アトピー性皮膚炎の発症率が低かったものの、10歳の時点ではアトピー性皮膚炎、気管支喘息、アレルギー性鼻炎の発症率、食物抗原特異IgE抗体やプリックテストの結果に有意差はなくなり、長期的に食物アレルギーの発症を予防する効果は認められなかったという報告もある[9]。現在のアメリカ小児科学会からの指針（後述）ではアレルギー発症リスクの高い児に対して母乳栄養を行っている場合、母親がピーナッツやナッツ類を除去することを推奨している[10]。しかし最近のアメリカでの研究ではピーナッツアレルギーになった児の母親とならなかった児の母親のピーナッツの摂取に差異がなく、母乳栄養とピーナッツアレルギーとの間に関連が認められなかった[11]。先にあげたMuraroらのメタ解析や最近のCochrane reviewでも授乳中の母親の食物制限により食物アレルギーの発症が予防されることはないと結論している[6,12]。授乳中の母親の食物除去は、身体的、精神的また経済的負担を強いるものであるため、本当に食物除去が必要と考えられる対象に限って、栄養バランスなどに気を配りながら慎重に行うべきものである。母親が自らの判断で妊娠中・授乳中に食物除去を行っている場合には、食物除去を行うことにより栄養素の不足が生じ、妊婦の体重増加不良や胎児および出生後の児の成長障害をきたす可能性についても説明する必要がある。

3. 現時点でのアレルギー予防のための乳児栄養についての指針

表1に欧米と日本における食物アレルギーの予防のための乳児栄養指針を示す。アメリカの予防指針では、ピーナッツやナッツ類の除去を勧めている点が若干欧州の指針と異なるが、基本的にはいずれにおいても、「妊娠中・授乳期の食事制限の効果は明かでなく食事制限は推奨しない」とされており[13,14]、日本の厚生労働科学研究班による「食物アレルギーの診療の手引き2005」および小児アレルギー学会食物アレルギー委員会による「食物アレルギー診療ガイドライン2005」においても、妊娠中・授乳中の母親の食事制限は推奨されていない[15]。食物アレルギーを発症するリスクが高いと考えられる児（アレルギーの家族歴がある、IgE値が高いなど）に関しては、低アレルゲン性ミルクの使用が考慮されるが、現時点では、食物アレルギーを含めたアレルギー疾患の発症を予防する方策として母親に食事制限を勧める根拠はないとされている。

表1　現在の欧米と我が国でのアレルギー発症予防のための乳児栄養指針

		AAP, 2000	ESPACI/ESPGHAN, 1999	食物アレルギーの診療の手引き 2005
ハイリスク児の定義		両親・同胞に2人以上のアレルギー疾患	両親・同胞に1人以上のアレルギー疾患	両親・同胞に食物アレルギー
ハイリスク児に対して	母親の妊娠中の食物抗原除去	ピーナッツ以外は推奨しない	推奨しない	推奨しない（偏食はしない）
	母親の授乳中の食物抗原除去	ピーナッツ・ナッツ類除去（卵・牛乳・魚も考慮）	推奨しない	推奨しない（偏食はしない）
	乳児期の加水分解乳	推奨する	推奨する	医師の指導の下推奨する

AAP：American Academy of Pediatrics
EPACI：European Society for Pediatric Allergology and Clinical Immunology
ESPGHAN：European Society for Pediatric Gatstroenterology, Hepatology, and Nutrition
Zeiger RS, Pediatrics 2003：111：1662-71.より一部抜粋改変

表２　完全母乳栄養児における食物アレルギーの臨床症状

標的臓器	症状
消化管	頻回の逆流・嘔吐
	下痢・便秘
	血便
	鉄欠乏性貧血
皮膚	アトピー性皮膚炎
	じんま疹
呼吸器	鼻汁
	慢性咳嗽
	喘鳴
全身症状	不機嫌・元気がない

表３　母乳中に存在するアレルギー促進および防御因子

物質の種類	促進因子	防御因子
食物抗原	感作抗原	寛容誘導抗原
免疫グロブリン		IgA
サイトカインなど	IL-4、IL-5、IL-13	TGF-β、IL-10、sCD14
ケモカイン	RANTES、IL-8	
好酸球由来顆粒	ECP	
不飽和脂肪酸	n-6系	n-3系
ポリアミン		スペルミン、スペルミジン

4. 経母乳感作によるアレルギーの発症と治療

わが国の乳児の食物アレルギーの有病率は５～10%程度であり、その多くがアトピー性皮膚炎を合併している[16]。逆にアトピー性皮膚炎を有する乳児ではアトピー性皮膚炎のない乳児に比べて、牛乳アレルギーの発症率が４倍、卵アレルギーの発症率が８倍高いという[16]。したがって完全母乳栄養である乳児にアトピー性皮膚炎があるときには食物アレルギーが合併している可能性が高い。Vandenplas らがまとめた完全母乳栄養における食物アレルギーの臨床症状を**表２**に示す[17]。この表には記載されていないが完全母乳栄養でも重症のアトピー性皮膚炎を呈することは決してまれではない。確定診断は母親の摂取している食事からの当該食物の除去と負荷によって行い、陽性と判断された場合には母親の除去を行い母乳栄養を継続する。これによっても症状が軽快しない場合には牛乳アレルギー用の加水分解乳等による栄養に切り替えることが必要なこともある。従来から母乳中には直接摂取した食物の10万分の１程度の微量が検出されることが知られており、母乳を介して児が曝露する食物抗原量はきわめて少ないため症状はほとんどが非即時型であり、母乳中の食物アレルゲン曝露により全身性の即時型アレルギー反応が惹起されることはきわめてまれとされていた。しかし最近われわれは母親が生の魚を摂取した後にあげた母乳により児に全身性の蕁麻疹や嘔吐が誘発されたケースを経験した。本児では採血での魚類に対する RAST（radioallergosorbent test）は陰性であったが皮膚プリックテストは明らかに陽性であり、経過から母乳を介して摂取された魚による全身性即時型アレルギーと診断した。この例では母親が寿司が好きで妊娠中から出産後によく生の魚を摂取していた。他にも妊娠中にしばしばピーナッツを摂取していた母体から出生した児がピーナッツアレルギーであった例も経験している。したがって、妊娠中の食物除去はアレルギーを予防できる証拠はないものの、どんな食物であれ過剰な摂取は慎んでおいた方が食物アレルギー予防の点からはいいと筆者は考えている。

5. アレルギーと関連する母乳中の成分

母乳がアレルギーを予防する理由としては、母乳摂取により食物という異種タンパクへの曝露量が減少することの他に、母乳中に積極的にアレルギーを予防する成分が含まれることが考えられる。しかしながら経母乳感作があり得ることは、母乳中にはアレルギーの発症を抑制する物質があったとしても食物アレルゲンを含めてアレルギーの発症を促進する物質も存在することを意味する。母乳中に含まれる主なアレルギー発症の促進あるいは防御物質を**表３**に示す。母親の摂取した食物が母乳中に出現することは以前から知られている。これらの研究では母乳中に牛乳由来のタンパクであるβラクトグロブリンやカゼインなどが nanogram（10^{-9}g）単位で検出されることや、

卵や小麦のタンパクが母親の摂取後2～6時間後から4日後まで検出されることが報告されている。これらの母乳中の食物抗原は感作アレルゲンとして働く場合もあり、寛容誘導抗原として働くこともあると考えられる。またいったん感作が成立すると（特異IgE抗体が産生されること）、先に述べたように経母乳的なアレルゲン曝露によりアレルギー症状が発症、悪化することがある。母乳中には大量のIgA（免疫グロブリン）が含まれており、アレルギーの発症を抑制するとされる。IgA欠損症の患者では食物アレルギーの頻度が高いとの報告もある。胎盤を通して母体からIgGは児に輸送されるがIgAは胎盤を通過しないために児は母乳を介してIgAを受け取る。サイトカインではアレルギー反応を促進するTh2サイトカインに属するインターロイキン4（IL-4）、IL-5、IL-13などとIgA産生を促進してアレルギーを抑制するとされるtransforming growth factor beta（TGF-β）が知られている。TGF-βは免疫寛容に関わるサイトカインでもありアレルギーを発症した児の母親の母乳中のTGF-βはアレルギーにならなかった児の母親の母乳中のTGF-βよりも低値であることが報告されている。また単球などの自然免疫細胞を刺激してアレルギーを抑えるTh1反応を誘導する可溶性CD14分子も母乳に多く含まれている。アレルギー性炎症に関わる好酸球などの遊走に関わるケモカインであるRANTES（Regulated on Activation, Normal T Expressed and Secreted）やIL-8も母乳に存在する。不飽和脂肪酸にはアレルギー反応を促進するといわれるアラキドン酸の産生につながるn-6系の不飽和脂肪酸とエイコサペンタエン酸などのアレルギーを抑制するn-3系の不飽和脂肪酸が存在する。両者とも生体には必須であるがそのバランスはアレルギーの発症に関連すると考えられる。ポリアミンの一つであるspermineやspermidineは腸管粘膜細胞の透過性を低下させてアレルギーを予防する作用があることが報告されている。

6. 母乳の抗アレルギー作用を増加する食品

上記のように児のアレルギーの予防に母乳栄養が望ましいが、母乳栄養によってもアレルギーを発症してしまう児も存在する。したがって抗アレルギー作用を有する母乳が出るように母体の食生活等に気をつけることは意味があると思われる。以下に母親が摂取することで母乳の抗アレルギー作用が増加する可能性のある食品について述べる。

1）プロバイオティクス：プロバイオティクスは消化管内の細菌叢を改善し、健康に有益な作用をもたらす生きた微生物のことである。いくつかの乳酸菌は既に医薬品や食品として利用されている。妊娠中に母親に乳酸菌を摂取させると母乳中のTGF-β2濃度がプラセボ群の2倍になったことが報告されている[18]。

2）不飽和脂肪酸：不飽和脂肪酸は炎症に関わる栄養素の一つである。植物油の主成分であるリノール酸などのn-6系多価不飽和脂肪酸を摂取すると、アラキドン酸カスケードにてロイコトリエンが産生され、炎症やアレルギー反応が亢進しうる。一方、シソ油、エゴマ油などに含まれるα-リノレン酸や魚介類に含まれるエイコサペンタエン酸（EPA）やドコサヘキサエン酸（DHA）などのn-3系多価不飽和脂肪酸は、リノール酸の働きを抑え、炎症を抑制する効果を持つ。食事が欧米化し、n-6系脂肪酸の摂取量が増え、n-3系脂肪酸の摂取量が減ったことが、近年アレルギー疾患が増えている一因であるという説もある。妊娠中に魚油のサプリメントを摂取することで、臍帯血のIL-13（IgE抗体産生促進に関わる）が低下したという報告や、卵のプリックテストの陽性率が有意に低くなったという報告があるが、不飽和脂肪酸がアレルギー疾患に与える影響についてはまだ評価が定まっていない。

3）抗酸化物質：生体内で殺菌やエネルギー代謝に伴って生成される活性酸素などのフリーラジカルは、アレルギー性炎症における細胞障害や組織障害にも関わっている。そこで、フリーラジカルの活性を抑える抗酸化物質（カロテノイド、ビタ

ミンA、ビタミンC、ビタミンE、セレン、キトサン、ポリフェノール、フラボノイドなど）をアレルギー疾患の発症予防や症状の緩和に応用できる可能性があると考えられている。実際にアレルギー疾患の治療に利用できるどうかについては、今後の検討が必要である。

おわりに

母乳栄養児はアレルギー疾患の発症頻度が少ないとされ、欧米の指針では積極的に母乳栄養が勧められている。一方、わが国でのアンケート調査では母乳栄養児にアレルギーがむしろ多いとの報告が多い。また最近の海外の報告でも母乳栄養は児のアレルギー発症予防効果はないか促進的であるとの論文も見られる。母乳とアレルギーの関連を考える上でいくつか注意しなくてはならないことがある。第一に、海外で推奨されている母乳とは「完全母乳」のことであるのに対し、我が国の母親からのアンケートの「母乳栄養」の多くが出産後数日間に人工乳を与えられていることから、完全母乳には該当しないことである。第二に食生活や母体をとりまく環境は年代や地域により大きく異なることから海外でのデータや過去のデータが現在の日本に当てはまるとは考えにくいことである。今後は、わが国におけるきちんとした前方視的調査により母乳栄養とアレルギーに関する疫学調査およびアレルギー発症児と非発症児に与えられた母乳中の成分の解析などが必要と考えられる。現在までの報告を筆者なりにまとめてみると、①児が直接大量の異種タンパクに曝されることはアレルギーの発症リスクを高めることになるので、発症リスクの高い児に対して母乳以外に粉ミルクを与える場合には加水分解乳のほうが望ましい、②母乳中に出現する食物抗原はきわめて微量のため、児がアレルギーを発症していない限り母親が食物除去を行う必要はない、③アレルギー発症を予防しうる免疫調整物質の母乳中濃度がアレルギー予防には重要である、の3点となる。母乳はアレルギーの予防のみに意味があるわけではない。小児の健やかな成長に母乳にまさる栄養法はない。アレルギーの発症予防にもいい母乳のためにも科学的な検証、解析が望まれる。

文献

1. Gdalevich M, Mimouni D, David M, et al, Breast-feeding and the onset of atopic dermatitis in childhood : a systematic review and meta-analysis of prospective studies, J Am Acad Dermatol, 45(4) : 520-527, 2001
2. Laubereau B, Brockow I, Zirngibl A, et al, Effect of breast-feeding on the development of atopic dermatitis during the first 3 years of life-results from the GINI-birth cohort study, J Pediatr, 144(5) : 602-607, 2004
3. Gdalevich M, Mimouni D, Mimouni M, Breast-feeding and the risk of bronchial asthma in childhood : a systematic review with meta-analysis of prospective studies, J Pediatr, 139(2) : 261-266, 2001
4. Wright AL, Holberg CJ, Taussig LM, et al, Factors influencing the relation of infant feeding to asthma and recurrent wheeze in childhood, Thorax, 56(3) : 192-197, 2001
5. Sears MR, Greene JM, Willan AR, et al, Long-term relation between breastfeeding and development of atopy and asthma in children and young adults : a longitudinal study, Lancet, 360(9337) : 901-907, 2002
6. Muraro A, Dreborg S, Halken S, et al, Dietary prevention of allergic diseases in infants and small children, Part III : Critical review of published peer-reviewed observational and interventional studies and final recommendations, Pediatr Allergy Immunol, 15(4) : 291-307, 2004
7. Kramer MS, Kakuma R. Optimal duration of exclusive breastfeeding, Cochrane Database Syst Rev, (1) : CD003517, 2002
8. Chandra R.K, Puri S, Hamed A, Influence of maternal diet during lactation and use of formula feeds on development of atopic eczema in high risk infants, BMJ, 299(6693) : 228-230, 1989
9. Hattevig G, Sigurs N, Kjellman B, Effect of maternal dietary avoidance during lactation on allergy in children at 10 years of age, Acta Paediatr, 88(1) : 7-12, 1999
10. American Academy of Pediatrics, Committee on Nutrition, Hypoallergenic infant formulas, Pediatrics, 106(2Pt1) : 346-349, 2000

11. Lack G, Fox D, Northstone K, Golding J, Avon Longitudinal Study of Parents and Children Study Team, Factors associated with the development of peanut allergy in childhood, N Engl J Med, 348(11)：977-985, 2003
12. Kramer MS, Kakuma R, Maternal dietary antigen avoidance during pregnancy and/or lactation for preventing or treating atopic disease in the child, Cochrane Database Syst Rev, (4)：CD000133, 2003
13. Friedman NJ, Zeiger RS, Prevention and natural history of food allergy, In：Leung DYM, Sampson HA, Geha RS, Szafler SJ, eds, Pediatr allergy, principles and practice, St. Louis：Mosby, 496, 2003
14. Zeiger RS, Food allergen avoidance in the prevention of food allergy in infants and children, Pediatrics, 111(6Pt3)：1662-1671, 2003
15. 海老澤元宏他『厚生労働省科学研究班による食物アレルギー診療の手引き』2005
16. Schoetzau A, Filipiak-Pittroff B, Franke K, et al, German Infant Nutritional Intervention Study Group, Effect of exclusive breast-feeding and early solid food avoidance on the incidence of atopic dermatitis in high-risk infants at 1 year of age, Pediatr Allergy Immunol, 13(4)：234-242, 2002
17. Vandenplas Y, Koletzko S, Isolauri E, et al, Guidelines for the diagnosis and management of cow's milk protein allergy in infants, Arch Dis Child, 92(10)：902-908, 2007
18. Rautava S, Kaaliomaki M, Isolauri E, Probiotics during pregnancy and breast-feeding might confer immunomodulatory protection against atopic desease in the infant, J Allergy Clin Immunol, 109(1)：119-121, 2002

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TABLE 1. *Number of Community Visits Performed by the Pediatric Dermatology Nurse Specialist (PDNS) (home, school, GP)*

	Eczema	Psoriasis	Allergy	Other conditions	Total number of patients
Home visits	54	0	8	7	69
School/ nursery visits	3	0	6	0	9
GP visits	1	0	0	0	1
n	58	0	14	7	79

TABLE 2. *Table Demonstrating Liaison Work (telephone calls/letters) Performed by Pediatric Dermatology Nurse Specialist (PDNS)*

Method of correspondence	Parents	School nurses/ teachers	Health professionals	Social services/ agencies	Total number
Telephone calls	19	13	17	4	53
Letters	3	4	2	9	18
Total	22	17	19	13	71

clinic availability, more aggressive treatment modalities, and less availability of dermatology beds could also contribute to this finding. Despite the numbers of doctors in clinic remaining unchanged in the 2 years recorded new patient reviews in the outpatient clinic in 2005 to 2006 increased by 70%, most likely due to the PDNS seeing almost 1/3 of the follow up patients in this year. There were no other changes in clinic operations that could account for this change.

It is widely accepted that family quality of life and disease severity in atopic children is directly related (4) and it is imperative therefore that care of patients with eczema include consideration of the whole family. Home visits therefore remain an essential part of our PDNS's role ($n = 54$).

In conclusion, we accept that we have not performed cost analyses and have only examined 12 months of the PDNS's work. We also appreciate that the actions of one individual may not be mirrored by others. However, we do feel we have shown that the PDNS is an integral part of the dermatology team and must remain supported.

REFERENCES

1. Jones S. The development of the paediatric nurse specialist. Br J Nurs 1995;4:34–36.
2. Gradwell C, Thomas KS, English JS et al. A randomised controlled trial of nurse follow up clinics: do they help patients and do they free up consultants time. Br J Dermatol 2002;147:513–517.
3. Cork MJ, Britton J, Butler L et al. Comparison of parent knowledge, therapy utilisation and severity of atopic eczema before and after explanation of topical therapies by a specialist dermatology nurse. Br J Dermatol 2003;149:582–589.
4. Ben Gashir MA, Seed PT, Hay RJ. Are quality of family life and disease severity related in childhood atopic dermatitis. J Eur Acad Dermatol Venereol 2002;16:455–462.

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EFFECTS OF SKIN CARE WITH SHOWER THERAPY ON CHILDREN WITH ATOPIC DERMATITIS IN ELEMENTARY SCHOOLS

Abstract: **For elementary school children with atopic dermatitis, a skin care program using shower therapy was performed during the school lunch break for 6 weeks from June to July in 2004 and 2005. All 53 participants showed an improvement in their atopic dermatitis during the 6-week periods. Skin care with daily showering at an elementary school was thus found to be effective for the treatment of atopic dermatitis.**

Atopic dermatitis in elementary school children may often be difficult to control with standard therapy. Skin itching may be exacerbated by sweat, sand, and dust induced by physical education and games during a normal school day (1), which can exacerbate dermatitis. We examined the effects of a skin care regimen using showers with plain water in the early summer season, a time when heat and perspiration are believed to aggravate dermatitis.

Skin care with shower therapy was performed during school lunch breaks for 6-week periods from June to July in 2004 and 2005, and evaluations of skin lesions was performed every 2 weeks by nurse-teachers (school nurses). Fifty-four children in seven elementary schools in Gunma prefecture, Japan, participated in this study. No other on-going atopic dermatitis therapies were modified during the study period. Observations of patient's parents and nurse-teachers were recorded after the conclusion of the study period.

When shower therapy was used, no soap or shampoos were used, and topical treatments were used after the shower. We evaluated the effect of the shower therapy by observing changes in skin lesions, using the

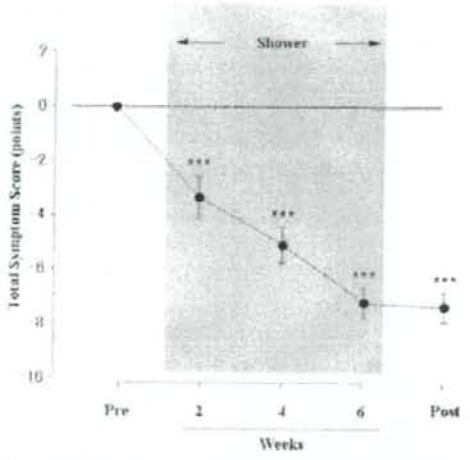

Figure 1. Changes in atopic dermatitis symptom score during the 2-year study period.

TABLE 1. *Parental Comments in 53 Patients*

Skin lesion	Marked improvement	9 (17%)
	Improvement	39 (74%)
	No change	5 (9%)
	Aggravation	0 (0%)
	Marked aggravation	0 (0%)
Itching	Marked improvement	8 (15%)
	Improvement	39 (74%)
	No change	6 (11%)
	Aggravation	0 (0%)
	Marked aggravatin	0 (0%)
Clinical impression*	Improvement of itching	19 (36%)
	Marked decrease of scratch	11 (21%)
	Marked decrease of irritancy	6 (11%)
	Volition to skin care	5 (9%)
	Good sleep	3 (6%)
	Decrease of medicine	2 (4%)
	Others or no answer	7 (13%)
Free comments*	Hope to continue shower bath	34 (64%)
	Marked improvement	9 (17%)
	Thanks to teachers	4 (8%)
	Hope to spread shower bath	3 (6%)
	Others or no answer	3 (6%)

*Almost parents replied a single answer in clinical impression and free comments.

atopic dermatitis symptom score (2). The body was divided into 25-block units and each block unit scored with a zero to two point scale: erosion or strongly scratched eczema; 2 points, normal skin; 0 points, and between these extremes, 1 point. Five phases of change over time were recorded: marked aggravation, aggravation, no change, improved, and markedly improved. Evaluations were performed every 2 weeks by the nurse-teachers who directed the skin care with shower and by the patient's parents when the study finished. A parametric analysis of variance (ANOVA) was performed to assess any differences in the symptom scores between the groups.

During this study, 53 of the 54 patients were given showers for 6 weeks. Each individual patient demonstrated a significant improvement of their skin lesion. In this study, we did not check the amount of medication used, because we explained to the parents that "other on-going therapies should not be changed during this examination" at the starting point. However, two parents in fact did decrease the medication because of an improvement in the skin lesions, and we did not delete these data. The clinical symptom score gradually decreased every 2 weeks, and reaching a minimum at 6 weeks for both years. The summarized data of the first and the second years are shown in the Fig. 1, thus illustrating a significant decrease in the symptom score from the base line during the shower therapy study at 2, 4, 6 weeks in comparison with the score in pretreatment ($p < 0.05$, $p < 0.01$, $p < 0.001$, respectively). Many parents reported that they wanted to continue the shower therapy in the elementary schools (Table 1), and nurse-teachers in seven elementary schools also reported that the shower therapy had a positive effect on the treatment of atopic dermatitis in the elementary schools.

Guidelines, which have been published for its effective management of atopic dermatitis (3,4), indicate that basic therapy includes the avoidance of triggering factors and conducting appropriate skin care. However, there are no evidence-based reports that demonstrate a significant effect of skin care and a practical method of skin care that can be administered in elementary school. This study confirmed that skin care using shower therapy during the normal elementary school day appears to be an effective and useful treatment for atopic dermatitis. For the continuing treatment of atopic dermatitis in elementary school children, routine skin care using showers should be considered.

REFERENCES

1. Leung DY. Atopic dermatitis: The skin as a window into the pathogenesis of chronic allergic diseases. J Allergy Clin Immunol 1995;96:302–318.
2. Endo K, Fukuzumi T, Adachi J et al. Effect of vacuum cleaning of room floors and bed clothes of patients on house dust mites counts and clinical scores of atopic dermatitis, A double blind control trial. Jpn J Allergol (in Japanese) 1997;46:1013–1024.
3. American Academy of Dermatology. Guidelines of care for atopic dermatitis. J Am Acad Dermatol 1992;26:485–488.
4. Yamamoto S. A Guideline for the treatment of atopic dermatitis. Jpn J Clin Exp Med 2002;79:211–213 (in Japanese).

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CONGENITAL HEMANGIOMA: A REPORT OF EVOLUTION FROM RAPIDLY INVOLUTING TO NONINVOLUTING CONGENITAL HEMANGIOMA WITH ABERRANT MONGOLIAN SPOTS

Abstract: Congenital hemangiomas are unusual vascular tumors that are fully developed at the time of delivery. We report a case of an infant with an exophytic congenital hemangioma with features of a rapidly involuting hemangioma on the arm which over 3 years decreased in volume but continued to persist with features of a noninvoluting congenital hemangioma. He also had aberrant, persistent Mongolian spots on both legs. To our knowledge, this association has not been reported to date.

Congenital hemangiomas are rare vascular tumors that are fully formed at birth without accelerated postnatal growth (1). Two forms of congenital hemangiomas have been described: rapidly involuting congenital hemangioma (RICH) and noninvoluting congenital hemangioma (NICH). Mongolian spots (a form of dermal melanocytosis) are most frequently located in the sacral region. Aberrant Mongolian spots refer to the presence of these lesions in extrasacral locations. We report a case of a congenital hemangioma evolving from features of RICH to NICH in association with aberrant Mongolian spots.

CASE REPORT

A 6-day-old white male infant was referred for evaluation of a congenital nodule. On examination, a well defined 35 × 30 × 10 mm nodular lesion involving his left cubital fossa was noted. It had a purple tinge with coarse telangiectasias on the surface and no thrill was palpable (Fig. 1A). Doppler ultrasonography demonstrated a fast-flow hypoechoic vascular mass with arterio-venous microshunts. A diagnosis of congenital hemangioma was suspected. Echocardiogram showed no abnormalities and platelet count was within normal limits. He was also noted to have extensive greyish-blue hyperpigmentations on the lateral aspect of his legs consistent with aberrantly-located Mongolian spots (Fig. 2). Over time, slow and progressive decrease in the vascular mass was observed, but at 34 months of age the lesion still persisted as a nearly flat pale pink plaque, with peripheral blanched halo and telangiectasias (Fig. 1B). The areas of aberrant Mongolian spots had faded but were persistent.

DISCUSSION

Congenital hemangiomas are much less common than infantile hemangiomas. They present as raised violaceous tumors with large radial veins, hemispheric tumors with multiple tiny telangiectasias and a pale rim, or pink-to-violaceous tumors firm to palpation (2), and with both Doppler and angiographic examination are noted be high-flow vascular masses. On angiography, large and irregular feeding arteries, arterial aneurysms and direct

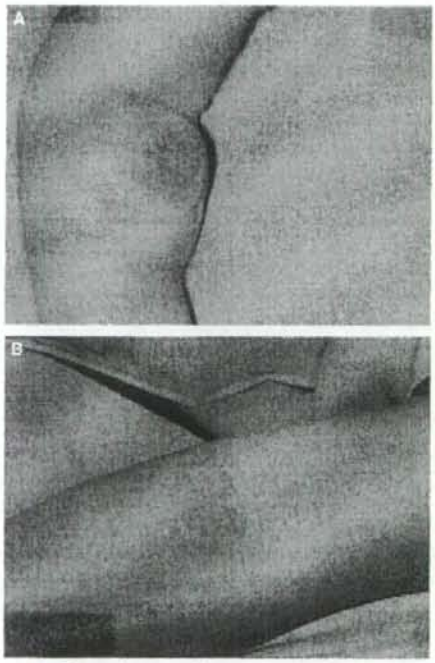

Figure 1. Bossed tumor with coarse telangientasias on the cubital fossa at birth (**A**), flattened plaque with fine telangiectasias at 34 months of age (**B**).

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Evaluation of out–in skin transparency using a colorimeter and food dye in patients with atopic dermatitis

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Conflicts of interest
None declared.

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Summary

Background Atopic dermatitis is a disease of skin barrier dysfunction and outside stimuli can cross the skin barrier.

Objectives To examine a new method for evaluating the outside to inside skin transparency with a colorimeter and yellow dyes.

Methods In study 1, a total of 28 volunteer subjects (24 normal and four with atopic dermatitis) participated. After provocation with yellow dye, the skin colour of all the subjects was measured using a colorimeter. The skin transparency index was calculated by the changes of the skin colour to yellow. Other variables of skin function, including transepidermal water loss (TEWL) and stratum corneum hydration, were also measured. In study 2, the skin transparency index was evaluated for a cohort of 38 patients with atopic dermatitis, 27 subjects with dry skin and 29 healthy controls.

Results In study 1, the measurement of skin colour (b*) using tartrazine showed good results. There was a significant relationship between the skin transparency index with tartrazine and the atopic dermatitis score ($P = 0{\cdot}014$). No other measurements of skin function, including the TEWL, were correlated. In study 2, the skin transparency index score obtained with tartrazine in the patients with atopic dermatitis was significantly higher than that of the controls and those with dry skin ($P < 0{\cdot}001$ and $P = 0{\cdot}022$, respectively). However, the TEWL in patients with atopic dermatitis was not significantly higher than that of patients with dry skin and the TEWL in subjects with dry skin was not higher than that of the controls.

Conclusions This method, which used a colorimeter and food dye, is noninvasive, safe and reliable for the evaluation of out–in skin transparency and can demonstrate the characteristic dysfunction in the skin barrier in patients with atopic dermatitis.

Atopic dermatitis is a common chronic inflammatory skin disease in children.[1,2] Recent studies suggest that the prevalence of atopic dermatitis is increasing in many countries, as is the prevalence of other allergic diseases.[3] Atopic dermatitis commonly begins in infancy or early childhood and patients experience discomfort caused by continuous itching, which induces more scratching and more itching in a vicious circle. The symptoms of itching, scratching and sleeplessness can place a burden on the whole family.

There have been many reports concerning skin dysfunction in atopic dermatitis. Recently a number of reviews have addressed the origin of atopic dermatitis using genetic analysis.[4,5] The impaired barrier function of the stratum corneum in atopic dermatitis has been found to result from the decreased production of ceramides[6] and filaggrin.[7] Barrier dysfunction induces water loss in the skin and dry skin is a characteristic of atopic dermatitis.

The most common causes of skin itching and exacerbation are sweat and the microparticles of sand and dust that individuals are exposed to in everyday life.[8,9] In atopic dermatitis, the dysfunction of the stratum corneum seems to be associated with an increased permeability and penetration of environmental irritants and allergens.[10] Stimuli such as sweat and microparticles of sand and dust easily enter into the skin in patients with atopic dermatitis. A reliable evaluation of skin transparency from the outside to the inside of the skin could

indicate an effective strategy for each patient. However, there are few simple, noninvasive methods for objectively evaluating skin transparency.[11]

The tristimulus photocolorimeter is an instrument for measuring changes in colour by expressing the colour numerically in the L*a*b* colour space, which is the standard of the Commission Internationale de l'Eclairage (CIE) for colour assessment.[11] The CIE L*a*b* colour space can be transformed into other well-known colour systems such as the CIE RGB (red, green, blue) colour space. The system provides an unambiguous description of three coordinates, L*, a* and b*. These indicate the total quantity of lightness or darkness, with the colour ranging from red (positive value) to green (negative value) and from blue (negative value) to yellow (positive value), respectively.[12]

The increased out–in transparency of the skin in atopic dermatitis might induce a continuous transport of outside stimuli across the stratum corneum, resulting in persistent itching and exacerbation of the dermatitis. For a precise evaluation of skin dysfunction a new, simple method of out–in skin transparency measurement using a colorimeter and yellow dye was evaluated.

Patients and methods

Patients

Study 1 was a preliminary trial. Twenty-eight subjects, including 24 normal volunteers who had no skin diseases and no atopic diseases (mean age 19·0 years; male to female ratio 1 : 3) and four patients with atopic dermatitis (mean age 22·6 years, male to female ratio 12 : 12) participated (Table 1).

In study 2, 42 patients with atopic dermatitis (mean age 10·6 years, male to female ratio 19 : 23), 27 patients with dry skin (mean age 18·4 years, male to female ratio 10 : 17) and 26 normal volunteers (mean age 22·3 years, male to female ratio 12 : 14) participated (Table 1). Atopic dermatitis was diagnosed according to the duration, itching and specific skin lesions.[14] The simple atopic dermatitis symptom score (AD score) was used for the evaluation of the severity of atopic dermatitis. The whole body was divided into 25 sections and each section was scored as follows: erosion and heavily scratched eczema, 2; normal skin, 0; and intermediate, 1. Dry skin was diagnosed as dry skin without a typical atopic dermatitis lesion.

Table 1 Profiles of subjects in studies 1 and 2

	n	M/F	Age (years), mean ± SD
Study 1	28		
Atopic dermatitis	4	1/3	19·0 ± 0·0
Controls	24	12/12	22·6 ± 7·7
Study 2	95		
Atopic dermatitis	42	19/23	10·6 ± 9·3
Dry skin	27	10/17	18·4 ± 14·6
Controls	26	12/14	17·3 ± 8·4

Methods

Measurement of physiological skin functions, stratum corneum hydration and transepidermal water loss

Hydration of the stratum corneum was measured on the flexor aspect of the forearm near the cubital fossa more than 1 h after the patient arrived at the hospital. All tests were performed in a special patients' room with a controlled environment, with the room temperature ranging from 22 to 24 °C and a humidity of 50–60%. Skin temperature remained stable during the examination for all subjects. Stratum corneum hydration was measured using a moisture meter (ASA-M1; Asahi Biomed, Tokyo, Japan),[15] based on capacitance and electrical conductance determined at two different frequencies (160 and 143 kHz) with two concentric surface electrodes. The probe was pressed on to the skin surface for 1–2 s. Each measurement was obtained twice at the same site; the data were rejected when children were crying or visibly sweating.[15] The measurements obtained included the moisture content of the skin surface and the moisture content of the stratum corneum.

All water loss measurements were obtained using the DermaLab modular system with transepidermal water loss (TEWL) probes, which were manufactured by Cortex Technology (Hadsund, Denmark). The TEWL probes contain two sensors that measure the temperature and relative humidity at two fixed points along the axis normal to the skin surface, which allows the device to derive a value electronically corresponding to the evaporative water loss expressed in gram per metre per hour.

The data from the DermaLab modular system were completely computerized and continuously transferred to a personal computer through a serial port using an RS-232C cable and the associated cyber Derm, Inc. software program for the evaporimeters. The application program C1BASIX1 was used to capture the water loss data from the attached evaporimeter at a sampling rate of four inputs per second. These inputs were displayed as graphs in real time on the computer monitor. The extracted value indicated the average rate of evaporative water loss collected over a 20-s interval once steady-state conditions were achieved. The values were directly transferred to an Excel file using a dynamic data exchange (DDE) link. The probe was placed lightly on the skin of the forehand for 1–2 min[16] and the water loss values were electronically recorded using a spreadsheet format based on the Excel software program.

Measurement of out–in skin transparency

The relationship between skin colour and skin transparency was evaluated by using an objective method. A tristimulus

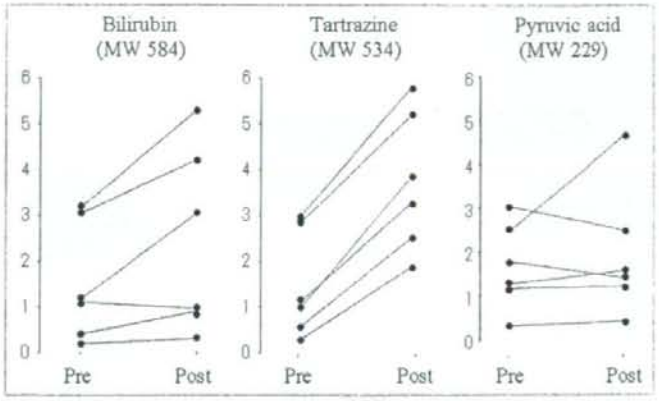

Fig 1. Changes in b* values (using the standard CIE L*a*b* system) measured with a colorimeter.

photocolorimeter model CR-400 (Konica Minolta, Osaka, Japan)[13,17] was used to measure objectively the skin colour of the subjects (Fig. 1). This instrument records colours in a three-dimensional space known as the CIE 1976 L*a*b* colour space developed from the CIE XYZ system.[13,17] The values of L*, a* and b* ranged from 0·0 for black to 100·0 for a diffuse white, from −60 for green to +60 for red and from −60 for blue to +60 for yellow, respectively.[13] This colour system and the CIE RGB system are interacting.[13,17] The standard D65 illumination and 2° angle supplementary standard observer were used.

With this instrument the skin surface is illuminated by a pulsed xenon arc lamp. The light that is reflected perpendicular to the surface is collected for a tristimulus colour analysis, using the L*a*b* colour system.

The skin area for the measurement is 11 mm in diameter (95 mm^2 surface area). The probe is applied to the skin surface of the forearm. To measure the skin colour under the same conditions, the room temperature was kept between 24 and 26 °C.

Study design

In study 1, the time course of the L*, a* and b* values, the selection of dyes and reproducibility of the method were evaluated.

To investigate whether L*, a* and b* values changed with time, they were measured after 5, 10, 15 and 30 min of provocation. The hydrophilic yellow dyes tartrazine ($C_{16}H_9N_4Na_3O_9S_2$, MW 534), bilirubin ($C_{33}H_{36}N_4O_6$, MW 585) and pyruvic acid (2,4,6-trinitrophenol, $C_6H_3N_3O_7$, MW 229) were selected for testing. The dyes were dissolved in saline; all dye solutions were prepared on each trial day. To examine the reliability of the measurement of L*, a* and b*, one doctor measured them in the same subjects twice at an interval of 1 min. To examine the validity of the measurements of L*, a* and b*, two doctors measured them in the same subjects with an interval of 1 min.[18]

In study 2, the relationship between the common skin measurements and the skin transparency index, and the skin transparency index with tartrazine and the TEWL were evaluated in controls, subjects with dry skin and patients with atopic dermatitis.

Data analysis

The intraobserver and interobserver reproducibility of measurements (reliability and validity, respectively) were evaluated using the Bland–Altman method and the correlation coefficient. A correlation coefficient of 0·75 was considered as a minimal requirement for the reproducibility of the results. Chronological changes of L*, a* and b* were evaluated by means of Student's *t*-test or a two-way analysis of variance. Correlations between the colorimetric values and the common skin measurements were calculated by a linear regression analysis using Pearson's correlation coefficients. SPSS for Windows release 11.01J (SPSS, Chicago, IL, U.S.A.) was used for the statistical analysis. A parametric analysis of variance was performed to assess any differences in symptom scores between the groups. The data are expressed as the means ± SD. A *P*-value < 0·05 was considered to indicate a significant difference.

Results

Study 1

Time course of L*, a* and b* values

Fifty microlitres of tartrazine, bilirubin or pyruvic acid solution was applied to a small water-proofed cotton patch (5 × 5 mm) just before attachment to the skin. The L*, a* and b* values changed after provocation with the dyes (n = 6, data not shown). For each dye, the values of b*, which indicates the yellow colour, levelled after 15–30 min of provocation. None of the dyes produced any

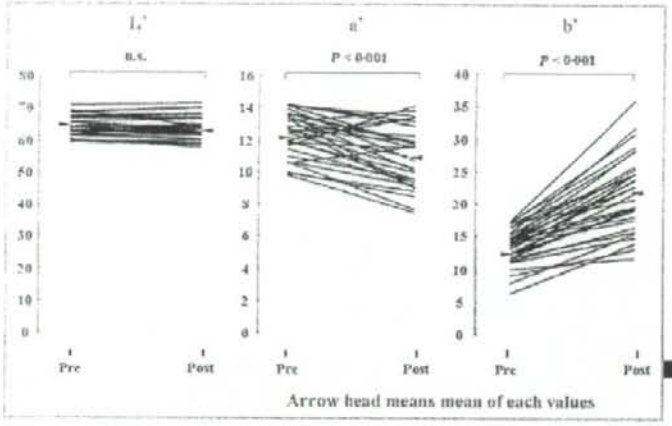

Fig 2. Changes in L*, a*, b* values (using the standard CIE L*a*b* system) after provocation of the skin with tartrazine.

side-effects during a 30-min skin provocation or after the trial. The reliable provocation time was determined to be 30 min.

Selection of dyes

In the measurement of the out–in skin transparency using tartrazine, bilirubin and pyruvic acid (each 10 mg mL^{-1}, 30 min provocation), bilirubin and pyruvic acid demonstrated unreliable data ($P < 0{\cdot}01$, $n = 6$) (Fig. 1). In all study 1 patients, b* values significantly increased after provocation with tartrazine and the dye showed good penetration into the skin ($n = 28$, $P < 0{\cdot}001$) (Fig. 2). Therefore, the food dye tartrazine was chosen for this study.

Measurement of out–in skin transparency

The intraobserver correlation coefficient for b* was 0·97, implying small variations within and between observers (Table 2). The repeatability coefficients for intra- and interobservers for b* were 1·47 and 1·63, respectively. Using the Bland–Altman method, the difference in b* values showed a small variation for both intra- and interobservers (Fig. 3).

Study 2

Relationship between common skin measurements and skin transparency index

An examination of the relationship between the common skin measurements and the skin transparency index was carried out in 42 subjects. The skin transparency index using tartrazine showed a good correlation with the AD score ($P = 0{\cdot}001$, Table 3, Fig. 4). However, other common skin measurements did not show a relationship with the skin transparency index using tartrazine (Table 3). The moisture content of the skin surface and the stratum corneum significantly correlated ($P < 0{\cdot}001$, Table 3).

Table 2 Intra- and interobserver variation of skin transparency with tartrazine

Method*		SDD	RC	CC
L*	Intraobserver	0·92	2·55	0·94
	Interobserver	0·94	2·59	0·94
a*	Intraobserver	0·87	2·40	0·85
	Interobserver	0·95	2·62	0·77
b*	Intraobserver	0·53	1·47	0·97
	Interobserver	0·59	1·63	0·97

SDD, standard deviation of the difference between the first and second measurements by the same observer (intraobserver) and those by different observers (interobserver); RC, repeatability coefficient (the 95% confidence limit of difference); CC, correlation coefficient.
*Using the standard CIE L*a*b* system.

Skin transparency index with tartrazine and transepidermal water loss in controls and patients with dry skin or atopic dermatitis

The differences in these variables were examined between patients with atopic dermatitis, subjects with dry skin and the controls. The skin transparency index using tartrazine in patients with atopic dermatitis was significantly higher than in controls ($P < 0{\cdot}001$, Fig. 5). In addition, the skin transparency index in patients with atopic dermatitis was significantly higher than in patients with dry skin ($P < 0{\cdot}022$, Fig. 5). However, the TEWL in the patients with atopic dermatitis was not higher than that of those with dry skin and the TEWL in subjects with dry skin was not higher than that of controls (Fig. 6). There were no significant differences between patients with atopic dermatitis, dry skin and controls in the moisture content of the skin surface and the stratum corneum (data not shown).

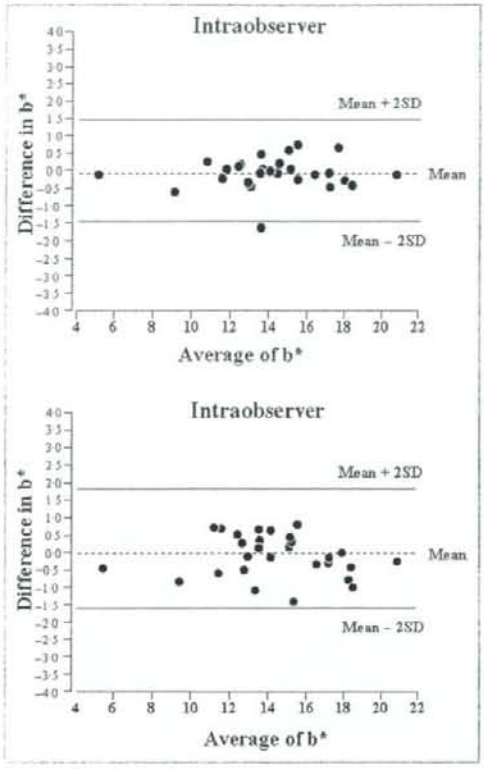

Fig 3. Bland–Altman plots for intra- and interobserver variability of skin transparency with tartrazine.

Table 3 Pearson's coefficients between variables in patients with atopic dermatitis (AD)

	STI	TEWL	P	W	AD score
STI		−0·022	−0·125	−0·265	0·529*
TEWL			−0·547**	0·101	0·136
P				−0·541**	−0·190
W					−0·247
AD score					

STI, skin transparency index; TEWL, transepidermal water loss; P, moisture content on the skin surface; W, moisture content in the stratum corneum.
*$P = 0·001$; **$P < 0·001$.

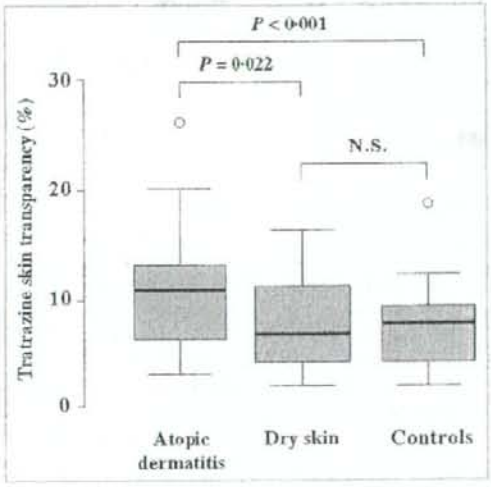

Fig 5. Tartrazine skin transparency in each clinical group. N.S., not significant.

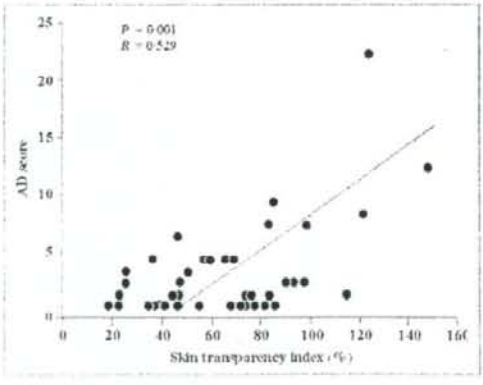

Fig 4. Relationship between the skin transparency with tartrazine and the atopic dermatitis score in patients with atopic dermatitis.

Discussion

Recently, several reviews have addressed the origin of atopic dermatitis using genetic analysis[4,5] and a dysfunction of the skin barrier has been suggested to be one of the fundamental mechanisms of atopic dermatitis.[19,20] Dysfunction of the skin barrier is most often demonstrated by measurement of stratum corneum hydration and TEWL,[21] which mainly evaluates the dysfunction of in–out skin transparency. Hata *et al.*[11] monitored the noninvasive, objective out–in measurements of skin function. Their method is excellent, but is difficult for routine measurements in children with atopic dermatitis.

Previously, Post *et al.*[22] measured the skin reflectance of red, green and blue light in 99 Caucasian infants and reported that the reflectance of each light wave increased with gestational age. The CIE L*a*b* colour space was developed as a standard of the colour space to be used for the specification of colour differences. Watanabe *et al.*[18] found that L*, an indicator of the darkness or lightness, using a tristimulus photocolorimeter strongly correlated with the gestational age.

This colorimeter was used to evaluate a new, unique method for the evaluation of direct out–in skin transparency.

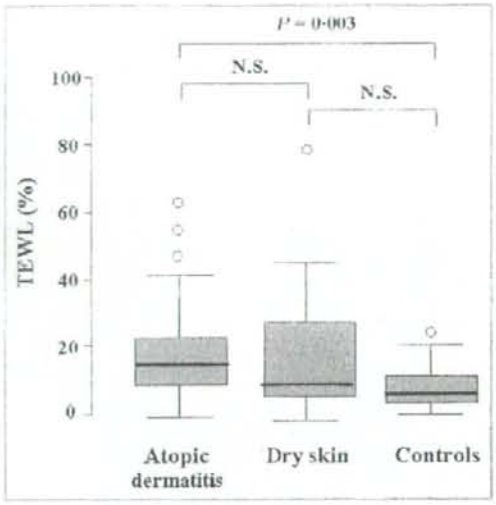

Fig 6. Transepidermal water loss (TEWL) in each clinical group.

The skin colour measurement before and after provocation of the skin with food dye using the CIE L*a*b* colour space colorimeter was assessed and it demonstrated that the b* value, the indicator of yellow, strongly indicated the out–in skin penetration of the hydrophilic yellow food dye, tartrazine. In addition, the results showed that both intra- and interobserver correlations were satisfactory for b*. This method was simple and reliable enough to measure the skin transparency.

This study demonstrated that the skin transparency index of tartrazine in patients with atopic dermatitis is apparently higher than that in subjects with dry skin and controls and that the skin transparency index in patients with a high AD score is higher than in those with a low AD score. These results suggest that the out–in skin transparency is significantly increased in atopic dermatitis and especially increased in the severe type and that in patients with atopic dermatitis outer stimuli may easily be transported across the skin surface.

Many scientific studies on atopic dermatitis have established guidelines for the effective management of this condition.[23,24] These guidelines suggest that basic therapy should consist of avoidance of triggering factors and optimal skin care. It is clear that outside irritations and stimuli to the skin contribute to the onset and the aggravation of atopic dermatitis.[25] One of the irritants is allergens which induces allergic inflammation in atopic patients.[26,27] Studies on the effects of house dust mite exposure on eczema have demonstrated specific effects of different mite species.[28] Other reported nonspecific irritants are sweat,[8] sand dust[9] and staphylococcal enterotoxin.[29]

Clinically, the symptoms in most young patients with atopic dermatitis are exacerbated after exercise and playing during and/or after school, and taking a shower or bath showed a good result for the treatment of atopic dermatitis.[30] One can easily speculate that increased out–in skin transparency could induce chronic skin inflammation and/or prolonged aggravation in patients with atopic dermatitis. In addition, there is the danger theory, i.e. nonspecific irritants stimulate dendritic cells, resulting in the induction of immunological advance reactions. This supports the mechanism that uric acid in sweat may exacerbate the itch–scratch cycle with skin inflammation in atopic dermatitis.[31,32] The measurement of out–in skin transparency can be useful for the evaluation of skin physiology in atopic dermatitis and using this method can thus allow the physician to make a more precise plan for the long-term treatment of each individual patient with atopic dermatitis.

Furthermore, the skin transparency index of patients with atopic dermatitis showed a significant difference from that of patients with dry skin, who had the same dry skin but without eczema lesions. TEWL, which mainly indicates the in–out skin transparency, showed no difference between patients with atopic dermatitis and those with dry skin and between subjects with dry skin and controls. The defect of the barrier function in atopic dermatitis has been demonstrated by an increased TEWL measured with an evaporimeter, which evaluates the evaporation rate of water through the skin.[33] Although previous data demonstrate a close correlation between the values of TEWL and the penetration of chemicals through the skin *in vitro*,[34] it should be noted that the diffusion of evaporated water molecules through the stratum corneum represents only an in–out barrier function and does not necessarily correlate with the diffusion of proteins and chemicals that often affect the inflammatory processes of atopic dermatitis.[11]

The current data suggest an apparent difference in skin physiological function between atopic dermatitis and dry skin. The characteristic lesions of atopic dermatitis may be induced by a specific dysfunction in the patients who have skin disorders in in–out and out–in skin transparency. Considering these results, we therefore speculate that there are two types of skin barrier dysfunction: one is the dysfunction of in–out skin transparency, while the other is the dysfunction of in–out and out–in skin transparency. The latter may occur in atopic dermatitis, while the former may occur in dry skin. The dysfunction of in–out and out–in skin transparency, which may be induced by the large spaces that exist among the skin cells, could show more severe, chronic symptoms due to both water loss and nonspecific irritants.

This result is very interesting with regard to the mechanism of onset and the establishment of atopic dermatitis. As clinically normal skin in patients with atopic dermatitis may have minimal inflammation,[35] the current observations suggest the possibility of masked skin inflammation which induces a prolonged barrier dysfunction in atopic dermatitis. Although no precise mechanism of the underlying dysfunction in the skin barrier related to out–in skin transparency is indicated, the differential diagnosis of atopic dermatitis from dry skin, which has little dysfunction of out–in skin transparency could be undertaken using this method. This indicates that this method

is more useful than TEWL for evaluating the barrier function of the skin.

The dry skin associated with atopic dermatitis, leading to disruption of the skin barrier, has attracted attention as a nonallergic aetiological factor in atopic dermatitis.[6] Several studies have demonstrated a lower water-holding capacity in the visually 'uninvolved' skin of children with atopic dermatitis in comparison with children without atopic dermatitis.[36] The earliest lesions of infantile atopic dermatitis are erythematous weepy patches on the cheeks, with subsequent extension to the rest of the face and neck. With increasing age, there is a tendency toward drying and thickening of the skin in the involved areas. In infants, a positive relationship has been suggested between stratum corneum hydration and TEWL.[37] Furthermore, the current method using a colorimeter is available for estimating dysfunction of the skin barrier in newborns. Evaluating the skin dysfunction in newborns using these measurements is recommended in order to permit effective management in the early stage of life. This report determined the out–in skin transparency only on the forehand and the subjects were 2–39 years old. A new study is planned utilizing the same protocol with younger subjects and using several skin areas.

In conclusion, a useful method for determining the out–in skin transparency was evaluated and it showed a significant increase of out–in skin transparency in patients with atopic dermatitis, which was not found in patients with dry skin or in control subjects. The new method, using a colorimeter and yellow dyes, provides measurements of the barrier function distinct from those related to water evaporation. The development of atopic dermatitis is thought to depend on a complex interplay of genetic factors, environmental exposure to allergens and nonspecific adjuvant factors. However, only a few prospective birth cohort studies have addressed atopic dermatitis occurring in the first year of life.[38,39] This unique, simple method should be habitually performed for the evaluation of skin dysfunction and the prediction of exacerbation of atopic dermatitis in infants and younger children.

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References

1 Williams HC, Robertson CF, Stewart AW. Worldwide variations in the prevalence of atopic eczema symptoms. *J Allergy Clin Immunol* 1999; **103**:125–38.

2 Saeki H, Iizuka H, Mori Y *et al.* Prevalence of atopic dermatitis in Japanese elementary schoolchildren. *Br J Dermatol* 2005; **152**:110–14.

3 Diepgen TL. Is the prevalence of atopic dermatitis increasing? In: *Epidemiology of Atopic Eczema* (Williams HC, ed.). Cambridge: Cambridge University Press, 2000; 96–109.

4 Walley AJ, Chavanas S, Moffatt MF *et al.* Gene polymorphism in Netherton and common atopic disease. *Nat Genet* 2001; **29**:175–8.

5 Nishio Y, Noguchi E, Ito S *et al.* Mutation and association analysis of the interferon regulatory factor 2 gene (IRF2) with atopic dermatitis. *J Hum Genet* 2001; **46**:664–7.

6 Imokawa G, Abe A, Jin K *et al.* Decreased level of ceramides in stratum corneum of atopic dermatitis: an etiologic factor in atopic dry skin? *J Invest Dermatol* 1991; **96**:523–6.

7 Smith FJ, Irvine AD, Terron Kwiatkowski A *et al.* Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. *Nat Genet* 2006; **38**:337–42.

8 Yosipovitch G, Goon AT, Wee J *et al.* Itch characteristics in Chinese patients with atopic dermatitis using a new questionnaire for the assessment of pruritus. *Int J Dermatol* 2002; **41**:212–16.

9 Leung DY, Bieber T. Atopic dermatitis. *Lancet* 2003; **361**:151–60.

10 Cooper KD. Atopic dermatitis: recent trends in pathogenesis and therapy. *J Invest Dermatol* 1994; **102**:128–37.

11 Hata M, Tokura Y, Takigawa M *et al.* Assessment of epidermal barrier function by photoacoustic spectrometry in relation to its importance in the pathogenesis of atopic dermatitis. *Lab Invest* 2002; **82**:1451–61.

12 De Felice C, Flori ML, Pellegrino M *et al.* Predictive value of skin color for illness severity in the high-risk newborn. *Pediatr Res* 2002; **51**:100–5.

13 Fairchild MD. *Color Appearance Models*, 2nd edn. New York: John Wiley & Sons, 2005.

14 Tagami H. Japanese Dermatological Association criteria for the diagnosis of atopic dermatitis. *J Dermatol* 1995; **22**:966–7.

15 Horikoshi T, Matsumoto M, Usuki A *et al.* Effects of glycolic acid on desquamation-regulating proteinases in human stratum corneum. *Exp Dermatol* 2005; **14**:34–40.

16 Sugiyama M, Arakawa H, Ozawa K *et al.* Early-life risk factors for occurrence of atopic dermatitis during the first year. *Pediatrics* 2007; **119**:716–23.

17 Ohta N, Robertson AR. *Colorimetry: Fundamentals and Application*. New York: John Wiley & Sons, 2005.

18 Watanabe M, Ohki Y, Yoshizawa Y *et al.* Maturational changes in skin color of Japanese newborn infants. *Neonatology* 2007; **91**:275–80.

19 Shahidullah M, Raffle EJ, Rimmer AR *et al.* Transepidermal water loss in patients with dermatitis. *Br J Dermatol* 1969; **81**:722–30.

20 Gehnetti C. Skin cleansing in children. *J Eur Acad Dermatol Venereol* 2001; **15** (Suppl.):12–15.

21 Yosipovitch G, Maayan-Metzger A, Merlob P *et al.* Skin barrier properties in different body areas in neonates. *Pediatrics* 2000; **106**:105–8.

22 Post PW, Krauss AN, Waleman S *et al.* Skin reflectance of newborn infants from 25 to 44 weeks gestational age. *Hum Biol* 1976; **48**:541–57.

23 American Academy of Dermatology. Guidelines of care for atopic dermatitis. *J Am Acad Dermatol* 1992; **26**:485–8.

24 Yamamoto S. A guideline for the treatment of atopic dermatitis. *Jpn J Clin Exp Med* 2002; **79**:211–13 [In Japanese].

25 Kusel MM, Holt PG, de Klerk N *et al.* Support for 2 variants of eczema. *J Allergy Clin Immunol* 2005; **116**:1067–72.

26 Tan BB, Weald D, Strickland I *et al.* Double-blind controlled trial of effect of housedust-mite allergen avoidance on atopic dermatitis. *Lancet* 1996; **347**:15–18.

27 McNally NJ, Williams HC, Phillips DR. Atopic eczema and the home environment. *Br J Dermatol* 2001; **145**:730–6.

28 Kramer U, Lemmen C, Bartmsel E *et al.* Current eczema in children is related to Der f 1 exposure but not to Der p 1 exposure. *Br J Dermatol* 2006; **154**:99–105.

29 Ide F, Matsubara T, Kaneko M *et al.* Staphylococcal enterotoxin-specific IgE antibodies in atopic dermatitis. *Pediatr Int* 2004; **46**:337–41.

30 Mochizuki H, Morikawa A. Effect of taking showers on atopic dermatitis in elementary school children. *J Jpn Pediatr Soc* 2003; **107**:1342–6 [In Japanese].

31 Shi Y, Evans JE, Rock KL. Molecular identification of a danger signal that alerts the immune system to dying cells. *Nature* 2003; **425**:516–21.

32 Jerome KR, Corey L. The danger within. *N Engl J Med* 2004; **350**:411–12.

33 Watanabe M, Tagami H, Horii I *et al.* Functional analysis of the superficial stratum corneum in atopic xerosis. *Arch Dermatol* 1991; **127**:1689–92.

34 Imokawa G. Water and the stratum corneum. In: *Bioengineering of Skin: In Vitro and In Vivo Models* (Elsner P, Berardesca E, Maibach HI, eds). Vol. 1. Boca Raton, FL: CRC Press, 1993; 23–47.

35 Wakita H, Sakamoto T, Tokura Y *et al.* E-selectin and vascular cell adhesion molecule-1 as critical adhesion molecules for infiltration of T lymphocytes and eosinophils in atopic dermatitis. *J Cutan Pathol* 1994; **21**:33–9.

36 Kusunoki T, Asai K, Harazaki M *et al.* Month of birth and prevalence of atopic dermatitis in school children: dry skin in early infancy as a possible etiologic factor. *J Allergy Clin Immunol* 1999; **103**:1148–52.

37 Saijo S, Tagami H. Dry skin of newborn infants: functional analysis of the stratum corneum. *Pediatr Dermatol* 1991; **8**:155–9.

38 Moore MM, Rifas-Shiman SL, Rich-Edwards JW *et al.* Perinatal predictors of atopic dermatitis occurring in the first six months of life. *Pediatrics* 2004; **113**:468–74.

39 Kurzius-Spencer M, Halonen M, Garla Lohman I *et al.* Prenatal factors associated with the development of eczema in the first year of life. *Pediatr Allergy Immunol* 2005; **16**:19–26.