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Plasma Chemokines in Early Wheezers Predict the Development of Allergic Asthma

To the Editor:



Wheeze is a common respiratory symptom in preschool children. Up to 40–50% of all children suffer at least one period of wheezing before the age of 3 years. Less than 40% of these early wheezers (EW) continue to wheeze between the ages of 3 and 6 years (1). Even smaller numbers have reversible airflow obstruction and are diagnosed with asthma. Early asthma identification enables us to start appropriate treatment and prevent unnecessary prescription of asthma drugs in the majority of EW without asthma (2). In attempts to differentiate asthma from transient wheeze in early infancy, several clinical parameters, such as gestational age, parental atopy, and early-life sensitization, have been associated with development of asthma (3, 4) and used to develop asthma prediction rules and models (5). However, these clinical prediction models have only been moderately successful.

The characteristic Th2 cell responses in asthma involve Th2 cell proliferation, but also the production of soluble mediators that sustain the inflammatory response (6). Although there are studies that have identified such mediators as biomarkers for the diagnosis and/or grading of asthma (7, 8), prospective data on their predictive value for asthma are scarce (9). We therefore investigated whether plasma cytokine levels in EW could be used in early prediction of allergic asthma (AA). In a prospective follow-up study, 39 EW were followed from age 3 until 6 years. Characteristics of the study population are listed in Table E1 in the online supplement. At age 6 years, 26% were diagnosed with AA, which is slightly less than in the literature (1). The diagnosis of AA was based on the presence of

obstructive lung function reversible with β_2 -agonists, persistent wheezing, specific IgE to one or more inhalation allergens together with current medication use, according to NHLBI guidelines (10). The lower rate of AA in our study population is most likely the result of this strict asthma definition. Correspondingly at age 6 years, this group had a significantly lower FEV₁/FVC ratio prior to β_2 -agonists than the no-AA (NAA) group ($P = 0.02$, data not shown). The NAA group had normal lung function, and if sensitized to one or more inhalation allergens, they had not reported wheezing symptoms, including on exposure to these allergens. The majority of the cohort were male (72%), and there was no difference in sex whether children were diagnosed with AA or not. The AA group, diagnosed at age 6 years, differed at baseline (age 3 yr) significantly from the NAA group for the clinical parameters sensitization to food or aeroallergens, total IgE levels, and number of eosinophils (Table E1), known to be significantly associated with the development of AA (3–5). Thus, although it was small, we included a representative group of EW in our study, with a strong endpoint definition.

In this cohort, we determined selected cytokine levels in plasma samples at age 3 years using multiplex assay. Blood was drawn at a time without apparent respiratory symptoms or infections. There were no significant differences in IFN- γ , IL-6, IL-9, IL-13, IL-10, IL-22, thymic stromal lymphopoietin, and monocyte chemotactic protein 1 levels (data not shown). Cytokine levels of IL-4, IL-5, IL-17, IL-25, and eotaxin were below the detection limit in more than 50% of the samples and therefore not used in further analyses. The number of samples with undetectable cytokine levels did not significantly differ between the group of EW that developed AA and the group that did not (data not shown). IFN- γ -induced protein 10 (IP-10 [CXCL10]), thymus- and activation-regulated chemokine (TARC [CCL17]), and macrophage-derived chemokine (MDC [CCL22]) levels were increased in plasma of EW that developed AA (Table 1; $P = 0.018$, $P = 0.004$, and $P = 0.010$, respectively). To evaluate the predictive power, we used the predicted probabilities for the development of asthma to construct a receiver operating characteristic curve. The area under the receiver operating characteristic curve was 0.75 (0.56–0.94) for IP-10, 0.80 (0.63–0.97) for TARC, and 0.77 (0.61–0.93) for MDC (Figure 1). Using a cutoff level of 50 pg/ml for IP-10, 45 pg/ml for TARC, and 230 pg/ml for MDC, these chemokines were significant risk factors for development of AA (Table 1; odds ratio 8.9 [1.8–45.3], 9.3 [1.8–48.6], and 6.5 [1.2–36.6], respectively).

In mouse models, IP-10 has been shown to contribute to airway hyperresponsiveness and inflammation (11). TARC and MDC have been identified as important mediators in

TABLE 1. DIAGNOSTIC PARAMETERS OF CHEMOKINES ASSOCIATED WITH DEVELOPMENT OF ALLERGIC ASTHMA

	AA* (N = 10) (Mean $\pm$ SEM)	NAA* (N = 29) (Mean $\pm$ SEM)	P Value	OR† (95% CI) for AA
IP-10‡	102.1 ($\pm$ 29.5)	38.8 ($\pm$ 6.7)	0.018	8.9 (1.8–45.3)
TARC‡	58.9 ($\pm$ 9.6)	26.9 ($\pm$ 3.3)	0.004	9.3 (1.8–48.6)
MDC‡	302.6 ($\pm$ 33.8)	199.9 ($\pm$ 14.6)	0.010	6.5 (1.2–36.6)

Definition of abbreviations: AA = allergic asthma; CI = confidence interval; IP-10 = IFN- γ -induced protein 10; MDC = macrophage-derived chemokine; NAA = no allergic asthma; OR = odds ratio; SEM = standard error of the mean; TARC = thymus- and activation-regulated chemokine.

*Diagnosis at age 6 years.

†Diagnostic parameters are determined using the following plasma level cutoff values: IP-10 > 50 pg/ml, TARC > 45 pg/ml, and MDC > 230 pg/ml.

‡Measured in plasma at age 3 years.

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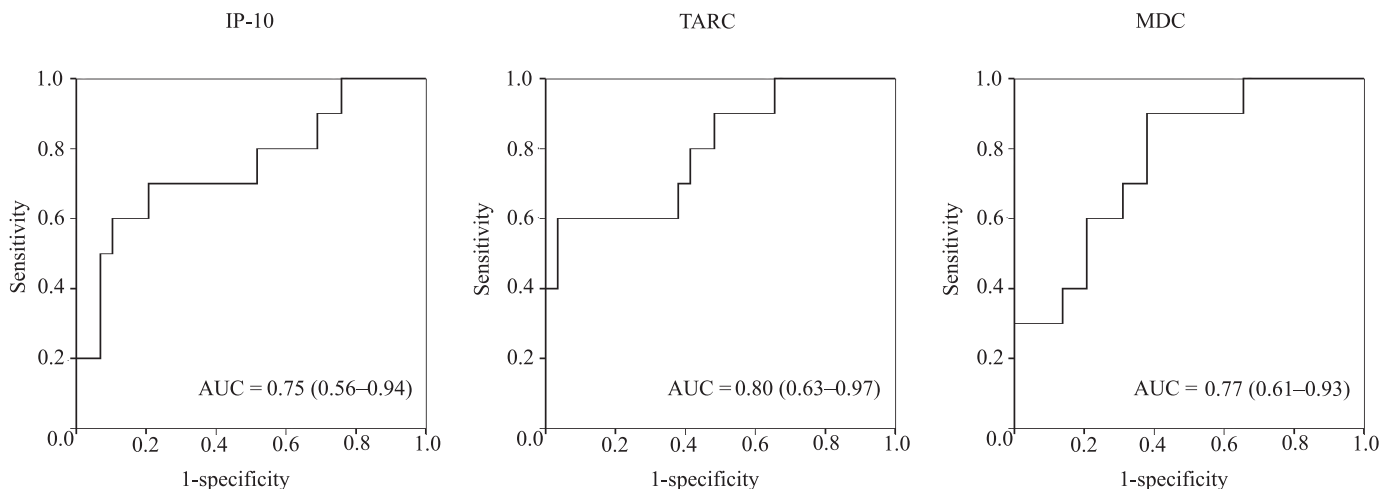


Figure 1. Receiver operating characteristic curves of chemokine levels in early wheezers to predict the development of allergic asthma at age 6 years. Receiver operating characteristic curves for IP-10, TARC, and MDC levels determined in plasma samples of EW at age 3 years. AUC = area under the curve; IP-10 = IFN- γ -induced protein 10; MDC = macrophage-derived chemokine; TARC = thymus- and activation-regulated chemokine.

the pathophysiology of allergic airway disease (12, 13) and cord blood levels of these Th2 associated chemokines have been associated with allergy development (14), supporting the early role for TARC and MDC in the development of Th2 diseases such as AA.

In conclusion, we have identified biomarkers, which can be detected as early as age 3 years and may be useful in the prediction of AA. To further evaluate the usefulness of these markers and establish cutoff levels for prediction and use in clinical practice, a larger prospective follow-up study is needed.

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