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Title: Skin biomarker changes precede the development of Atopic Dermatitis during the first 2 years of life

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Introduction

Identification of predictive biomarkers of pediatric atopic dermatitis (AD) is important so that future preventive strategies can be targeted thereby decreasing the incidence of AD without unnecessarily affecting children with little risk. In this prospective birth cohort of 450 children, we examined whether skin barrier and immune biomarkers predicted the onset and severity of AD during the first 2 years of life.

Materials and methods

The Barrier dysfunction in Atopic newBorns study (BABY) cohort is a Danish prospective birth cohort study of 300 term and 150 preterm newborns. Children were enrolled after birth and followed until the age of 2 years. They attended a clinical follow-up visit at 2 months of age and if they developed any signs of AD. AD was diagnosed by a physician and the severity was assessed using the Eczema Area and Severity Index (EASI). Tape strips were collected from the dorsal aspect of the hand at 0-3 days of age and 2 months of age in term children and from the skin between the shoulder blades at 2 months of age in preterm children. Tape strips were analyzed for immune biomarkers and dichotomized at a cut-off level of ≥75th percentile (defined as elevated levels). Hazard ratio (HR) with 95% confidence interval (CI) using COX-regression was calculated for the risk of AD. Children with AD at the time of collecting skin tape strips were excluded.

Results

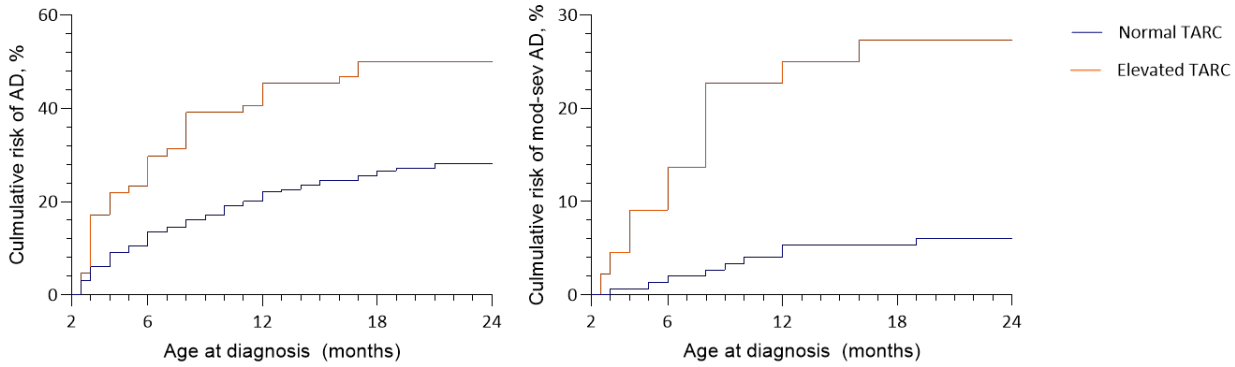
The prevalence of AD was 34.6% (99/286) among term children and 21.2% (25/118) among preterm children. The median EASI score was 4.2 (interquartile range [IQR] 2.0-7.9) and 1.6 (IQR 1.1-3.1) among respectively, term and preterm children with AD. In term children, elevated levels of TARC collected at 2 months of age significantly increased the risk of AD during the first 2 years of life in crude data analysis (HR 2.11, 95% CI 1.36-3.26, P=0.0008, Figure 1) and after adjusting for parental atopy and filaggrin gene mutations (aHR 1.85, 95% CI 1.18-2.89, P=0.007). TARC levels were elevated both in children with AD onset before 6 months of age (P=0.0004) and in children with AD onset between 6-24 months of age (P=0.003) when compared with children who did not develop AD. Elevated levels of TARC were more strongly associated with moderate-to-severe AD (aHR 4.65, 95% CI 1.91-11.31, P=0.0007, Figure 1). Further, elevated levels of interleukin (IL)-8 and IL-18 were associated with moderate-to-severe AD (aHR 3.01, 95% CI 1.24-7.31, P=0.02 and aHR 2.86, 95% CI 1.17-6.98, P=0.02, respectively). No immune biomarker measured at birth was associated with AD. In preterm children, TARC was borderline

significant associated with AD (aHR 2.60, 95% CI 0.98-6.85, P=0.05).

Discussion

This prospective birth cohort study is, to our knowledge, the first to show that non-invasively collected skin biomarkers can be used to predict subsequent onset of pediatric AD, and in particular more severe forms of AD. Importantly, AD occurring months after collection could be predicted suggesting that skin changes preceding AD could be constitutional early in life. These findings lend support to the notion that future targeted trials to prevent AD can be designed, and this common disease prevented.

Figure 1. The cumulative risk of atopic dermatitis and moderate-to-severe atopic dermatitis during the first 2 years of life for term children with normal vs. elevated cutaneous levels of TARC at 2 months of age



Abbreviations: AD: atopic dermatitis, mod-sev: moderate-to-severe, TARC: thymus and activation-regulated chemokine