

IL-31 significantly correlates with disease activity and Th2 cytokine levels in children with atopic dermatitis

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Abstract

Recently, we could show that IL-31 serum levels are significantly increased in adult patients with atopic dermatitis compared with skin healthy controls. However, the regulation of IL-31 in children with atopic dermatitis so far is not clear. Thus, we analyzed IL-31 serum levels together with IL-4, IL-13, ECP, and total IgE levels in 60 children with extrinsic, in five children with intrinsic atopic dermatitis, and 20 non-atopic healthy children. Further, we determined the SCORAD score, sleeplessness, and pruritus severity in all children with atopic dermatitis. IL-31 was significantly increased in children with the intrinsic and extrinsic type of atopic dermatitis compared with non-atopic healthy children ($p < 0.05$ – 0.001). Further, IL-31 serum levels significantly correlated with SCORAD score ($p < 0.01$), sleeplessness ($p < 0.05$), IL-4, and IL-13 levels ($p < 0.01$) in children with extrinsic atopic dermatitis. There was no correlation of IL-31 with pruritus, total IgE Ab, and ECP levels, whereas ECP levels significantly correlated with the SCORAD score in children with extrinsic atopic dermatitis. Together, IL-31 represents an interesting cytokine especially with regard to the severity of the inflammatory process indicated by the correlation of IL-31 with SCORAD score and Th2 cytokines including IL-4 and IL-13 in children with extrinsic atopic dermatitis.

Short report

Atopic dermatitis is one of the most common chronic childhood skin diseases (1). It is characterized by eczematous skin lesions and intense pruritus. Pruritus and skin inflammation have a high impact on the quality of life of the children and their families. These major symptoms are included in the SCORAD score assessing the disease activity of patients. Treatment of pruritus with H1-antihistamines is often not helpful in atopic dermatitis patients. Thus, other mediators than histamine, including neuropeptides, neurotransmitters, proteinases, and cytokines have been suggested to play a role in the pathophysiology of pruritus in atopic dermatitis (2).

Recently, we could show that IL-31 serum levels are significantly increased in adult patients with atopic dermatitis compared with skin healthy controls (3). Subdividing atopic dermatitis into the extrinsic and the intrinsic type of atopic dermatitis according to IgE-specific sensitization and history

for atopic diseases including allergic rhinitis, food allergy, and allergic bronchial asthma, we found no differences in IL-31 serum levels between both phenotypes of atopic dermatitis. Both the extrinsic and intrinsic type of atopic dermatitis were characterized by significantly higher IL-31 serum levels in comparison with skin healthy non-atopic subjects. Further, we found a significant correlation of IL-31 serum levels with SCORAD score in the extrinsic as well as in the intrinsic type of atopic dermatitis (3).

In the skin, regulation of IL-31 mRNA is increased in non-lesional skin of patients with atopic dermatitis in comparison with skin healthy controls. Further, IL-31 mRNA has been shown to be overexpressed in pruritic atopic dermatitis but not in non-pruritic psoriatic lesions compared with healthy skin (4). Also other skin diseases associated with acute inflammation including acute allergic contact dermatitis have been associated with higher IL-31 mRNA levels compared with healthy skin, correlating with Th2 cytokines including IL-4

and IL-13 (5). Possible sources of IL-31 are skin infiltrating CLA⁺ T cells and peripheral blood CD45R0 CLA⁺ T cells (6). Interestingly, staphylococcal superantigens, which represent a general trigger factor for atopic dermatitis rapidly induced IL-31 mRNA expression in the skin of atopic individuals in vivo and in PBMC in vitro, suggesting that superinfection can lead to the sensation of pruritus (4).

The first description of IL-31 to be involved in the development of severe pruritus and chronic dermatitis had been gained in a transgenic mice model with lymphocyte-specific overexpression of IL-31 (7). Accordingly, it was found that in the skin of NC/Nga mice – which is considered to be the model of atopic dermatitis for animals – expression of skin IL-31 mRNA levels was significantly higher in mice with scratching behavior compared with those without (8). In addition, scratching counts in mice with long-lasting scratching behavior correlated with skin IL-31 mRNA expression (9). Recently, intervention with IL-31 antibody 10 mg/kg intraperitoneally every fifth day in NC/Nga mice from age 7 wk reduced the scratching behavior, but displayed no impact on dermatitis (10). IL-31 signals through a heterodimeric receptor composed of IL-31 receptor A (IL-31RA) and oncostatin M receptor, which is expressed on epithelial cells including keratinocytes and on dorsal root ganglia (IL-31RA) (4).

Although it is quite clear that atopic dermatitis in adults is associated with increased IL-31 serum levels and with disease activity, there is a lack of data in childhood atopic dermatitis. Thus, we wanted to address the question first, whether IL-31 is increased in children with atopic dermatitis, secondly whether there is a difference in the extrinsic and intrinsic type of atopic dermatitis with regard to IL-31 levels, thirdly whether these levels are different from that of adult patients with atopic dermatitis, and fourthly, whether IL-31 serum levels correlate with disease severity, pruritus, sleeplessness, IL-4, IL-13, ECP, and total IgE levels in children with atopic dermatitis.

After informed consent (approved by the local ethics committee), peripheral venous blood was obtained from children with atopic dermatitis and control subjects at 9 AM to prevent daily variations. Children with the extrinsic type of atopic dermatitis ($n = 60$; mean age 34.9 ± 16.9 month, positive history for atopic diseases including food allergy or inhalant allergy or positive familiar history for atopic diseases including atopic dermatitis and inhalant allergies) defined according to the criteria of Hanifin and Rajka were included in the study. In addition, we included five children with the intrinsic type of atopic dermatitis (mean age 39.2 ± 16.7 month) without allergen-specific sensitization and normal total IgE levels. Twenty skin healthy non-atopic children (mean age 33.7 ± 18.2 month) were included as control group. Further, 15 adult patients with atopic dermatitis (mean age 32.4 ± 12.7 yr) with increased total serum IgE levels and positive history for atopic diseases including allergic rhinitis, food allergy, or allergic bronchial asthma were included in the study. All subjects did not receive systemic immunosuppressive treatment.

Severity of atopic dermatitis was assessed by the scoring atopic dermatitis score (SCORAD). Serum IL-31 levels were measured with commercially available ELISA kit (R&D Sys-

tems, Wiesbaden, Germany, detection limit 125 pg/ml) as previously described (3, 11). IL-4 and IL-13 levels were analyzed by commercial ELISA kit (IL-4; eBioscience, Frankfurt, Germany, detection limit 1.56 pg/ml; IL-13 R&D Systems, detection limit 93.8 pg/ml) according to the manufacturer's instructions. ECP serum levels and total IgE serum levels were analyzed using the commercial available Phadia ImmunoCap system (Phadia, Uppsala, Sweden). Statistical analysis was performed with the statistical software package SigmaStat (SigmaStat for Windows, Jandel Scientific Erkrath Wiesbaden, Germany). Data were analyzed with non-parametric Mann-Whitney *U*-test. The correlation between IL-31, SCORAD score, sleeplessness, serum ECP levels, and total IgE Ab was assessed with Spearman rank order correlation. A *p* value of <0.05 was considered to be statistically significant.

IL-31 serum levels were significantly higher in children with extrinsic atopic dermatitis (mean $\pm$ s.e.m.; 1438.0 ± 323.7 pg/ml, $p < 0.001$, Fig. 1) compared with non-atopic healthy control children (133.9 ± 41.8 pg/ml, Fig. 1). When we compared these IL-31 serum levels to adults with atopic dermatitis of extrinsic type, the adult patients displayed significantly higher IL-31 serum levels (3030.0 ± 701.3 pg/ml; $p < 0.05$). IL-31 serum levels in children with the intrinsic type of atopic dermatitis were also higher compared with non-atopic healthy control children (mean 1756.0 ± 1561 pg/ml; $p < 0.05$, data not shown). There was no significant difference in IL-31 serum levels in children with the extrinsic compared with the intrinsic type of atopic dermatitis.

The overall mean SCORAD score ($\pm$ s.d.) was 35.8 ± 20.9 for children with extrinsic atopic dermatitis ($n = 60$) and 14.0 ± 4.0 for children with the intrinsic type

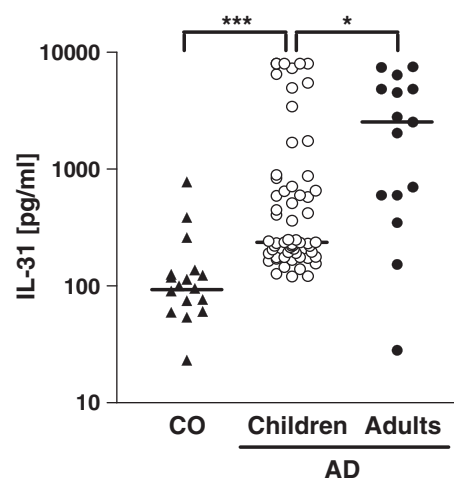


Figure 1 Significantly higher IL-31 serum levels (pg/ml) of children with extrinsic atopic dermatitis ($n = 60$, open circles) compared with non-atopic healthy control children (CO, $n = 20$, black triangles) and adult patients with atopic dermatitis of extrinsic type ($n = 15$, black dots). Data are presented as scattergram with median in a logarithmic scale; * $p < 0.05$; *** $p < 0.001$.

of atopic dermatitis ($n = 5$). The SCORAD score significantly correlated with serum IL-31 levels (Spearman $r = 0.29$; $p < 0.05$, Fig. 2a) and sleeplessness (Spearman $r = 0.37$; $p < 0.01$, Fig. 2b) in children with extrinsic atopic dermatitis. Further, we found a significant correlation of increased IL-31 levels with IL-4 (Spearman $r = 0.39$; $p < 0.01$, Fig. 3a) and IL-13 levels (Spearman $r = 0.36$, $p < 0.01$, Fig. 3b) in children with the extrinsic type of atopic dermatitis.

However, we did not find a significant correlation between pruritus score and ECP serum levels to IL-31 serum levels in children with extrinsic atopic dermatitis, whereas there was a significant correlation between SCORAD score and ECP serum levels (Spearman $r = 1.00$; $***p < 0.001$). In children with the intrinsic type of atopic dermatitis, there was no correlation of IL-31 with IL-4, IL-13, and ECP levels. Regarding total IgE Ab, there was no correlation with IL-31 serum levels in both children with intrinsic and extrinsic atopic dermatitis. This might be due to the fact that IgE can be seen to be associated with a severe form of atopic dermatitis in general, but it does not reflect the actual score in the course of the disease like IL-31 does (12).

In summary, our data give evidence that children with extrinsic atopic dermatitis have increased serum levels of IL-31, which correlate with sleeplessness, disease activity, and Th2 cytokine levels. In this regard, recent data support our

finding with increased serum levels of IL-31 (13). Interestingly, we could not find a correlation of IL-31 with total IgE serum levels. This may be explained by the fact that IL-31 expression is largely restricted to CD45R0+ memory/effector T cells (6) and not to B cells. Gutzmer and colleagues identified Th2 cells for the production of IL-31mRNA (14). In this regard, we could find a correlation of Th2 cytokines including IL-4 and IL-13 with increased levels of IL-31 in children with extrinsic atopic dermatitis. As we found no correlation of IL-31 with ECP serum levels, IL-31 regulation may not depend on eosinophils in first line. In comparison with the mice model, in which IL-31 had been shown to be involved in the scratching behavior (9), we could not find evidence for a correlation of pruritus score with increased IL-31 serum levels in the children with atopic dermatitis. In Nc/Nga mice, the use of IL-31 mAb significantly reduced the scratching activity, although with no impact on skin inflammation (10). It seems that in humans, the regulatory process of IL-31 in skin inflammation seems to be far more complex, as we assessed a correlation of IL-31 serum levels with the SCORAD score, sleeplessness, and Th2 cytokines including IL-4 and IL-13, in sixty children with the extrinsic type of atopic dermatitis.

Together, IL-31 represents an interesting cytokine with promising potential for the treatment of the inflammation in childhood atopic dermatitis.

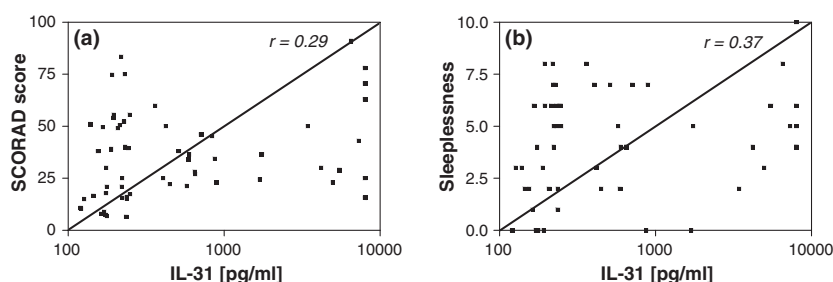


Figure 2 (a) Correlation of IL-31 serum levels (x axis, pg/ml) with SCORAD score (y axis) of 60 children with extrinsic atopic dermatitis (Spearman $r = 0.29$; $*p < 0.05$). (b) Correlation of IL-31 serum levels (pg/ml) with sleeplessness (y axis) of 60 children with atopic dermatitis of extrinsic type (Spearman $r = 0.37$; $**p < 0.01$).

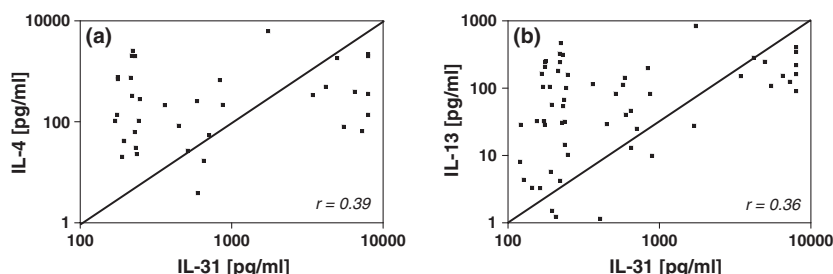


Figure 3 Correlation of IL-31 (x axis pg/ml) with (a) IL-4 (y axis, pg/ml, Spearman $r = 0.39$; $**p < 0.01$) and (b) IL-13 serum levels (y axis pg/ml; Spearman $r = 0.36$; $**p < 0.01$) in children with extrinsic atopic dermatitis ($n = 60$).

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