The searches were restricted to studies of only human subjects, and no language restrictions were applied. The reference lists and supplemental materials associated with the studies and review articles were examined manually to further identify any additional relevant publications.

To minimize this potential bias, we also investigate other sources of information. First, we hand searched the relevant conference proceedings for the previous 10 years in the following sources: Annual Pediatric Asthma Conference, Pediatric Allergy and Asthma Meeting, World Pediatric Congress, International Conference on Pediatric Allergy, Immunology and Pulmonary Disease, International Conference on Respiratory System Diseases, and Academic Conference on asthma in China. Second, we searched the Internet through search engines Google.com and Baidu.com, using the term 'clinical trial & IL33'. Third, we contacted researchers, graduate students in the field and pharmaceutical companies for information on unpublished and ongoing trials.

Those studies aiming to explore the association between serum IL33 expression and childhood asthma were included. The inclusion criteria of studies were: (1) children with asthma; (2) healthy children in control group; (3) the articles focused on the serum IL33 level; (4) full text, original research articles could be found. The following were cause for exclusion: (1) a lack of data regarding the serum IL33 level and childhood asthma; (2) not a primary case–control study; (3) insufficient data was extracted from the articles or the full text could not be found. The study inclusion and exclusion procedures are summarized in Fig. 1.

Data extraction and quality assessment

Two investigators (Y Wang and L Wang) independently performed the data extraction. The general characteristics of the study were extracted using a standardized data extraction form: publication information (first author's name, publication year), characteristics of asthma and control (country, measure method, reagent source, study design, sample size, mean age), and outcomes (asthma severity addressing by the studies). Discrepancies were resolved by discussion with a third investigator (S Hua). The quality of studies was evaluated according to the quality assessment of diagnostic accuracy studies (QUADAS) tool including seven questions. Answers are ''Low risk of bias'', ''Unclear risk of bias'', and ''High risk of bias'', respectively. If a study has more than four answers with a high risk of bias, it was considered a ''low-quality'' study. The ''low-quality'' study was excluded from the meta-analysis.

Statistical analysis

The meta-analysis was performed using Review Manager 5.3 software. Serum IL33 levels were extracted as the mean ± standardized difference (SD) in each study. If the mean level differences were significant across studies, or different units were used, standardized mean difference (SMD) is used to estimate the effect size. In the included studies, the serum IL33 were measured in ELISA with different source reagent, and the differences in the mean levels of IL33 were considered significant, therefore, SMD in serum IL33 was used to estimate the effect size. Heterogeneity was assessed using a chi-squared Q test and I-squared statistics. If $PQ < 0.1$ or $I^2 > 50\%$, the heterogeneity was considered significant, and a random-effects model was used.

Results

Search results

The steps for screening and the study selection procedure are presented in Fig. 1. A total of 355 relevant articles were initially identified from PubMed, Embase, the Cochrane Library and other Chinese Medical Databases. Through screening of titles and abstracts, nine papers met our inclusion criteria screening, published between 2013 and 2016. We excluded 346 irrelevant or duplicate articles.

Quality and characteristics of included studies

In this meta-analysis, according to QUADAS, one of the reports ($n = 9$ studies) was classified as low quality, and the other eight studies were considered high quality. The