

Short communication

Circulating Interleukin 16 (IL-16) in children with atopic/eczema dermatitis syndrome (AEDS): a novel serological marker of disease activity

Background: Chemokines play a central role in atopic eczema/dermatitis syndrome (AEDS). Interleukin 16 (IL-16) has been described as a main cytokine involved in CD4⁺ cell recruitment during inflammation. Recently the influx of CD4⁺ lymphocytes has been related to the up-regulation of IL-16 in AEDS skin lesions. Circulating β -chemokines (Eotaxin and RANTES) and IL-16 were investigated in children with AEDS to correlate their presence with the severity of the disease. We also measured serum levels of soluble CD30 (sCD30), a marker of Th2 immune responses related to AEDS disease activity.

Methods: Serum levels of eotaxin, RANTES, IL-16 and sCD30 were measured by immunoenzymatic assay in paediatric patients with pure AEDS (pAEDS, $n = 39$); the severity of the disease was graded by SCORAD. Fifteen children with AEDS in presence of respiratory allergy (AEDS + A), 15 with allergic asthma (A) and 20 age-matched healthy donors were investigated as control groups.

Results: When compared to normals, high amounts of Eotaxin and IL-16 were detected in sera of pAEDS ($P = 0.002$; $P < 0.0001$), AEDS + A ($P = 0.02$; $P = 0.01$) and A patients ($P = 0.004$; $P = 0.03$) with respect to normals. Serum levels of RANTES were also elevated in pAEDS patients, significantly higher than normals ($P = 0.009$), whereas no statistically significant differences could be detected between pAEDS and AEDS + A or A groups. IL-16 was progressively increased in the different stages of pAEDS, with a positive correlation between IL-16 and both SCORAD and sCD30 ($P < 0.0001$).

Conclusion: We suggest that IL-16 could serve as a useful marker of disease activity in childhood pAEDS.

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Atopic dermatitis is a chronic relapsing skin disorder characterized by pruritic and eczematous skin lesions, often associated with increased IgE production and eosinophilia (1). A revised nomenclature task force for allergy has been recently proposed using the term of atopic/eczema dermatitis syndrome (AEDS) to describe what is presently referred to as atopic dermatitis (2). Although the pathogenesis of AEDS is not well defined, immunological abnormalities are thought to play a central role. A biphasic pattern of cytokine expression has been well demonstrated during the development of AEDS; acute skin lesions show a prevalence of CD4⁺ Th2 lymphocytes able to produce and release IL-4 and IL-13, whereas macrophages and eosinophils are recruited during the chronic phase, associated with the presence of Th1-type cytokines (IL-12, IFN- γ) (1, 3, 4). It is well known that the accumulation of specific leukocytes migrating from blood into inflamed tissues is highly dependent on chemokine–chemokine receptors network. Chemokines are small proteins playing a major role in

controlling leukocyte traffic; the two main subclasses of α - and β -chemokines are, respectively, associated with acute and chronic inflammation, since α -chemokines act primarily on neutrophils whereas β -chemokines exert their action on other leukocyte types, such as T cells, eosinophils, monocytes/macrophages, basophils and dendritic cells (5–7). In this light several studies demonstrated an increased expression and release of β -chemokines, such as RANTES, eotaxin, monocyte chemoattractant protein (MCP)-4, macrophage-derived chemokine (MDC), thymus and activation regulated chemokine (TARC), in AEDS skin lesions and/or sera, in relation to the presence of inflammatory cells and/or to the activity of the disease (8–15). Among chemotactic factors IL-16 has been fully characterized as an immunomodulatory cytokine playing a pivotal role in recruitment of CD4⁺ T cells, monocytes and eosinophils at sites of inflammation; besides its chemotactic properties, IL-16 is able to induce IL-2 receptor α chain expression and to activate CD4⁺ T cells in synergy with IL-2 or

IL-15 (16, 17). The relevance of IL-16 in the pathogenesis of asthma, autoimmune diseases and HIV-infection has been well demonstrated (18–23), and recently the influx of CD4⁺ lymphocytes has been associated with an up-regulation of IL-16 mRNA skin expression in the early stage of AEDS (24). The present study was undertaken to investigate serum levels of Eotaxin, RANTES and IL-16 in a population of paediatric patients affected with AEDS, in order to correlate the presence of circulating chemotactic factors with the activity of the disease.

Material and methods

Patients

We enrolled for the study a group of paediatric patients ($n = 39$) admitted to our division of paediatric dermatology with the diagnosis of allergic AEDS according to the criteria of Hanifin & Rajka, all suffering from a “pure” form of AEDS (pAEDS) without concomitant respiratory allergies (age range: 0–6 years, mean age: 2.57 ± 1.55). On the basis of total IgE serum levels, 20 out of 39 patients were classified as High-IgE pAEDS (IgE > 100 KU/l) and 19 out of 39 as Low-IgE pAEDS. The severity of the disease was established by the SCORAD index (25) and patients were thus subdivided into mild (SCORAD < 25, $n = 8$), moderate ($25 < \text{SCORAD} < 50$, $n = 14$) and severe (SCORAD > 50, $n = 17$) pAEDS. As controls, a group of paediatric patients with AEDS in presence of respiratory allergies (AEDS + A, $n = 15$), children with allergic asthma without AEDS (A, $n = 15$) and 20 age-matched non-atopic healthy donors were studied. None of the subjects had received any topical and/or oral medication at least two weeks before entering the study.

Evaluation of circulating chemokines, IL-16 and sCD30

Serum levels of Eotaxin, RANTES (R & D Systems, Minneapolis, USA), IL-16 (Bender MedSystems, Vienna, Austria) and sCD30

(DAKO, Glostrup, Denmark) were measured using commercially available ELISA kits, according to manufacturer’s instructions. All sera, stored at -80°C until use, were evaluated in duplicate. Blood samples were also evaluated for total IgE and specific IgE for common food and aero-allergens (UniCAP Pharmacia; Uppsala, Sweden). The detection limits of each assay were as follow: 5 pg/ml for Eotaxin, 8 pg/ml for RANTES, 8 pg/ml for IL-16, 1 U/ml for sCD30. Results greater than 100 KU/l and 0.35 KU/l were considered positive for total IgE and specific IgE, respectively.

Statistical analysis

Data were evaluated by nonparametric statistical tests; the Mann–Whitney *U*-test was used to compare variables between AEDS patients and control groups and the correlation index (*r*) was determined by Spearman’s Rank correlation coefficient matrix. Probability (*P*) values of less than 0.05 were considered to be statistically significant. All data are shown as mean values $\pm$ standard deviation (MV $\pm$ SD).

Results

As shown in Table 1, our results demonstrated, with respect to normals, significantly high amounts of eotaxin and IL-16 in sera of pAEDS ($P = 0.002$; $P < 0.0001$, respectively), AEDS + A ($P = 0.02$; $P = 0.01$) and A patients ($P = 0.004$; $P = 0.03$). Serum levels of RANTES were also elevated in pAEDS patients when compared to both AD + A and A groups and normal donors. As expected sCD30 serum levels were elevated in pAEDS patients, significantly higher than those observed in AEDS + A ($P < 0.0001$), A patients ($P = 0.002$) and normal donors ($P < 0.0001$). When pAEDS patients were subdivided into High-IgE and Low-IgE groups, no differences could be detected in serum levels of

Table 1. Values of SCORAD index, Total IgE, Interleukin-16 (IL-16), chemokines and soluble CD30 (sCD30) serum levels in patients with “pure” atopic/eczema dermatitis syndrome (pAEDS) – further divided in subsets with high (High-IgE pAEDS) and low (Low-IgE pAEDS) IgE serum levels – atopic/eczema dermatitis syndrome with respiratory symptoms (AEDS+A), allergic asthma without AEDS (A) and in normal healthy donors. Data are reported as mean levels $\pm$ SD and statistically significant *P*-values with respect to healthy donors are given in parenthesis below

	SCORAD (min–max)	Total IgE (KU/l)	IL-16 (pg/ml)	Eotaxin (pg/ml)	RANTES (ng/ml)	sCD30 (U/ml)
Healthy donors ($n = 20$)		45 ± 12	346 ± 88	71 ± 27	69 ± 14	10 ± 5
pAEDS ($n = 39$)	45.8 ± 19.7 (10–84.4)	234 ± 358 ($P = 0.04$)	874 ± 360^a ($P < 0.0001$)	118 ± 42 ($P = 0.002$)	108 ± 47 ($P = 0.009$)	$78.6 \pm 37.9^{b,d}$ ($P < 0.0001$)
High-IgE pAEDS ($n = 20$)	40.5 ± 24 10–84.4	445 ± 424 ($P < 0.0001$)	806 ± 372^b ($P = 0.002$)	104 ± 44 ($P = 0.01$)	110 ± 42 ($P = 0.005$)	$71.4 \pm 38^{c,d}$ ($P < 0.0001$)
Low-IgE pAEDS ($n = 19$)	36.4 ± 16.1 (15–62.4)	34.7 ± 23.3	761 ± 369^c ($P = 0.003$)	103 ± 31 ($P = 0.01$)	102.3 ± 42 ($P = 0.03$)	$71 \pm 32^{c,d}$ ($P < 0.0001$)
AEDS+A ($n = 15$)	55.2 ± 15.6 (21.4–75)	594 ± 1115 ($P < 0.0001$)	674 ± 440 ($P = 0.01$)	112 ± 40 ($P = 0.02$)	80 ± 34	33 ± 29 ($P = 0.002$)
A ($n = 15$)		592 ± 709 ($P < 0.0001$)	476 ± 140 ($P = 0.03$)	118 ± 38 ($P = 0.004$)	83 ± 20	45 ± 17 ($P < 0.0001$)

^a Indicates $P < 0.0001$ vs A.

^b Indicates $P < 0.009$ vs A.

^c Indicates $P < 0.02$ vs A.

^d Indicates $P < 0.0001$ vs AEDS + A.

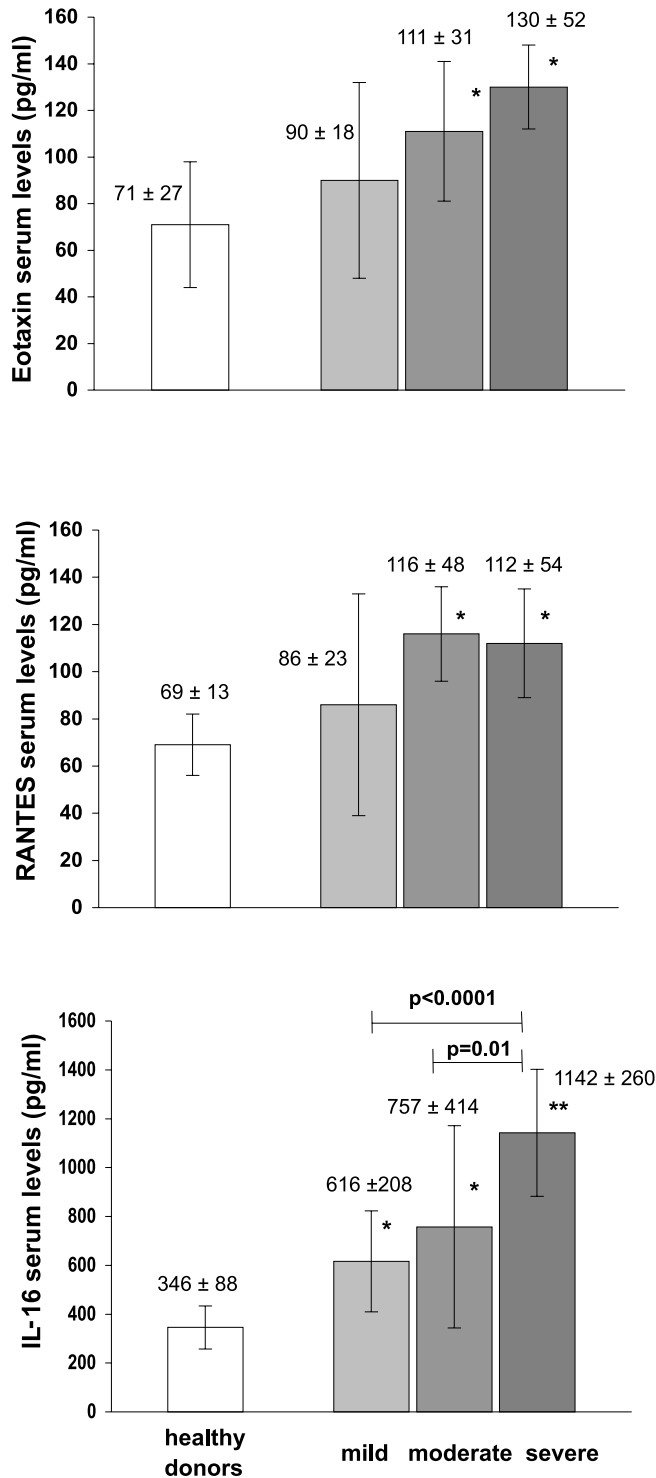


Figure 1. Serum levels of eotaxin, RANTES and IL-16 in patients with mild ($n = 8$), moderate ($n = 14$) and severe ($n = 17$) pAEDS with respect to healthy control subjects ($n = 20$). * $P < 0.01$ and ** $P < 0.0001$ vs. healthy donors.

chemokines and soluble factors between these groups, both showing very similar data to those observed in pAEDS considered as a whole (see Table 1). A progressive although not significant increase in circulating eotaxin and RANTES was detected in the different stages

of pAEDS. In contrast, as shown in Fig. 1, IL-16 serum levels were found to be significantly higher in severe pAEDS (1142 ± 260 pg/ml), with respect to both moderate (757 ± 414 pg/ml; $P = 0.01$) and mild pAEDS (616 ± 208 pg/ml; $P < 0.0001$). More interestingly, a strict correlation was found between IL-16 and both SCORAD ($r = 0.69$, $P < 0.0001$) and sCD30 ($r = 0.56$, $P < 0.0001$) in pAEDS patients (Fig. 2). Total IgE was elevated in sera of 20/39 (51.2%) patients with pAEDS, in 13/15 (86.6%) AEDS + A subjects and in 12/15 (80%) children with allergic asthma. Serum specific IgE for common food and aero-allergens was detected in 25/39 (64.1%) pAEDS, in 12/15 (80%) AD + A and in 15/15 (100%) children with A. No significant correlation was found between total or specific IgE and the other immunological and clinical parameters.

Discussion

AEDS is a chronic inflammatory skin disease associated with several immunological abnormalities: lymphocytes, macrophages, eosinophils are able to infiltrate the skin during AEDS and to locally produce and release cytokines and soluble factors responsible for the amplification of the inflammatory process (1, 4). It has been documented that the cytokine-producing pattern during AEDS skin lesion development changes from a Th2 to a Th1 pattern, with a biphasic model of cytokine expression; a predominance of IL-4 and IL-13 producing Th2 lymphocytes has been detected in acute skin lesions, replaced by Th1 cells responsible for IFN- γ production in the chronic phase of the immunological response (3).

Chemokines are well characterized small cytokines regulating the selective recruitment and activation of circulating leukocytes into inflamed tissue; based on a cystein motif, CXC (α), CC (β), C and CX₃C sub-families have been identified (5). The expanding family of β -chemokines is involved in the chronic inflammation process, since they exert their action on several leukocyte types including monocytes, basophils, eosinophils, T cells, dendritic cells, and natural killer cells during homeostasis and pathological conditions (6, 7). Recent studies document that T-cell differentiation under conditions that favour Th1 or Th2 polarization induces a different pattern of chemokine receptors, with CXCR3 and CCR5 preferentially expressed on Th1s, whereas Th2 cells selectively express CCR3, CCR4 and CCR8 (26, 27). To date, several studies documented a high expression of β -chemokines (Eotaxin, MCP-4, RANTES, TARC, macrophage inflammatory protein (MIP)-3 α), as well as chemokine receptors (CCR3, CCR4), on infiltrating cells and keratinocytes from both acute and chronic AEDS skin lesions (10, 12, 14, 15, 28, 29), suggesting their role in regulating skin invasion by eosinophils and Th2-type cells. Our results

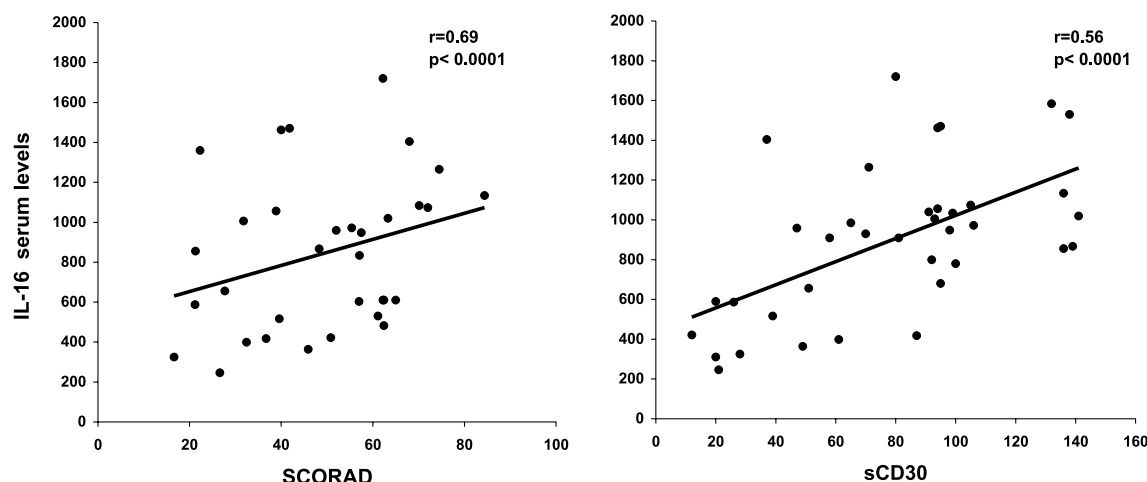


Figure 2. Circulating IL-16 is significantly correlated with both SCORAD and sCD30 serum levels in patients with pAEDS, as determined by the Spearman Rank correlation coefficient (r).

showed that circulating levels of Eotaxin and RANTES in pAEDS patients were significantly higher than those observed in normal donors, the highest levels of these chemokines being observed in patients with severe pAEDS. Eotaxin serum levels were also significantly higher in AEDS+A and A patients when compared to normals, thus confirming the importance of eotaxin in the pathogenesis of both AEDS and allergic disorders (30). Recently, a functional mutation in the proximal promoter of the RANTES gene has been identified and the mutant allele has been demonstrated to be associated with childhood AEDS but not with asthma (31); indeed, we detected no difference in serum levels of RANTES between patients with pAEDS and those with AEDS+A, indicating that the production and release of RANTES could be ascribed to atopic dermatitis by itself and not to other symptoms, such as asthma and/or rhinitis.

Beside chemokines, IL-16 has been described as the main cytokine able to induce CD4⁺ cell recruitment and activation at sites of inflammation during asthma and autoimmune diseases; it is produced by several immune (CD8 and CD4 T cells, mast cells, eosinophils, dendritic cells) and non-immune (epithelial cells, fibroblasts) cell types both constitutively and under stimuli such as histamine, antigen, mitogen, cytokines and complement fragments (16, 17). In autoimmune diseases, as well as in HIV-1 infection, IL-16 serum levels correlate with disease progression (20–23). Epithelial expression of IL-16 is considered a main feature of allergic asthma, and its presence in bronchoalveolar lavage and in induced sputum of asthmatic patients is strictly related to the earliest infiltration of CD4⁺ T cells and eosinophils, and to other markers of inflammation (18,19).

In this study we demonstrated that serum levels of IL-16 in patients with both pAEDS and AEDS+A were

elevated with respect to normals and that, in pAEDS, circulating IL-16 is significantly related to the presence of sCD30, a Th2 activation index we previously described as a serological marker of disease activity in childhood AEDS (32, 33). This observation may suggest a role of IL-16 in the specific recruitment of CD4⁺ Th2 cells during atopic disorders, thus amplifying immunological reactions responsible for the development of skin lesions and inflammation. Further, the increasing levels of IL-16 detected in subjects with A studied as control group confirm the well described role of this cytokine in the pathogenesis of asthma (18, 19). We also revealed a progressive increase of IL-16 serum levels with the clinical severity of pAEDS, documented by the significant correlation between circulating IL-16 and SCORAD index.

Several biological markers of disease activity have been largely described in relation to the activation of effector cells and/or endothelium during AEDS, such as eosinophil cationic protein (ECP), eosinophil protein X (EPX), stem cell factor (SCF), soluble E-selectin (sELAM) (34–36); in this light, IL-16 seem to be a novel marker strongly related to the activated T cells infiltrating AEDS skin lesions. Recently, Laberge et al. demonstrated an up-regulation of IL-16 mRNA expression on dermal infiltrate and keratinocytes of AEDS acute skin lesions in association with the increased number of CD4⁺ cells (24) and Reich et al. provided evidence that IL-16 released by allergen-activated epidermal Langerhans cells may contribute to the recruitment and activation of dendritic cells, T lymphocyte and eosinophils during AEDS (37). On the whole our results confirm the central role of chemokines and IL-16 in the pathogenesis of AEDS, further providing the first evidence that the evaluation of circulating levels of IL-16 may be an additional useful tool in establishing disease activity during childhood AEDS.

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