

ความสัมพันธ์ของภาวะลำไส้รั่วกับผื่นผิวหนังอักเสบเซ็บเดิร์ม

Correlation of Intestinal Hyperpermeability and Seborrheic Dermatitis

Phaisit Trakulkongsmut¹, Akkarach Bumrungpert²,
Walun Vilaihong³, Thamthiwat Nararatwanchai⁴

นิติตระดับปริญญาโท สาขาวิชาเวชศาสตร์ชะลอวัยและฟื้นฟูสุขภาพ มหาวิทยาลัยแม่ฟ้าหลวง

บทคัดย่อ

การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาความสัมพันธ์ระหว่างภาวะลำไส้รั่วหรือภาวะการดูดซึมผ่านเยื่อผนังลำไส้มากเกินไปกับผื่นผิวหนังอักเสบเซ็บเดิร์ม โดยศึกษาอาสาสมัครจำนวน 32 คน แบ่งเป็น กลุ่มควบคุมที่สุขภาพร่างกายปกติจากเจ้าหน้าที่และนักศึกษาสำนักวิชาเวชศาสตร์ชะลอวัย และฟื้นฟูสุขภาพ มหาวิทยาลัยแม่ฟ้าหลวง กรุงเทพมหานคร จำนวน 16 คนและกลุ่มคนไข้ที่ได้รับการวินิจฉัยผื่นผิวหนังอักเสบเซ็บเดิร์มจากแพทย์ผิวหนัง ที่มารับการรักษาแผนกผู้ป่วยนอก โรงพยาบาลมหาวิทยาลัยแม่ฟ้าหลวง กรุงเทพมหานคร จำนวน 16 คน ประเมินด้วยชุดทดสอบตรวจวัดการดูดซึมของเยื่อผนังลำไส้เล็ก โดยวัดการดูดซึมน้ำตาลทั้ง 2 ชนิดคือน้ำตาลแลคโตสและน้ำตาลแมนนิทอล โดยประเมินผ่านทางน้ำตาลที่ถูกขับออกมาในปัสสาวะ ผลสรุปพบว่า ในกลุ่มคนไข้ผื่นผิวหนังอักเสบเซ็บเดิร์มพบค่าเฉลี่ยการขับน้ำตาลแลคโตสออกทางปัสสาวะ (mean 0.46 ± 0.09) สูงกว่ากลุ่มควบคุมที่สุขภาพร่างกายปกติอย่างมีนัยสำคัญ (mean 0.29 ± 0.06) ($p < 0.001$) และอัตราส่วนระหว่างน้ำตาลแลคโตสต่อแมนนิทอลที่ขับออกทางปัสสาวะในกลุ่มคนไข้ ผื่นผิวหนังอักเสบเซ็บเดิร์ม (mean 0.021 ± 0.005) สูงกว่ากลุ่มควบคุมที่สุขภาพร่างกายปกติอย่างมีนัยสำคัญ (mean 0.013 ± 0.003) ($p < 0.001$). จากข้อมูลสรุปได้ว่าภาวะการดูดซึมผ่านเยื่อผนังลำไส้ที่มากเกินไปมีความสัมพันธ์กับผื่นผิวหนังอักเสบเซ็บเดิร์ม.

คำสำคัญ: ผื่นผิวหนังอักเสบเซ็บเดิร์ม / การดูดซึมผ่านเยื่อผนังลำไส้ / แลคโตส / แมนนิทอล

ABSTRACT

Seborrheic dermatitis (SD) is considered one of the most frequent chronic inflammatory skin disorders. The etiology of seborrheic dermatitis is not fully understood but is known to involve various factors such as genetics, stress, drugs, neurological disorder, nutritional disorder, weather and immunity defect. An increased intestinal permeability or leaky gut has been proposed as possible culprits of seborrheic dermatitis but the evidence remain elusive. Sixteen healthy volunteers and sixteen patients with a diagnosis of seborrheic dermatitis were recruited from the outpatient department (OPD), Mae Fah Luang University Hospital and by

local advertisement. The diagnosis of seborrheic dermatitis is based on clinical features by dermatologist. 16 seborrheic dermatitis patients with mild to moderate severity evaluated by Seborrhea Areas Severity Index (SASI score). Absorption of lactulose and mannitol was measured in 16 patients with seborrheic dermatitis and healthy control subjects by using intestinal permeability test. There was no significant difference between mean mannitol excretion in patients with seborrheic dermatitis (mean 22.75 ± 2.14) and the healthy control subjects (mean 22.39 ± 2.02) ($p = 0.621$). The mean lactulose excretion in the patients with seborrheic dermatitis (mean 0.46 ± 0.09) was significantly higher than that of the healthy control subjects (mean 0.29 ± 0.06) ($p < 0.001$). Lactulose/mannitol excretion ratios (L/M Ratio) in the patients with seborrheic dermatitis, range 0.015-0.031 (mean 0.021 ± 0.005) were significantly higher than those of the healthy control subjects, range 0.010-0.022 (mean 0.013 ± 0.003) ($p < 0.001$). These data indicate that small intestinal permeability is increased in patients with seborrheic dermatitis. Impairment of the intestinal mucosal barrier appear to be involved in the pathogenesis of seborrheic dermatitis. There was no correlation between either seborrheic dermatitis's severity or the excretion ratio.

Keywords: *Seborrheic dermatitis / Intestinal permeability / Lactulose / Mannitol*

Introduction

Normally, Nutrients are absorbed from the intestinal lumen via 2 pathways: through the intestinal epithelial cells or enterocytes (transcellular, controlled by the cell membrane) and via the junctions between cells (paracellular, controlled by the permeability tight junctions). The intestinal lining is supposed to have tight junctions between the intestinal epithelial cells (Nusrat, Turner & Madara, 2000) The tight junctions located at the base of epithelial microvilli are the physical regulator of passive absorption of molecules. In a normal healthy intestine, the tight junctions constitute a barrier that provides limited access for substances from the outside (lumen) to be absorbed inside the body. The intestinal epithelial cells must establish them to seal off the barrier from passage of large molecules. The number and density of tight junctions regulate the diffusion of molecules. When they become destroyed by ulceration or inflammatory process between cells, thus increasing paracellular transport. This allow toxins, antigens, large molecules, and microorganisms to leak from the intestine into bloodstream. This condition is known as intestinal hyperpermeability or leaky gut (DeMeo, 2002; Gardner, 1988; Thomson, 1997).

Intestinal hyperpermeability or leaky gut describes a pathological increase in permeability of the intestinal mucosa, subsequent to the loss of intestinal mucosa integrity. It is caused by exposure to substances which damage the tight junctions between intestinal epithelial cells and increases passive, paracellular absorption. The common causes of damage are non-steroidal anti-inflammatory drugs (NSAIDs), ethanol, cytotoxic drugs, antibiotics, viral and bacterial gastroenteritis. This can be a direct effect (NSAIDs, ethanol, cytotoxic drugs) or an indirect effect as with bacterial overgrowth associated with antibiotic therapy (Cappell & Simon, 1993). Leaky gut or intestinal hyperpermeability causes increased absorption of toxin, antigens, inflammatory mediators, large molecules and pathogenic microorganisms. These agents can cause local and systemic reactions associated with a broad range of chronic diseases.

The lactulose-mannitol permeability test is one of the methods most widely used to diagnose intestinal permeability defects because it is simple and reliable to assess many clinical conditions (Dastyh, 2008; Farhadi, 2006). Lactulose-mannitol intestinal permeability test is being utilized in assessment of gut permeability in a wide range of conditions, including eczema, food sensitivity, pancreatitis, Crohn's disease and cirrhosis. Lactulose-mannitol intestinal permeability is assessed non-invasively by measuring the urinary excretion of orally administered test substances, chosen because they are non-toxic, not degraded, not metabolized or not normally present in urine but completely excreted and easy to measure.

Recent studies suggest that the increased IP is significantly increased in a number of health conditions or disease processes, including eczema (Caffarelli, 1993; Pike 1986; Przybilla, 1990; Rosenfeldt, 2004), urticaria (Paganelli, Fagiolo, Cancian & Scala, 1991), psoriasis (Hamilton, 1985), asthma (Benard, Desreumeaux, Huglo, 1996), rheumatoid arthritis (Fagiolo 1989; Mielants, 1991; Smith, 1985), ankylosing spondylitis (Smith, Gibson & Brooks, 1985), acute gastroenteritis (Ioslauri, Juntunen & Wiren, 1989), post-surgery (Riddington, Venkatesh & Boivin, 1996), alcoholism (Bode, 2003; Purohit, 2008), food allergy (Heyman, 2005; Husby, 1986; Pena, 1998; Ventura, 2006), pancreatic dysfunction (Mack, Flick & Durie, 1992), celiac disease (Festen, 2009; Visser, 2009), inflammatory bowel disease (Mankertz, 2007; McGuckin, 2009; O'Mahony, 1992), irritable bowel disease (Zeng, Li & Zhen, 2008), fibromyalgia (Goebel, Buhner, Schedel, Lochs & Sprotte, 2008), chronic fatigue syndrome (Maes, Mihaylova & Leunis, 2007), migraine (Scarpellini E, 2009) and depression (Maes, Kubera & Leunis, 2008). Increased IP may be implicated in the pathogenesis of several diseases and appears to correlate with a number of diseases.

Seborrheic dermatitis (SD) is considered one of the most frequent skin disorders and it is one of the most conditions for which patients consult a dermatologist. Seborrheic dermatitis

is considered as one of the endogenous eczema. Seborrheic dermatitis is a chronic, relapsing inflammatory cutaneous disease characterized by erythema covered with yellow gray scales in the affected areas. The lesions are mainly located in areas containing a large number of sebaceous glands such as the mid-facial region, scalp, and certain areas of the trunk. It typically presents on the scalp, lateral sides of the nose, nasolabial folds, eyebrows, glabella, ears, upper chest and back (Plewing, & Janssen, 2008). Dandruff is considered to be the mildest or perhaps initial form of seborrheic dermatitis (Gupta, Ryder, Nicol & Cooper, 2003). The course of seborrheic dermatitis involves periods of remission and exacerbation. However, the disease rarely causes serious complications, it always leads to a marked aesthetic deterioration that lead to emotional and social difficulties. Seborrheic dermatitis can have an effect on the quality of life of affected individuals..

This study focuses on seborrheic dermatitis because it is considered one of the most skin disorders and has an impairment of quality of life. The etiology of seborrheic dermatitis is not fully understood but is known to involve various factors. Factors that may increase susceptibility to the disease are genetics, stress, depression, fatigue, weather, and oily skin and hair. An increased intestinal permeability or leaky gut has been proposed as possible culprits of seborrheic dermatitis but the evidence remain elusive. Many works on increased intestinal permeability in patients with atopic eczema are available. On the contrary, no data on increased intestinal permeability in patients with seborrheic dermatitis can be found. The lack of defined data on the intestinal permeability in patients with seborrheic dermatitis encourage to perform the present study. The aim of this study is to measure intestinal permeability in patients with seborrheic dermatitis of varying severity.

Research Objective

To study the correlation between seborrheic dermatitis and intestinal permeability.

Materials and Methods

Sample preparation: Normal healthy controls and patients with a diagnosis of seborrheic dermatitis who attended the outpatient clinic, Mae Fah Luang University Hospital are invited to participate. The diagnosis of seborrheic dermatitis is based on clinical features by dermatologist. There is still no laboratory test or definite marker for establishing the diagnosis of seborrheic dermatitis. Clinical evaluation is the most important.

Methodology

1. Sixteen healthy control subjects and sixteen patients with seborrheic dermatitis aged between 20-60 years are enrolled in the study at Mae Fah Luang University Hospital, Bangkok. The diagnosis of seborrheic dermatitis is based on clinical features by dermatologist.

2. All patients are performed complete physical examination and history taking concerning signs, symptoms, severity, past and current medication, underlying diseases, alcohol drinking and smoking by physician in order that their qualifications are fallen into inclusion criteria.

3. Explaining the procedure of intestinal permeability test to all subjects and give them the intestinal permeability collection instruction document. They all were informed consent to the intestinal permeability study. Female subjects should not collect urine during menstrual period.

4. All subjects are fast overnight (do not eat any food from 11 pm onwards), water may be consumed during this time. After getting up in the morning and passing the morning urine, thereafter the procedures are performed by using two non-metabolized sugar 10 ml solution containing 2.5 g lactulose and 1.5 g mannitol. To perform the test, subjects have to add warm water to the syrup in the brown plastic bottle of premeasured amount of lactulose and mannitol until $\frac{3}{4}$ full and replace the lid firmly and shake the container vigorously to dissolve the white powder, thereafter drink the challenge substance.

5. Over the collection time of this test (6 hours after ingestion of lactulose and mannitol) avoid food containing fructose as these will affect the test results. Common food containing fructose include fruit, fruit juice and honey. It is advisable to check food labels for added fructose.

6. For the following 6 hours, all urine must be collected into 4 liter urine collection bag and stored in 4°C in the refrigerator. The total urine volume is read from the scale on the side of the bag and recorded on the request form. Using the plastic dropper, transfer 10 ml of well-mixed urine from the bag into the 10 ml urine specimen tube by nurse or medical technician. Label the tube with patient's names, the date and time. Place the 10-ml samples of urine in the padded envelope and seal it. Being stored in 4°C in refrigerator until the chromatographic analysis

Statistical analysis

The basic data are presented as percent, mean, and standard deviation. Analyzing lactulose excretion, mannitol excretion and lactulose/mannitol ratio (mean \pm SD) in patients with seborrheic dermatitis and in healthy controls were compared using independent t-test.

Correlation between severity of seborrheic dermatitis (using seborrhea area severity index; SASI) and lactulose excretion, L/M ratio in patients was analyzed by using Pearson test.

Results

Table 1 reports lactulose excretion, mannitol excretion, and L/M ratio in each patient with seborrheic dermatitis. All of patients with seborrheic dermatitis had increased lactulose excretion (normal range is 0.0-0.3%). Out of 16 patients, 2 patients had increased mannitol excretion (normal range is 9.5-25%). One patients with seborrheic dermatitis had L/M ratio outside the normal range (normal ratio is 0.00-0.03)

Table 1 Lactulose Excretion, Mannitol Excretion and Lactulose/Mannitol Ratio in Patients with Seborrheic Dermatitis.

Patient	Sex	Age	Lactulose excretion (%)	Mannitol excretion (%)	Lactulose/Mannitol Excretion ratio
M.M.	M	39	0.39	23.67	0.016
W.V.	M	43	0.37	20.88	0.018
S.L.	M	51	0.41	24.82	0.017
K.C.	M	43	0.38	19.87	0.019
W.C.	M	30	0.37	27.58	0.018
T.R.	F	29	0.46	20.80	0.022
A.K	F	47	0.35	23.45	0.015
A.A.	F	30	0.58	20.76	0.027
S.T.	M	48	0.59	21.60	0.027
T.N.	M	57	0.44	23.84	0.018
L.T.	F	37	0.56	20.80	0.027
P.T	M	30	0.44	23.80	0.018
P.J.	M	27	0.58	25.14	0.023
Pi.T.	M	34	0.42	24.18	0.017
J.B.	F	38	0.64	20.51	0.031
S.S.	F	41	0.44	22.36	0.020

Table 2 Lactulose Excretion, Mannitol Excretion and Lactulose/Mannitol Ratio in Healthy Control Subjects.

Controls	Sex	Age	Lactulose excretion (%)	Mannitol excretion (%)	Lactulose/Mannitol Excretion Ratio
J.K.	M	30	0.25	20.51	0.012
N.P.	F	37	0.30	22.93	0.013
N.M.	F	53	0.25	22.84	0.011
P.D.	F	27	0.30	18.46	0.016
S.K.	F	60	0.30	23.88	0.013
S.S.	F	44	0.26	25.12	0.010
T.P	F	42	0.25	24.18	0.010
V.T.	F	29	0.26	21.56	0.010
W.S.	M	36	0.41	25.19	0.016
S.A.	M	31	0.46	20.81	0.022
S.H.	M	45	0.25	20.83	0.012
M.A.	F	35	0.28	20.71	0.014
J.P.	F	44	0.29	25.44	0.011
C.K.	F	29	0.25	22.83	0.011
P.M.	M	35	0.28	20.69	0.014
S.P.	F	30	0.23	22.20	0.010

Table 2 reports lactulose excretion, mannitol excretion, and L/M ratio in each healthy control subjects. Out of 16 healthy controls, only 2 subjects had increased lactulose excretion (normal range is 0.0-0.3%), whereas other 14 subjects had normal lactulose excretion. In addition, out of 16 controls, 3 subjects had increased mannitol excretion (normal range is 9.5-25%). None of control subjects with seborrheic dermatitis had L/M ratio outside the normal range (normal ratio is 0.00-0.03)

Table 3 Lactulose Excretion, Mannitol Excretion and Lactulose/Mannitol Ratio (mean \pm SD) in Patients with Seborrheic Dermatitis and in Healthy Controls.

	Patients	Controls	Mean Difference	p-value
Mannitol excretion				
%	22.75 \pm 2.14	22.39 \pm 2.02	0.368	0.621
Lactulose excretion				
%	0.46 \pm 0.09	0.29 \pm 0.06	0.175	<0.001
L/M ratio	0.021 \pm 0.005	0.013 \pm 0.003	0.008	<0.001

Note. Patients and controls were compared using independent T-test. P value < 0.001 denotes very significant difference of lactulose excretion and L/M ratio.

Mannitol : There was no significant difference between mean mannitol excretion in patients with seborrheic dermatitis (mean 22.75 \pm 2.14) and the healthy control subjects (mean 22.39 \pm 2.02) ($p = 0.621$) (Table 4.6). The mean difference between two groups was 0.368. The difference in mannitol excretion between patients with seborrheic dermatitis and healthy controls did not reach significance. (Figure 1)

Lactulose : The mean lactulose excretion in the patients with seborrheic dermatitis (mean 0.46 \pm 0.09) was significantly higher than that of the healthy control subjects (mean 0.29 \pm 0.06) ($p < 0.001$) (Table 4.6). The mean difference between two groups was 0.175. The difference in lactulose excretion between patients with seborrheic dermatitis and healthy controls reached significance. (Figure 1)

Lactulose/mannitol excretion ratios (L/M Ratio) : L/M ratio in the patients with seborrheic dermatitis, range 0.015-0.031 (mean 0.021 \pm 0.005) were significantly higher than those of the healthy control subjects, range 0.010-0.022 (mean 0.013 \pm 0.003) ($p < 0.001$) (Table 4.6). One patients with seborrheic dermatitis had L/M ratio outside the normal range. (normal range 0.00-0.03). (Figure 2).

Discussion

Demography

1. **Sex** : There were relatively more males in patient group than in the healthy control group.

In general, seborrheic dermatitis can affect both males and females but it is much more common in men than women, probably because sebaceous gland activity is under androgen control.

2. **Age** : In the study, the mean age of patients with seborrheic dermatitis was 39 ± 8.82 years that was similar to the incidence. Seborrheic dermatitis has two age peaks, one in infancy within the first 3 months of life and the second around the third and fourth decade of life.

3. **Underlying disease** : Only one patient had Hepatitis B and the remaining 15 patients did not have any other underlying diseases. There was no underlying disease in all of healthy control subjects. There was no difference significantly in underlying disease between patients with seborrheic dermatitis and healthy controls. Therefore it was not an obstacle to the study.

4. **Occupation** : Most of healthy control subjects and patients were officers and doctors respectively. Because they were recruited from Mae Fah Luang university officers.

5. **Signs and symptoms** : The most severe symptoms were erythema followed by scaling and pruritus consecutively.

6. **Affected areas** : The most commonly affected area were the scalp followed by glabella or eyebrows and ears. More than one area could be affected in the same patient. Generally, the lesions favor scalp, face and ears.

7. **Factors that trigger outbreaks** : Both of the stress and inadequate sleep were the most common factor followed by dairy product consumption, followed by colder climate or exposure to air conditioning and exposure to the intense sunlight or heat.

8. **Frequency of outbreaks** : The most common frequency of outbreaks was 3-4 times a month.

9. **Severity index** : By using Seborrhea Area Severity index (SASI), The mean score of severity index was 18.8 out of 48. The severity of seborrheic dermatitis in patients was mild to moderate.

Intestinal permeability test

This method was chosen because it can be performed easily and non-invasive. By combining a small oral dose of lactulose and mannitol and then assessing for urine excretion, an intestinal permeability test quantifies malabsorption and leaky gut. The advantage of this method is that it is the most common test used for intestinal permeability studies. In addition, lactulose and mannitol meet most of the criteria for an ideal test substance. The degree of

leak can be assessed by ingesting lactulose and measuring for its presence in the urine. Lactulose is the large molecule and should not be absorbed or excreted through urine. Under leaky gut condition, it is absorbed through paracellular pathway and present in urine. On the other hand, mannitol is absorbed across the healthy mucosa and should be found in the urine, when ingested.

The result showed one of the sixteen patients had L/M ratio greater than the normal range. Although only one of 16 patients had L/M ratio outside the normal range whereas the other patients had L/M ratio within the normal range, patients with seborrheic dermatitis had L/M ratio higher than the normal healthy controls significantly. In addition, all patients with seborrheic dermatitis had increased lactulose excretion in urine indicating an abnormality of passive permeability (paracellular pathway) of small intestine. The increased lactulose absorption, indicating that the mucosa of the patients was more leaky than normal. On the contrary, mannitol absorption was normal that reflects small intestinal surface area was normal.

Immune cell function in seborrheic dermatitis is defective and it has been proposed that this defect contributes to the pathophysiology of seborrheic dermatitis. It may speculate that a leaky gut barrier in patients may facilitate specific immunological responses to cause disease. There is evidence that the restoration of normal intestinal permeability may improve disease. For example, in children with atopic dermatitis, probiotics treatment normalizes intestinal permeability and reduces eczema severity

Seborrheic dermatitis is considered as one of the endogenous eczema as well as atopic dermatitis but no data on increased intestinal permeability in patients with seborrheic dermatitis can be found. Many works on increased intestinal permeability in patients with atopic eczema are available. There were atopic dermatitis has been reported associated with increased intestinal permeability. Baseline intestinal permeability measurements of children with eczema are higher than normal individuals. (Caffarelli, 1993; Pike 1986; Przybilla, 1990; Rosenfeldt, 2004; Ukabam, 1984). Accordingly, the demonstration of increased excretion of lactulose in atopic dermatitis (AD) would indicate a leaky mucosa. This finding supports the hypothesis of the correlation between seborrheic dermatitis and leaky gut.

There was a negative correlation between the L/M ratio and the clinical severity of seborrheic dermatitis because not only increased intestinal permeability affects the severity of it, but also other factors that influence in the severity of seborrheic dermatitis. Several factors that may influence in the severity such as stress, inadequate sleep, cold weather, sunlight and heat. Thus, the study has limitation because it is difficult to control factors that affect the severity of disease. However, in other clinical conditions, which are known to be associated

with increase IP, and where IP is considered of pathophysiological relevance, such as irritable bowel syndrome, no correlation between the degree of IP and disease severity. (Zhou, Zhang & Verne, 2009).

Conclusion

Sixteen healthy volunteers and sixteen patients with a diagnosis of seborrheic dermatitis were recruited from the outpatient department (OPD), Mae Fah Luang University Hospital and by local advertisement. The diagnosis of seborrheic dermatitis is based on clinical features by dermatologist. There is still no laboratory test or definite marker for establishing the diagnosis of seborrheic dermatitis. Clinical evaluation is the most important.

Initially, the hypothesis of this study states that there is a correlation between seborrheic dermatitis and increased intestinal permeability (leaky gut) that was measured by means of lactulose and mannitol test.

After the statistical analysis of the data obtained from 16 randomized patients with seborrheic dermatitis and 16 healthy control subjects; the results yielded a significant finding. In other words, the results obtained from the data support the original hypothesis.

Comment

The summary from this study will support that seborrheic dermatitis develop associated with increased intestinal permeability. Both pathophysiological and therapeutic implication of such an increased intestinal permeability in seborrheic dermatitis await for further studies. For example, the application for therapy directed toward reversing the increased intestinal permeability is logical such as elimination the causative factors, digestive enzyme replacement, reintroduction of friendly bacteria or probiotics (oral bacteriotherapy) , and providing nutritional support for regeneration or healing of the intestinal mucosa. The study has the limitation. In the study, laboratory test or definite marker to confirm the diagnosis of seborrheic dermatitis were not performed especially skin biopsies to confirm the diagnosis precisely. Skin biopsies may effectively distinguish seborrheic dermatitis from similar disorders such as psoriasis, rosacea, and superficial fungal infection. Histological findings of seborrheic dermatitis are hyperkeratosis, acnathosis, accentuated rete ridges, focal spongiosis, and parakeratosis are characteristic. Psoriasis is distinguished by thin rete ridges, exocytosis, parakeratosis and an absence of spongiosis. Fungal culture can be used to rule out tinea capitis. The skin biopsies were not performed because it is an invasive technique

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