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Urinary aquaporin-2 is elevated in infant atopic dermatitis

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MADAM, One of the key features of atopic dermatitis (AD) is increased transepidermal water loss (TEWL),^{1,2} a phenomenon

attributable partly to impaired barrier function of the skin due to some genetic defects such as filaggrin gene (FLG) mutations, or to inflammatory status in AD.¹ Remarkable loss of body fluid would induce a series of systemic regulatory reactions. The functional antidiuretic hormone (ADH)–aquaporin (AQP)–2 axis is a major regulatory system to keep water balance. AQP-2 mediates water transport across the apical plasma membrane of the renal collecting ducts. Kidney AQP-2 expression can be estimated quantitatively by urinary excretion of AQP-2. Moreover, the amount of urinary AQP-2 (u-AQP-2) is positively correlated with the plasma levels of ADH in normal subjects.³ Increased serum ADH was detected in severe AD, a result possibly due to a dehydrated state caused by increased TEWL in these patients.² Therefore, it is possible that u-AQP-2 is altered in AD. We conducted a case–control study to measure the u-AQP-2 level in paediatric patients with AD, and assessed its correlation with several clinical and laboratory parameters.

Fifty paediatric patients with AD (35 boys and 15 girls, aged 2 months to 8 years, mean 2.1 years) and 35 age- and sex-matched controls (23 boys and 12 girls, aged 2 months to 5 years, mean 3.1 years) were enrolled (Fig. 1). Random urine samples were collected from infants and first morning urine samples were collected from children. Objective SCORAD (O-SCORAD) index was used to measure the severity of AD.⁴ u-AQP-2 was measured by enzyme-linked immunosorbent assay protocol as described by the kit supplier (USCN Life Science & Technology Co., Ltd, Wuhan, China). We expressed the amount of u-AQP-2 relative to urinary creatinine as

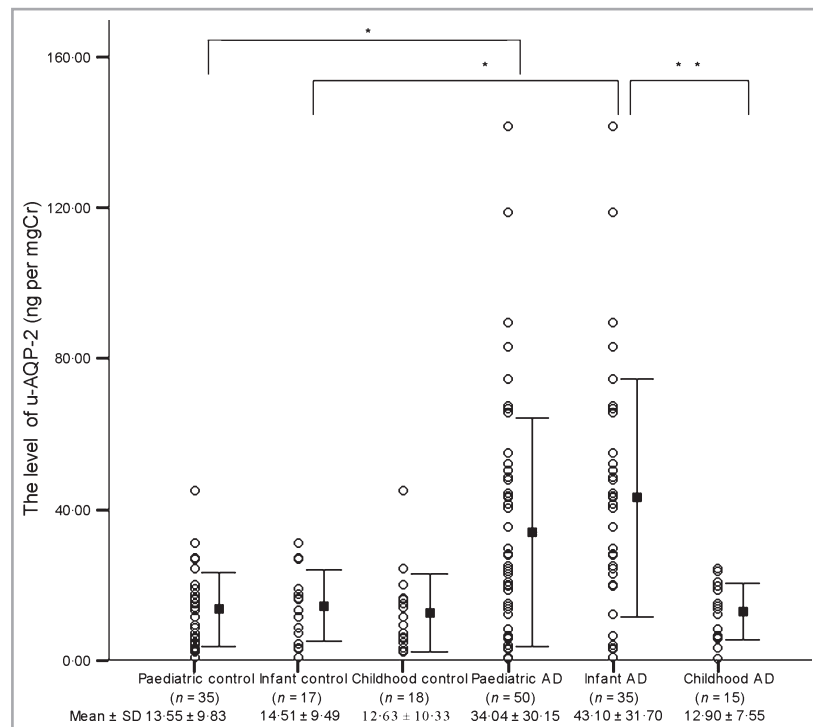


Fig 1. Distribution of urinary aquaporin-2 (u-AQP-2) level relative to urinary creatinine (Cr) in paediatric patients with atopic dermatitis (AD) and controls. Data are given as mean ± SD. Student's t-test was used for comparisons of the mean levels of u-AQP-2. *P < 0.01, **P ≤ 0.001. Infants with AD or infant controls: < 2 years old; childhood patients with AD or childhood controls: ≥ 2 years old.

ng mg⁻¹. Informed consent was obtained from the parents. The study was approved by the Ethics Committee of China Medical University. SPSS 15.0 software (SPSS Inc., Chicago, IL, U.S.A.) was used for statistical analyses.

Regarding u-AQP-2, the paediatric AD level was significantly higher than the normal paediatric control level, and the infant AD level was significantly higher than the childhood AD and infant control levels (Fig. 1). There was no difference in u-AQP-2 levels between boys with AD and girls with AD. There was no association between u-AQP-2 levels and O-SCORAD index,⁵ either in infant AD or in childhood AD (Fig. 2). There was no association between level of u-AQP-2 and pooled score of inflammatory parameters. There was no association between level of u-AQP-2 and score of skin dryness in the whole cohort. However, there was a statistically significant association between u-AQP-2 level and skin dryness in infant AD ($r = 0.375$, $P = 0.029$, Spearman's rank test), although the significant association was lost after Bonferroni correction used for adjustment of α to 0.025. There was no association of level of u-AQP-2 with number of eosinophils, serum IgE, urine pH or urine specific gravity in the entire cohort (data not shown).

Among the 13 characterized members of the AQP family, only AQP-3 and AQP-10 are expressed in the plasma membrane of keratinocytes. AQP-3 expression can be upregulated in accordance to water loss and dry skin in AD.⁶ AQP-2 is involved in water reabsorption and urine concentration. Our

results showed that u-AQP-2 level was elevated only in infant AD and that there was a positive association between u-AQP-2 level and skin dryness in infant AD, but not in childhood AD. These findings might be attributable to the following factors: firstly, inflammatory parameters are restricted to the lesion area, while skin dryness reflects the general state of the skin; secondly, the ratio of body area to weight is higher in infants than in older children, a condition that further increases the possibility of increased TEWL; thirdly, the disabling of active water intake by infant AD; and finally, it was reported that there was a reduced TEWL when infant AD turned to childhood AD,⁷ a phenomenon supporting our observation that correlation of u-AQP-2 with disease parameters was lost in childhood AD. In addition, we postulate that a mechanism may be involved in long-lasting AD that causes escape from the ADH-AQP-2 pathway.⁸ AD is most prevalent in infants. An objective, easy and noninvasive test for evaluation of infant AD is greatly desired by both healthcare workers and parents. A follow-up study is needed to see if the level of u-AQP-2 could be used as an indicator for fluid supplementation and skin moisturization in infant AD. FLG mutations have recently been implicated in vulnerability to AD, especially in patients from European populations.⁹ We previously reported an association of the 3321delA mutation in Chinese patients with AD.¹⁰ Considering the relatively large size of the FLG gene, a high-throughput screening of FLG mutations would be valuable in understanding the genetic barrier defect of

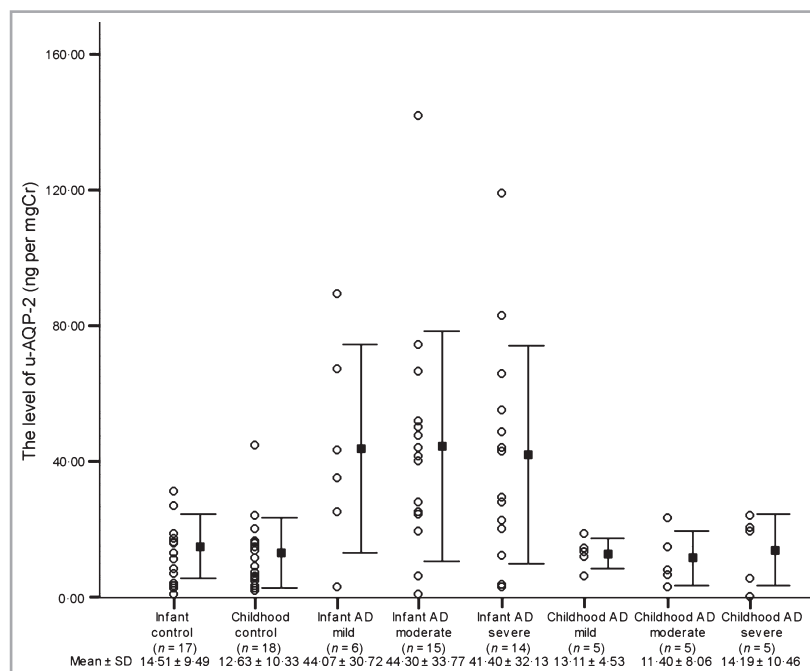


Fig 2. The levels of urinary aquaporin-2 (u-AQP-2) relative to urinary creatinine (Cr) in paediatric patients with atopic dermatitis (AD) and controls, stratified according to the severity of AD. Data are given as mean $\pm$ SD. Disease severity was categorized as mild (objective SCORAD index < 15), moderate (objective SCORAD index 15–40) and severe (objective SCORAD index > 40).⁵ No statistically significant differences were found among AD subgroups of different severity: infants with AD ($F = 0.015$, $P = 0.985$, ANOVA analysis), childhood patients with AD ($F = 0.272$, $P = 0.767$, ANOVA analysis). Infants with AD or infant controls: < 2 years old; childhood patients with AD or childhood controls: ≥ 2 years old.

Chinese AD, and its subsequent correlation with u-AQP-2. A limitation of the study was that we were unable to measure the TEWL, a good indicator to reflect barrier defects of skin, and made subsequent correlational analysis with u-AQP-2 level in AD.

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*State Key Department of Dermatology,
No. 1 Hospital of China Medical University,
155 North Nanjing Street, Heping District,
Shenyang 110001, China

†Department of Dermatology, Shengjing Hospital
of China Medical University, 36 San Hao Street,
Heping District, Shenyang 110004, China

Correspondence: Xing-Hua Gao.

E-mail: gaobarry@hotmail.com

Z.H. DI*†

Y.N. LV*

L. ZHANG*

Y.X. HONG*

H.D. CHEN*

X.H. GAO*

J. XU†

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Key words: aquaporin-2, atopic dermatitis, paediatric, urine

Conflicts of interest: none declared.

Pruritic reddish-brown papules and plaques as initial skin lesions in a case of antilaminin γ 1 pemphigoid without psoriasis

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MADAM, Antilaminin γ 1 pemphigoid is an autoimmune sub-epidermal bullous disease characterized by the presence of IgG autoantibodies to a 200-kDa protein (p200) at the dermal–epidermal junction (DEJ).^{1,2} This protein has recently been identified as laminin γ 1.³ The clinical presentation in some cases of antilaminin γ 1 pemphigoid may mimic bullous pemphigoid, linear IgA bullous dermatosis or dermatitis herpetiformis. Among these presentations, bullous pemphigoid-like bullous lesions are the most common and are characterized by itchy urticarial papules and plaques, and tense blisters.² In about half of the patients with antilaminin γ 1 pemphigoid, psoriasis vulgaris precedes blister formation by 0.5–30 years.^{2,4} The association of these two diseases is not considered to be merely a coincidence. Some cases without psoriasis present with clinical features of vesicular pemphigoid. However, antilaminin γ 1 pemphigoid with initial skin lesions other than blisters has not been reported to date. We describe a patient with antilaminin γ 1 pemphigoid who showed pruritic, reddish-brown papules and plaques without blisters.

A 64-year-old Japanese man who had no past history of psoriasis presented with intensely pruritic, reddish-brown papules and plaques on the trunk and extremities which had been present for more than 1 year (Fig. 1a, b). Histopathological examination of a biopsy specimen obtained from the abdominal region showed a mixed-cell perivascular infiltrate containing numerous neutrophils and eosinophils in the upper dermis (Fig. 2a, b). The patient was diagnosed with prurigo chronica multiformis, and was prescribed prednisolone 10 mg daily. The skin lesions improved within 3 weeks. After prednisolone was reduced to 5 mg daily, however, these papules and plaques suddenly turned reddish and spread extensively over the trunk and extremities. Small tense blisters also appeared on some of these papules and plaques (Fig. 1c, d). There was no oral mucosal involvement. On laboratory examination, the serum IgE level was elevated to 2414 U mL⁻¹. Histopathological examination of a second biopsy specimen obtained from the abdominal region showed subepidermal blistering and an inflammatory infiltrate of neutrophils and eosinophils in the blister cavities and upper dermis (Fig. 2c, d). Neutrophilic microabscesses were also seen at the tips of the dermal papillae (Fig. 2e). Direct immunofluorescence demonstrated linear deposits of IgG (Fig. 2f) and complement C3 at the DEJ. Indirect immunofluorescence using normal human skin as a substrate showed circulating IgG autoantibodies against the basement membrane zone, which were reactive exclusively with the dermal side of 1 mol L⁻¹ NaCl-split human skin (Fig. 2g). Immuno-