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Case Report

Importance of oral food challenge and identification of atopic dermatitis in child with Netherton syndrome: A case report

Kosei Yamashita*, Yuki Okada, Mayu Maeda,
Taro Kamiya and Takanori Imai

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Abstract

Children with Netherton syndrome are likely to be sensitized to multiple allergens due to skin barrier dysfunction. Owing to substantial increases in total and food allergen-specific IgE levels, some children with Netherton syndrome are diagnosed with food allergies (FAs) and advised to avoid particular foods. However, it is unclear whether such children actually have FAs. We report a child with Netherton syndrome without atopic dermatitis (AD) who was able to stop avoiding certain foods (hens' eggs and peanuts) after undergoing oral food challenge (OFC). A 5-year-old Japanese boy with Netherton syndrome without AD consulted at our hospital to evaluate the possibility of allergies to hens' eggs and peanuts. Netherton syndrome had been diagnosed at birth. At 1 year old, the levels of specific IgE for egg white and peanuts were >100 and 14.6 kU/l, respectively. He had not consumed or experienced allergic symptoms to these foods. However, he was instructed to completely avoid these foods in his diet. At 5 years old, he still completely avoided these foods. The levels of specific IgE for egg white, ovomucoid, and peanuts were 34.5, 9.4, and 17.4 kU/l, respectively. Since the serum-specific IgE levels and the serum-specific IgE/total IgE ratio decreased, we performed OFCs for hens' eggs and peanuts. The results of the OFCs using half a baked egg and 10 g of peanuts were all negative. The same dosing schedule was repeated at home, again with negative results. Therefore, the avoidance could be stopped. This report suggests that we should identify whether patients have AD or not, and OFCs should be performed before requesting food restriction in patients with Netherton syndrome.

Key words: atopic dermatitis, food allergy, Immunoglobulin E, Netherton syndrome, oral food challenge

Introduction

Netherton syndrome (OMIM no. 256500) is an autosomal recessive inherited disorder characterized by congenital ichthyosiform erythroderma, distinctive hair shaft defects, trichorrhexis invaginata, and atopic manifestations[1]. The prevalence of Netherton syndrome is estimated to be 1 in 100,000-200,000 births globally[2,3]. Netherton syndrome is caused by a mutation of the Serine Protease Inhibitor Kazal Type 5 (SPINK5), which leads to hypoactivity of the Lympho-Epithelial Kazal-Type-related Inhibitor, causing severe skin barrier defects[4,5].

Owing to this dysfunction of the skin barrier, children with Netherton syndrome are highly sensitized to multiple allergens from early infancy[6,7]. A case-series study of 10 Finnish children and adults showed increased serum total IgE levels in 9 of 10 patients and that the sensitization rate for one or more food antigens was 100%[5]. The rate of patients with Netherton syndrome and complicating food allergies (FA) remains unknown. However, since this syndrome is characterized by substantial increases in total and food allergen-specific IgE levels, most Netherton syndrome patients are diagnosed with one or more FAs. Therefore, without undergoing an oral food challenge (OFC), they are advised to strictly

* Corresponding author
✉ Kosei Yamashita
meko11115@med.showa-u.ac.jp

Department of Pediatrics, Showa University School of Medicine, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan.

avoid suspected foods. Allergies such as to hens' eggs, cow's milk, wheat, and peanuts in the general pediatric population can be diagnosed using symptom-evoked prediction models based on specific IgE levels and predictive models for the provocation of allergic symptoms. However, it is unclear whether the models constructed from data on the general population can be applied to children with Netherton syndrome. Hence, Netherton syndrome patients are more likely to have an inherent need for a diagnosis of FA using an OFC.

Herein, we report the case of a child with Netherton syndrome without atopic dermatitis (AD), for whom certain foods had been eliminated, due to sensitization, but whose food removal was shown to be unnecessary by OFC. This study was approved by the Ethical Committee of the School of Medicine, Showa University (No. 3196). His parents provided informed consent.

Case presentation and clinical course

A 5-year-old boy with Netherton syndrome consulted at our hospital for allergies to hens' eggs and peanuts. Netherton syndrome had been diagnosed at birth. No genetic test had been performed. His diagnosis had been based on his clinical symptoms of congenital ichthyosiform erythroderma and trichorrhexis invaginate or bamboo hair. There was no family history of Netherton syndrome.

At 1 year of age, his family doctor performed a capsulated hydrophilic carrier polymer radioallergosorbent test. The level of total IgE was 3,381 kU/l, and the levels of specific IgE for both egg white and ovomucoid exceeded 100 kU/l. The level of specific IgE to peanuts was 14.6 kU/l. Therefore, this patient was sensitized to hens' eggs and peanuts at that time. He had not consumed or experienced allergic symptoms to these foods. Based on the serology reports and a diagnosis of FAs for hens' eggs and peanuts, he was instructed to remove them completely from his diet and to take measures to avoid accidentally ingesting them.

At 5 years of age, at his first presentation to us, his height was 97.0 cm (2.3SD) and his body weight was 14.1 kg (21.5SD). On physical examination, ichthyosis linearis circumlexa was visible on his extremities, with extensive skin detachment and congenital ichthyosiform erythroderma noted on his trunk (Figures 1, 2). This patient's skin condition showed no eczematous findings such as papules or erythema on the symmetrical joint areas of the limbs or on the neck. This condition was not typical in infant AD with a long course. In addition, despite the chronic course of the disease, there was no lichenification phase. Therefore, we concluded that the rash of this patient was not caused by AD[8]. Laboratory findings showed that his total IgE level was 26,041 kU/l, and his serum egg white and ovomucoid-specific serum IgE levels were 34.5 and

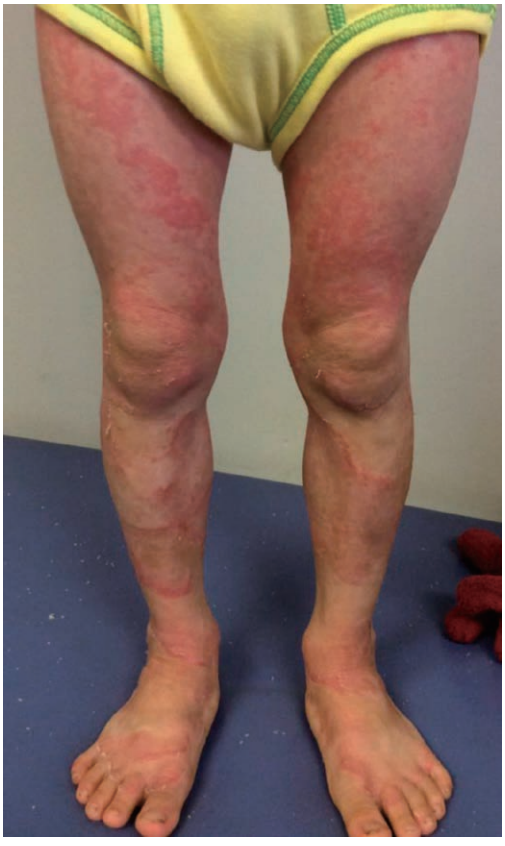

Fig. 1. Skin condition at admission, ichthyosiform erythroderma. Ichthyosis linearis circumlexa was visible on the extremities.

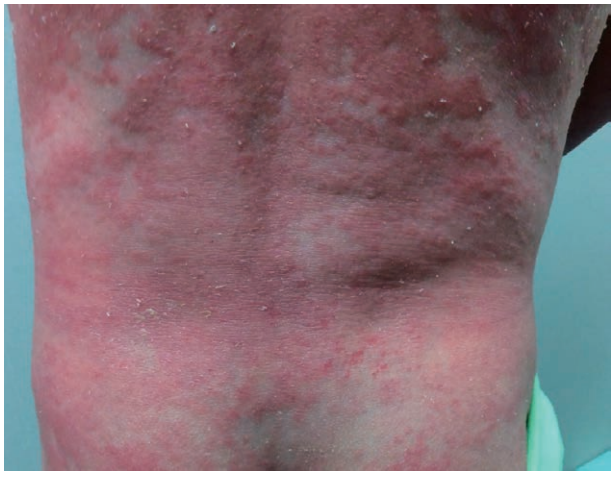

Fig. 2. Skin condition at admission, erythroderma. Epidermal detachment and congenital ichthyosiform erythroderma were noted on the trunk.

9.4 kU/l, respectively. The peanut-specific serum IgE level was 17.4 kU/l, and the thymus and activation-regulated chemokine level was 844 pg/ml. Since his serum-specific IgE levels of the two allergy-suspected foods and the serum-specific IgE/total IgE ratio decreased[9] (Table 1), we performed OFCs for hens' eggs and peanuts.

These OFCs were performed in accordance with the Japanese Pediatric Guidelines for Food Allergy 2016 (JPGL 2016)[10], and the ingestion was divided into one-third and two-thirds in all foods. Overall, one-eighth and one-half of a baked egg were ingested on the first and second days, respectively, and 10 g of peanuts on the third day. All of the OFC results were negative. The same dosing schedule was repeated at home, again with negative results. Thus, the patient stopped avoiding these specific foods after undergoing the OFCs.

Discussion

Because this patient had not undergone blood tests for allergies to hens' eggs and peanuts until 1 year old, it is unknown when he became sensitized to these foods. Since Netherton syndrome involves severe dysfunction of the skin barrier, percutaneous sensitization to foods and other substances tends to increase early in life, and total IgE and antigen-specific IgE levels are high[6,7]. The diagnosis of FA is essentially based on an OFC test. However, when the specific IgE is high, or the medical facility does not conduct OFC tests, the diagnosis is often made based on the results of the specific IgE value. In addition, Netherton syndrome is a rare disease, and physicians caring for patients with this disease are inexperienced in this condition. Hence, many patients with Netherton syndrome do not undergo OFCs due to strong sensitization. Moreover, many physicians advise the extensive elimination of foods from the diet, even before starting solid food. This case was also initially diagnosed on the basis of a high specific IgE level. However, there are cases, such as this one, in which strong sensitization to foods and other substances is observed, but FA is not diagnosed[5,11]. We recommend that the gold standard for diagnosing FA in Netherton syndrome patients, as generally for children with allergies to food, is the implementation of an OFC test.

It is suggested that transdermal sensitization is involved in the development of FA. Moreover, intestinal exposure, even at low levels, is more important in inducing the acquisition of tolerance[12]. However, if this is correct, patients with Netherton syndrome with strong barrier dysfunction should be transdermally sensitized and develop FA. In addition, when complete elimination of suspected foods is continued, as in this case, the acquisition of natural tolerance would be extremely difficult. However, there are patients, including this one, who have not necessarily developed FA[5,11]. The finding of Netherton syndrome patients without FA suggests that there are other triggers for developing FA besides skin barrier dysfunction.

This suggests that the presence of AD, namely, allergic predisposition, is a trigger for developing FA in cases with skin barrier dysfunction. A study in mice showed that there is a clear difference in mast cell induction in the intestinal epithelium. In mice with an allergic predisposition, FA tended to be induced when a skin barrier disruption intervention was performed in those with and without an allergic predisposition[13]. Thus, it was inferred that

Table 1. Changes in blood tests

	1 year old	5 years old
Eosinophils (/μl)	502	931
Total IgE (kU/l)	3,381	26,041
TARC (pg/ml)	−	844
Serum specific IgE antibody (Immuno CAP)		
Egg white (kU/l)	>100	34.5
Ovomucoid (kU/l)	>100	9.4
Peanuts (kU/l)	14.6	17.4

IgE : Immunoglobulin E, TARC : Thymus and Activation-Regulated Chemokine

Changes in serum eosinophils, total IgE antibody, TARC, and IgE antibodies specific to egg white, ovomucoid, and peanuts.

allergic reactions in mice are triggered by allergic predisposition-induced type II immune responses, in addition to skin barrier dysfunction. It is possible that the same phenomenon occurs in humans with disruption of the skin barrier. In fact, it has been reported that children with AD with an allergic predisposition have a higher risk of developing FA than children without AD[14]. The current patient had no skin findings characteristic of AD, so he may not have developed FA.

Currently, there are no assessment tools or biomarkers that can predict the presence of FA in Netherton syndrome patients with strong sensitization to food antigens. We recommend identifying whether patients have AD, and performing OFC before advising food restriction in patients with Netherton syndrome.

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Conflict of interest disclosure

The authors declare no conflicts of interest.

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