

# Serum Autotaxin Levels Correlate with Pruritus in Patients with Atopic Dermatitis

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## TO THE EDITOR

Autotaxin (ATX) has enzymatic lysophospholipase D activity and hydrolyzes lysophosphatidylcholine into lysophosphatidic acid (LPA). ATX is widely expressed, with the highest mRNA levels detected in adipose tissue, brain, placenta, ovary, and small intestine. ATX-LPA signaling is important in physiological and pathological processes, from vascular and neural development to lymphocyte homing, fibrosis, and cancer (Moolenaar and Perrakis, 2011). Recently, serum ATX levels were reported to correlate with pruritus of cholestasis (Kremer *et al.*, 2012). Atopic dermatitis (AD) is a major pruritic inflammatory skin disease. Scratching behavior from intensive itching results in skin barrier dysfunction and exacerbation of AD (Barnes, 2010). Severe pruritus in AD has been attributed to increased release of substance P, nerve growth factor, neurotrophin-3 and 4, brain-derived neurotrophic factor and histamine (Arck and Paus, 2006). Newly identified itch mediators include the histamine 4 receptor, interleukin-31, and Toll-like receptor 3 (Liu *et al.*, 2012). In this study, we measured serum ATX levels in AD patients and examined whether they could be an index marker of pruritus in AD.

Thirty-one AD patients (mean  $\pm$  SEM age:  $30.0 \pm 2.0$  years, 20 men and 11 women) and 28 healthy controls ( $28.8 \pm 1.7$  years, 10 men and 18 women) were enrolled in this study. All AD patients were given diagnoses according to the criteria of Hanifin and Rajka (1980). The disease severity was determined by Physician Global Assessment and the Eczema Area and Severity Index (EASI). We rated itch by visual analog scale (VAS) 0–10, asking the patients to mark

a point on the line corresponding to mean itch during the last 7 days. The medical ethical committee of the University of Tokyo approved all described studies, and the study was conducted according to the Declaration of Helsinki Principles. Written informed consent was obtained from participants. The 28 healthy controls had no history of allergic diseases such as AD, allergic rhinitis, or asthma. All AD patients were treated with topical medication and/or antihistamine drugs. We excluded patients treated with oral steroid or cyclosporine because they would affect serum ATX levels (Sumida *et al.*, 2013). Enzyme immunoassay was performed

using Quantikine Human ENPP-2/Autotaxin ELISA kit (R&D systems, Minneapolis, MN). Statistical analysis was performed using the Mann–Whitney's *U*-test for comparison of two groups. Correlation coefficients were determined by using the Spearman's rank correlation test. *P*-values of  $<0.05$  were considered statistically significant.

Serum ATX levels in AD patients were significantly higher than those in healthy individuals ( $74.8 \pm 12.3$  and  $32.9 \pm 5.9 \text{ pg ml}^{-1}$ , respectively;  $P < 0.01$ , Figure 1a). As ATX levels were reported to be higher in females than in males (Nakamura *et al.*, 2008), we analyzed serum ATX levels according to their sex.

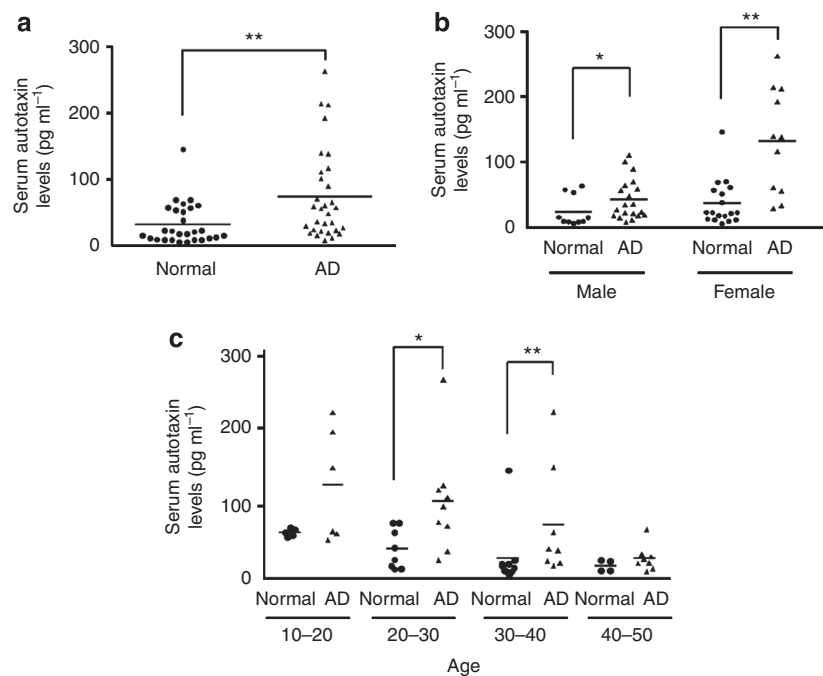


**Figure 1. Serum autotaxin levels in atopic dermatitis (AD) and healthy controls.** (a) Serum autotaxin levels in 31 AD patients and 28 healthy individuals. Each bar indicates the mean of the group. (b) Serum autotaxin levels in males and females. (c) Serum autotaxin levels in different age groups. \* $P < 0.05$  and \*\* $P < 0.01$ .

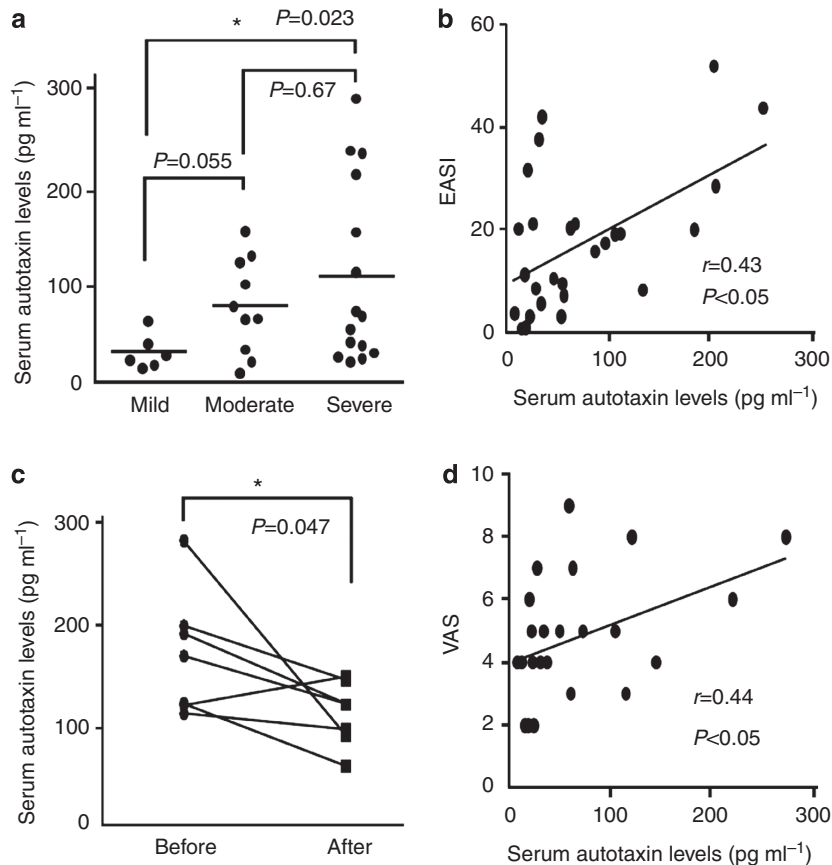


**Figure 2. Correlation between serum autotaxin levels and the disease markers of atopic dermatitis (AD).**

(a) Serum autotaxin levels in AD patients according to the disease severity. (b) Serum autotaxin levels significantly correlated with Eczema Area and Severity Index (EASI) scores. (c) Serum autotaxin levels significantly decreased after treatment. (d) Serum autotaxin levels significantly correlated with visual analog scale (VAS) itch scores.

Serum ATX levels in male AD patients were  $43.1 \pm 6.9 \text{ pg ml}^{-1}$ , which were significantly higher than those in healthy male controls ( $24.9 \pm 7.4 \text{ pg ml}^{-1}$ ,  $P<0.05$ , Figure 1b). Similar results were obtained between female AD patients and female healthy controls ( $132.3 \pm 24.4 \text{ pg ml}^{-1}$  vs.  $37.3 \pm 8.1 \text{ pg ml}^{-1}$ ,  $P<0.01$ , Figure 1b). Serum ATX levels in female AD patients were significantly elevated than those in male AD patients ( $P<0.01$ ). Moreover, we analyzed serum ATX levels according to their age. In the twenties, serum ATX levels in AD patients were significantly higher than those in healthy controls ( $97.0 \pm 23.4$  and  $37.2 \pm 8.9 \text{ pg ml}^{-1}$ , respectively;  $P<0.05$ , Figure 1c). In the thirties, AD patients exhibited significantly higher serum ATX levels compared with healthy controls ( $67.1 \pm 25.1$  and  $24.8 \pm 12.2 \text{ pg ml}^{-1}$ , respectively;  $P<0.01$ , Figure 1c), whereas in the forties, there

was no significant difference between AD patients and healthy controls. In the teens, serum ATX levels in AD patients tended to be higher than those in healthy controls ( $118 \pm 30.2$  and  $57.5 \pm 2.22 \text{ pg ml}^{-1}$ , respectively), although difference did not reach statistical significance. Serum ATX levels in AD patients decreased as they grew older, which might be associated with the improvement of the disease activity of AD by age. We also analyzed serum ATX levels according to the severity of AD; serum ATX levels were elevated as the disease severity increased (Figure 2a). Moreover, serum ATX levels significantly correlated with EASI ( $r=0.43$ ,  $P<0.05$ , Figure 2b) and decreased after treatment ( $P<0.05$ , Figure 2c). We next examined the correlation between serum ATX levels and VAS itch scores or other serum markers reflecting the disease activity of AD, such as IgE and CCL17.

Serum ATX levels significantly correlated with VAS itch scores ( $r=0.44$ ,  $P<0.05$ , Figure 2d), but not with serum IgE or CCL17 levels (data not shown).

Our study revealed that serum ATX levels in AD patients were significantly higher than healthy individuals and that serum ATX levels significantly correlated with EASI, a widely used quantitative evaluation of AD severity. Furthermore, serum ATX levels in each patient significantly decreased after treatment. As the patients in this study were under treatment, we cannot deny the possibility that topical steroids had influenced serum ATX levels as reported with oral steroid treatment (Sumida *et al.*, 2013). Interestingly, serum ATX levels correlated with VAS itch scores. Neuropeptides such as calcitonin gene-related peptide, substance P, gastrin-releasing peptide as well as nerve growth factor have been reported to have critical roles in the itch signaling pathways (Kagami *et al.*, 2013; Yarbrough *et al.*, 2013). Recent research shows that ATX is expressed in several human organs and correlates with the pruritus of cholestasis (Kremer *et al.*, 2012). ATX expression is elevated in reactive astrocytes adjacent to sites of neurotrauma, having a role in neuropathic pain (van Meeteren and Moolenaar, 2007; Nakanaga *et al.*, 2010; Okudaira *et al.*, 2010). In oligodendrocyte precursors before myelination, ATX promotes process branching and focal adhesion organization (van Meeteren *et al.*, 2006). Taken together, ATX is essential for neural development and might be associated with neurophysiological itch pathways. Our study revealed that serum ATX levels correlated with pruritus in AD, suggesting that ATX could be a therapeutic target for pruritus in AD.

#### CONFLICT OF INTEREST

The authors state no conflict of interest.

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# No Increased Risk of Fetal Death or Prolonged Time to Pregnancy in Women with Psoriasis

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## TO THE EDITOR

Early onset of psoriasis makes the understanding of pregnancy outcomes in patients with psoriasis important. Studies have shown that psoriasis is a risk factor for adverse pregnancy outcomes (Cohen-Barak et al., 2010; Yang et al., 2010) and that pregnant women with psoriasis are more likely to be depressed, obese, and to smoke compared with women without psoriasis (Bandoli et al., 2010). Psoriasis shares pathological mechanisms with other chronic inflammatory diseases. Studies have demonstrated that women with Crohn's disease have an increased risk of spontaneous abortion (Margarinos et al., 2007) and that women with rheumatoid arthritis have prolonged time to pregnancy (TTP) (Jawaheer et al., 2011), and therefore we wanted to determine whether women with psoriasis are at increased risk of fetal death and prolonged TTP.

We used data from the Danish National Birth Cohort (DNBC),

containing information on 100,418 pregnancies enrolled from 1996–2003. Information regarding reproductive history, lifestyle during pregnancy and demographic characteristics was obtained from telephone interviews. Information regarding psoriasis was self-reported. Data on pregnancy outcomes were obtained from linkage with the Danish National Patient Registry (Lynge et al., 2011) and from the Civil Registration System (Pedersen, 2011). Details of the cohort and its structure are given elsewhere (Olsen et al., 2001).

In all, 87,692 pregnancies were eligible for the analysis of fetal death (Supplementary Figure S1 online). Pregnancies eligible for analysis of TTP were restricted to first-time pregnancies, to avoid dependency between observations, resulting in 81,627 pregnancies. Of the 87,692 pregnancies included 2,553 (3%) were of women with psoriasis. Characteristics of the study population are presented in Table 1

and Supplementary Table S1 online. Compared to women without psoriasis, women with psoriasis more often smoked during pregnancy. Women with psoriasis were older, and were more often overweight with a body mass index (BMI) of  $\geq 25$  (WHO, 2013).

Fetal death included spontaneous abortions, stillbirths and twin births in which one or both babies had died. We analyzed the association between psoriasis and fetal death using Cox proportional hazards regression models, giving hazard ratios (HRs) with 95% confidence intervals (CIs). Analyses were run with delayed entry and gestational age as the underlying time scale. We took into account that some women contributed with more than one pregnancy, by including a robust sandwich variance estimator handling the within-person correlation between pregnancies. Of the 2,553 pregnancies in women with psoriasis, 36 (1.4%) ended in fetal death compared with 1,119 (1.3%) fetal deaths in women without psoriasis. This translated to a HR of 1.05 (95% CI 0.75–1.46) after adjustment (Table 2).