Narrative Review:
Cytokine Levels and Polymorphisms in Childhood Asthma Among the Iranian Population

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ABSTRACT

Context: Chronic airway inflammation in asthma is affected by a complex network of interacting cytokines. The exact role of each cytokine in childhood asthma development has remained poorly understood. In this study, we aimed to review articles investigating cytokine levels and polymorphisms in childhood asthma among the Iranian population to assess susceptible cytokines related to childhood asthma.

Evidence Acquisition: We performed a literature search in PubMed, Scopus, Science direct, and Embase databases to find articles that have evaluated the cytokine levels and gene polymorphisms in childhood asthma among the Iranian population until March 2, 2020. The terms used to search included "Cytokine", "Interleukin", "Polymorphism", "Asthma", and "Iran" in the international databases. Only case-control studies with a healthy control group that investigated cytokine levels and polymorphism in childhood asthma among the Iranian population have been included.

Results: Considering these criteria, we extracted 7 articles from international databases and included them in the current review. We investigated 4 cytokine levels and 4 cytokine polymorphism patterns in asthmatic and non-asthmatic subjects in Iran. Interleukin (IL)-23, IL-17, and IL-33 levels were statistically higher in asthmatic children, and also IL-33, IL-17 levels were associated with asthma severity. There were no significant differences between healthy and asthmatic subjects regarding IL-35 levels. Polymorphisms in cytokine IL-4, *IL-10*, Tumor Necrosis Factor (*TNF*)-α, and *IL-2* were susceptible to childhood asthma in the Iranian population.

Conclusions: Increased IL-33 and IL-17 levels were related to disease severity in childhood asthma. Four cytokine polymorphisms (IL-4, *IL-10*, IL-2, and *TNF*-α) were associated with the risk of pediatric asthma in the Iranian population.

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1. Context

Asthma is one of the most important chronic respiratory diseases in children. It is associated with airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and or cough varying over time (1). According to recent studies, its prevalence has increased worldwide during the last decades, especially in developed countries (2). In Iran, the prevalence of current childhood asthma was reported at about 8.8%. (3, 4).

It has been shown that some risk factors, such as genetic, environmental, and immunological backgrounds, affect asthma development. In the context of immunological factors, cytokines play an essential role in asthma pathogenies (5, 6). Within the range of various cytokines, T helper (Th) 2-related ones, including Interleukin (IL)-2, IL-3, *IL-4*, IL-5, IL-7, IL-9, IL- 15, IL-16, and IL-17, have been recognized as key participants in the pathophysiology of asthma to date (7). Besides, none-Th2-related cytokines including proinflammatory (IL-1, IL-6, IL-11, granulocyte-macrophage colony-stimulating factor [GM-CSF] and Tumor Necrosis Factor [TNF]-α) and inhibitory cytokines (*IL-10*, IL-12, IL-18, and interferon [IFN]-γ) have been found to affect asthma progression and inhibition, respectively (7).

Based on pathogenesis, the degree of airway obstruction, and responses to medications, childhood asthma can be divided into intermittent, mild, moderate, and severe stages (8). Many studies have been investigated the association between cytokine levels and clinical features of asthmatic patients in different populations (9-11). Cytokine single nucleotide polymorphisms have been extensively investigated among diverse populations as well as in association with disease. It can be used as genetic predictors of disease susceptibility, clinical outcome, and as a tool for anthropological studies (12). In this study, we aimed to review cytokine levels and polymorphisms in childhood asthma to assess their relationship with asthma susceptibility and severity among the Iranian population.

2. Evidence Acquisition

Two researchers separately conducted a literature search in PubMed, Scopus, Science direct, and Embase databases using the following keywords: “Cytokine”, “Interleukin”, “Polymorphism”, “Asthma”, and “Iran”. The following criteria were used for selecting articles in this review: the study should have a case-control design with healthy subjects as a control group that has evaluated the association between cytokine level and polymorphism in childhood asthma among the Iranian children populations. All qualified articles that have been published until March 2, 2020, were included in the search. By using keywords, 7 relevant articles were included in the final analysis. In these articles, we investigated 4 cytokine levels and 4 cytokine gene polymorphisms in asthmatic and non-asthmatic children in Iran.

3. Results

Results showed elevated levels of IL-17, IL-33, and IL-23 in childhood asthma (Table 1). Increased IL-17 and IL-33 levels were associated with asthma severity (Table 1). A study about serum IL-35 levels in children with asthma in the southeast of Iran showed no significant difference between asthmatic and healthy children (Table 1).

Table 2 presents a range of genetic associations of different polymorphisms in the gene that encode cytokines in childhood asthma. *IL-4* gene polymorphism at positions −33, −590, −1098, TNF-α at position −308, *IL-10* at positions −1089, −819, −592, and IL-2 at position −330 were significantly associated with childhood asthma susceptibility among the Iranian population (Table 2).

The mechanism of asthma development is complex, and many factors affect its development. Cytokine is one of the most important factors which play a critical role in asthma pathogenesis and severity. In this context, some cytokines are proposed as useful biomarkers for the differentiation of asthma susceptibility and severity.

In this study, we investigated cytokine expressed in Iranian children with asthma. Compared with healthy subjects, IL-17, IL-33, and IL-23 were statistically higher in asthma patients. Increased levels of IL-17 and IL-33 were associated with asthma severity.

IL-17 contributes to asthma pathogenesis by inducing airway remodeling in addition to inflammatory effects (20). Studies showed that the increased levels of IL-17A and IL-17F in the lung directly correlate with disease severity in both Iranian children and adult populations (13, 21-23). These results are consistent with other studies investigating IL-17 role in asthma worldwide (10, 24). Regarding its relationship with asthma severity, it has been proposed as an appropriate biomarker for asthma severity and exacerbation (25). IL-23 is another Th-17–cells cytokine that is crucial for maintaining these cells and stimulating neutrophilic airway inflammation

Table 1. Cytokine levels related to childhood asthma among the Iranian population

Cytokine	Study	Population	Sample	Function
IL-17	Alyasin et al. (13)	Children	Serum PBMC	Increase IL-17 mRNA and serum levels with increasing disease severity.
IL-33	Mahneh et al. (14)	Children	Serum	Increase IL-33 level with increasing disease severity.
IL-35	Khoshkhui et al. (15)	Children	Serum	No significant difference between the serum level of IL-35 in asthmatic and healthy children
IL-23	Alyasin et al. (16)	Children	Serum	Increase IL-23 level in childhood asthma.

IL: Interleukin; PBMC: Peripheral Blood Mononuclear Cells. Journal of Pediatrics Review

Table 2. Cytokine gene polymorphisms related to childhood asthma among the Iranian population

Gene	Location	SNP	Association	Study
IL-4	5q31.1	−33C>T (rs2070874) −590 C>T (rs2243250) −1098 G>T	Asthma susceptibility, IgE level	Amirzargar et al. (17)
TNF	6q21.3	−308G>A	Asthma susceptibility, Increased *TNF*-α level	Mahdaviani et al. (18)
IL-10	1q31-q32	−1082 (rs1800896) −819 (rs1800871) −592 (rs1800872)	Asthma susceptibility, Low-IL-10 producing haplotype	Movahedi et al. (19)
IL-2	4q27	−330 (rs2069762)	Asthma susceptibility, Lower *IL-2* production	Movahedi et al. (19)

SNP: Single Nucleotide Polymorphism; *TNF*-α: Tumor Necrosis Factor-alpha; IL: Interleukin. Journal of Pediatrics Review

in severe asthma. Literature has shown increased IL-23 levels in childhood asthma, consistent with a study in Iran (16, 26). IL-33 represents one of the vital signals for the bronchial epithelial cells that causes the development of asthma and has shown to be significantly correlated with asthma severity (27, 28). Correlation of IL-33 elevation with disease exacerbation has been confirmed by studies in both children (14) and adult (29) asthma population of Iran. This result is similar to what was found in other countries (30-33). Therefore, this cytokine has the potential to be used in the clinic to predict asthma severity.

No significant differences in IL-35 levels between asthmatic and non-asthmatic subjects have been recognized for childhood asthma in Iran (15, 34), which are inconsistent with other studies worldwide. The role of IL-35 has been demonstrated as an anti-inflammatory cytokine that maintains immune homeostasis. However, the effect of IL-35 on human asthma remains unclear. In contrast to Iranian studies, down-regulated IL-35 level was found in some literature that was inversely related to serum *IL-4* or IL-17, and IgE levels in childhood asthma (35, 36). These contrasting results might be due to the various factors involved in the studies, such as different populations or methodologies. Besides, asthma is a complex and multifactorial inflammatory disease that is affected by both environmental and genetic factors. Gene-environmental interaction plays an essential role in human disease and has been relatively well studied in model organisms (37). In the context of asthma, environmental risk factors are often complex. They include respiratory infections, allergens, emotions, air pollution, cigarette smoke, lifestyle, dietary and psychosocial factors that may affect cytokine gene expression in asthma. In addition to these factors, geographical variation may contribute to developing asthma and affect cytokine expression patterns among different populations (38). However, the methodology of studying affects the results. There are differences in some items such as sample size, tissue, method's sensitivity, and specificity between studies that may lead to different cytokine expression patterns in various studies.

Cytokine gene polymorphisms could influence the serum level of cytokines by affecting transcriptional regulation. In this study, cytokine polymorphisms were investigated in pediatric asthma within the Iranian population. *IL-4* is one of the most important cytokines in allergic inflammatory responses and IgE isotype switching. An association between *IL-4* gene promoter polymorphism at positions -1098, -590, and -33 and asthma, and between the haplotypes of these polymorphisms and total IgE have been reported among the Iranian children that are consistent with other studies results worldwide (17, 39-41). Like the children population, an

association at position -590 was reported for the Iranian adult population (42). Data on the relationship between *IL-4* polymorphisms and asthma exacerbation are controversial. In a British sample, the analysis of disease severity showed a positive relationship between both T–33C and T–590C and asthma severity (43), whereas the Iranian study could not confirm such an association. TNF-α, as a proinflammatory cytokine, has a key role in the initiation of airway inflammation and the generation of airway hyper-reactivity. TNF-α-308 polymorphism was associated with asthma susceptibility and increased TNF-α levels in the Iranian children population, which is consistent with Macedonian and Taiwan populations (18, 44, 45). However, some studies showed no significant association between TNF-α-308 polymorphism and the risk of asthma (46, 47). *IL-10* is an immune-regulatory molecule that plays a critical role in inflammatory and allergic diseases like asthma. Movahedi M et al. has reported that the low *IL-10* producing haplotype, ATA, is higher in childhood asthma among the Iranian population, similar to the previous studies in Indian and Caucasian people (19, 48, 49).

IL-2, as a Th1 cytokine, has a significant role in the activation and termination of T lymphocyte response by inducing the production of suppressive T cells. An Iranian study among children populations has revealed that at IL-2 (−330 T/G) gene locus, the GT genotype frequency in asthmatic patients was significantly higher than controls, which could be associated with increasing disease susceptibility by a lower production of IL-2 (19). These data are consistent with Denmark and Macedonian population studies, which showed an association between asthma susceptibility and IL-2 polymorphism at -330 position (44, 50). The controversial results on cytokine gene polymorphisms in the literature could be attributed to the study design differences and the different genetic environments (ethnic groups) (12).

In this review, only published articles in the selected electronic databases were included so that some unpublished studies may be missed. This research is the first review conducted on Iranian studies investigating cytokine profiles in asthmatic subjects.

4. Conclusion

This review indicated that increased IL-23, IL-33, and IL17 were related to childhood asthma susceptibility among the different Iranian populations, also increased levels of IL-17 and IL-33 were associated with asthma severity in children. Therefore, these cytokines can be used as a biomarker for predicting childhood asthma exacerbation. Polymorphisms in *IL-4* (-33, -590, -1098), *IL-10* (-1082, -819, -592), IL-2 (-330), and TNF-α (-308) were associated with the risk of pediatric asthma in Iranian population. Geographical variation may affect cytokine patterns in childhood asthma among different populations.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflicts of interest

The authors declared no conflict of interest.

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