

Transepidermal Water Loss as the Earliest Independent Marker of the Epidermal Barrier Dysfunction in Children with Food Hypersensitivity

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Abstract

Aim of the research was to study level of the transepidermal water loss (TEWL) in children with food hypersensitivity depending on the result of skin-prick test, oral challenge test with food allergens, IL-2, IL-4, TLR-2 levels and features of the course of the symptoms.

Methods. 424 eligible children 1 - 18 years old were recruited in the study. TEWL was assessed by measuring of the humidity of the skin (Queentone, France). Skin-prick tests (SPT) and oral challenge test (OCT) with common food allergens were used for diagnostics of the type of the hypersensitivity, venous blood samples were taken for analysis. ELISA method was used for detection of the IL-2, IL-4, TLR-2 in serum.

Results. Mean humidity of the skin in the locuses of the inflammation in children with FH was 26,5% [20,8;39,4]. Humidity level on the affected areas strongly correlated with TEWL on the unaffected parts ($r=0.73$, $p<0.05$). TEWL in children with clinical symptoms of the FH had no correlation with standard tests (skin prick- and oral challenge test), which are usually used for immune FH diagnostics. Humidity in the affected areas was linked with debut of the first FH symptoms before 1 month of age ($r=0.33$, $p<0.05$).

Conclusion. Transepidermal water loss which can be measured with relative humidity level is the earliest independent marker of the epidermal barrier dysfunction in children with clinical symptoms of the food hypersensitivity. Correction of the TEWL should be provided as in the affected as in the unaffected areas.

Keywords: food hypersensitivity, children, transepidermal water loss, Toll-like receptor, Interleukin, skin prick-test, oral challenge test

Introduction

Immune mechanism of the Food Hypersensitivity (FH) are the most frequently studied nowadays. Evidences of the effectiveness of the specific immunotherapy for treatment of the immune FH is doubtless. On the other hand, further studies of the non-immune mechanisms are considered as new targets for therapy. Aimed correction of the key parts of the FH pathogenesis is suspected to be effective independently from type of allergic reaction. Enough evidences were gathered regarding role of the transepidermal water loss (TEWL) in the prophylaxis of the skin allergic diseases and link with the severity of the Atopic dermatitis [4, 5]. It was demonstrated that TEWL in children up to 2 y.o. – is predictor of the FH symptoms onset even in children without allergic anamnesis [6]. Mechanisms are still not clear. Some studies showed correlation between TLR-2 expression and level of the TEWL ($r=-0.654$, $P=0.0004$) [7]. Serum IL-4 and IL-2 have previously been associated with allergic conditions on the skin [2]. The pathogenic aspects of the impairment in skin barrier functioning in development of skin symptoms of the FA is not fully understood.

Aim of the research was to study level of the transepidermal water loss (TEWL) in children with food hypersensitivity depending on the result of skin-prick test, oral challenge test with food allergens, IL-2, IL-4, TLR-2 levels and features of the course of the symptoms.

Methods. 424 eligible children 1 - 18 years old were recruited prospectively from the patients of the Children multiefield children hospital #5, Zaporizhya and University clinic, Zaporizhzhya, Ukraine. Diagnosis of food allergy was made with EAACI criteria in case of FA reproducible occurrence on exposure to the suspected food. Patients with food anaphylaxis were not included. Skin-prick tests (SPT) and oral challenge test (OCT) with common food allergens were used for hypersensitivity proof. Oral challenge test (OCT) was performed in accordance with the recommendations and local Ethical requirements [1]. Open oral provocation was used for infants up to 1 y.o. Double blind placebo controlled oral challenge was provided in others. Two main products were used for oral challenge: milk and egg.

TEWL was assessed by measuring of the relative humidity of the skin with device Queentone (France) in the locuses of inflammation and on visually healthy areas.

Principle of work of this device is based on the measurement of the continuous electrical capacitance. Measurement was provided on the resting subjects where air movement and temperature were constant without any source of radiation. Dryness of the skin was diagnosed following the manufacturer recommendations. If the humidity was between 0-33%, normal level was considered when humidity was between 34-56%, increased – higher than 57%.

Blood samples were collected after fasting in cooling vacutainer and after that it was immediately centrifugated (4°C for 3.000 × 30 min). After centrifugation serum was blind coded and stored at -25° until used. For levels of IL-2, IL-4 detection ELISA method was used (Human IL-2 Platinum ELISA and Human IL-4 Platinum ELISA, produced by Affymetrix Bioscience, Austria). TLR-2 in serum was detected by ELISA Kit for TLR-2 (Cloud-Clone Corp).

All statistical analyses were performed in commercial software Statistica (Statsoft, USA). All continuous variables were tested for a normal distribution using the Shapiro-Wilk's W test. Continuous variables were presented as median inter-quartile range because of the non-normal distribution. Linear association between two variables was assessed with Spearman Rank order correlation.

Results

Mean age of the patients was 26.3[12.1;54.2] months. Most part (59.4%) of the them was children of early age. Only 34.4% (n=146) of patients reported one or two causative products, other 63% - reported allergy to variety of food. Average duration of the disease was 15[3.5;35] months. 9.4% of patients (n=28) reported that FH symptoms on the skin debuted during the 1st month of age, 51% - after 1 year of age.

Skin prick-test was positive in 18% of patients (n=53/290). Oral challenge test – in 37% (n=128). In 72% of them cow milk was detected as causative product.

According to the protocol all children underwent measurement of the relative humidity of the skin barrier which corresponds to the level of the TEWL. Results showed that 67.5% of patients had humidity level less than 35%. Mean humidity level in the locuses of inflammation was 26.5%[20.8;39.4]. TEWL was significantly less on the unaffected areas (mean humidity 37.85%[32.59;48.35]) (p<0.05). Quartile range in both places of the measurement had levels less than normal (33%). This fact indicated that TEWL should be corrected in patients with FH. This was supported by correlation data. Humidity level on the affected areas strongly correlated with TEWL on the visually healthy parts (r=0.73, p<0.05).

It was detected that level of the humidity was minimal in patients with localization of the skin elements on the cheeks, maximal – on the back (Table 1).

Table 1.
Humidity of the skin in the different locuses of the skin elements
in children with FH symptoms

Areas	Humidity of the skin, Me[Q ₂₅ ;Q ₇₅]
cheek	29.5[20;38.1]
knee fold	32.2[28.6;38]
abdomen	33[28.1;40]
cubital fold	34.4[30;40.2]
neck	37[34;42]
spine	36.5[30.8;45.5]*

* - $p < 0,05$.

It was found that the less was age of the patient the less was humidity level of the skin. The highest difference (Δ) between TEWL level on the areas of the inflammation and on the visually healthy skin was in children of early age (Fig. 1).

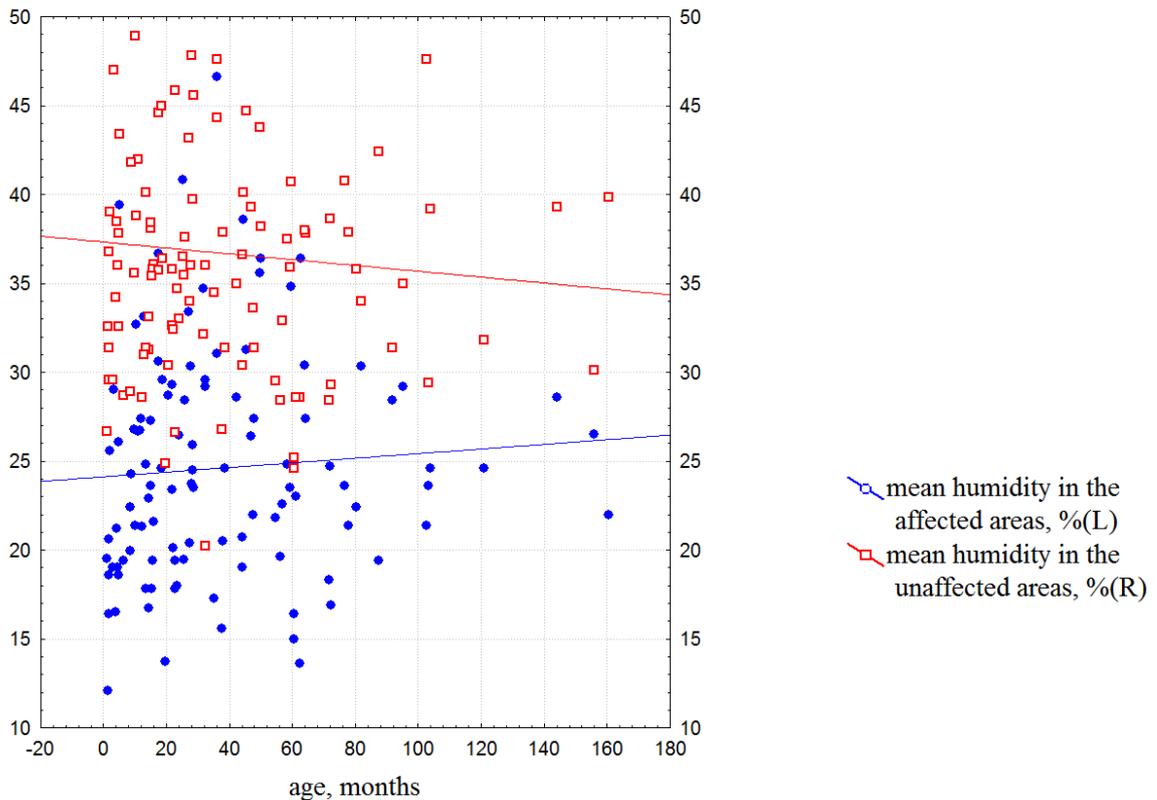


Figure 1. Humidity level of the skin in the areas of the inflammation and on the visually healthy skin depending on age.

Correlative analysis revealed link between TEWL in the affected areas and debut of the first FH symptoms before 1 month of age ($r=0.33$, $p<0.05$). But there was no correlation with duration of the disease and onset of the clinical symptoms after 1 months of age (Table 2).

Table 2.
Coefficients of the paired correlation between humidity level of the skin and features of the course of the FH symptoms

Anamnesis data	Parameter	Humidity level of the skin	
		in the areas of the inflammation	in the areas of the visually healthy skin
Duration of the disease		0.04	-0.03
First symptoms debut before 1 month of age		0.33*	0.27
First symptoms debut before 6 months of age		0.04	0.03
First symptoms debut before 12 months of age		0.03	0.1
First symptoms debut after 12 months of age		0.1	0.08

*- $p<0.05$.

Mean serum IL-2 level was 9.9 [6.7;16] pg/ml, IL-4 – 4.1 [1.6;18] pg/ml and TLR-2 – 0.154 [0.098;0.19] ng/ml. Further analysis showed no correlation between humidity level of the skin in children with symptoms of FH and IL-2, IL-4 and TLR-2 serum levels, results of the skin prick-test, OCT ($p>0.05$) (Table 3).

Table 3.
Coefficients of the paired correlation between Humidity level of the skin and cytokines levels, skin prick-test, OCT

Biomarker	Parameter	Humidity level of the skin	
		in the areas of the inflammation	in the areas of the visually healthy skin
IL-2		-0,28*	-0,29*
IL-4		-0,21	-0,23
TLR-2		-0,07	-0,21
Positive skin prick-test		0,08	-0,06
Positive oral challenge test		-0,04	-0,06

* - $p<0,05$.

Discussion and further perspectives. Literature review showed that basing on the clinical evidences therapeutic strategy in patients with FH has been confronted

with a paradigm shift from just avoidance allergenic foods to complex approaches aimed on the as immune as nonimmune mechanisms [8]. Retained results of the measurement of the relative humidity of the skin in children with FH clinical symptoms in this study showed that mean humidity level in the affected areas was decreased 26.5% [20.8;39.4] and in most part (67.5%) of the patients it was less than 35%. This underlines that FH should be considered not only as the simple reaction to the food consumption. This gives evidences that impaired barrier have principle role in this pathology. It was found in this research that the less was age of the patient the less was humidity level of the skin and the more was difference (Δ) between TEWL in the affected and unaffected areas of the skin. These facts correlate with the results of the studies of the epithelial cell-derived cytokines (thymic stromal lymphopoietin (TSLP), IL-33, IL-25) which may drive the progression from atopic dermatitis to asthma and food allergy [3]. In contrast in our study disturbances in skin barrier function did not have any link with serum IL-2, IL-4, TLR-2 and had no correlation with standard tests (skin prick- and oral challenge test), which are usually used for immune FH diagnostics. This finding reflects further diagnostic value of this simple test in determining of the therapeutic targets independently from the main standard tests which can be done before Th-2 polarization. As it was demonstrated by Kelleher M. et al. (2016), impairment of skin barrier function at birth and at 2 months precedes clinical AD. They supposed that TEWL is an important mechanism of the pathogenesis as it have implications for the optimal timing of interventions [6]. Our data supported that hypothesis as it was proved that humidity level on the affected areas strongly correlated with TEWL on the unaffected parts ($r=0.73$, $p<0.05$). And TEWL was linked with debut of the first FH symptoms before 1 month of age ($r=0.33$, $p<0.05$) In this regard, such interventions should be provided not only in the affected areas, but on the whole surface of the skin. Time of the start of the treatment approaches should be considered not only in relation to the age of the debut of the FH symptoms. But also in relation to the age of the patient.

Conclusions

Children with skin symptoms of the FH have epidermal barrier dysfunction which was demonstrated by decreased relative humidity of the skin. Transepidermal water loss which can be measured with relative humidity level is the earliest independent marker of the impairment of the skin barrier in children with clinical symptoms of the food hypersensitivity. Correction of the TEWL should be provided as in the affected as in the unaffected areas.

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Ethical Declaration: The study was approved by the local ethics committee of State Medical University, Zaporozhye, Ukraine. And this study was carried out in conformity with the Declaration of Helsinki.

Conflict of Interest: The author declares no conflict of interest.

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