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Two siblings affected by Netherton/Comèl syndrome. Diagnostic pathology and description of a new *SPINK5* variant

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Abstract

Netherton syndrome is a severe, autosomal recessive form of ichthyosis associated with mutations in the *SPINK5* gene encompassing three main clinical findings: 1) ichthyosiform dermatitis and/or ichthyosis linearis circumflexa, 2) hair shaft defects with peculiar "trichorrhexis invaginata" (bamboo pole hair) findings, 3) atopic dermatitis. We describe two siblings affected by Netherton/Comèl syndrome who were referred to our Center for Genodermatosis. A diagnostic pathway and the description of a new *SPINK5* variant has been determined for these two patients. A novel genetic mutation has been found.

Keywords: Netherton/Comèl syndrome, intellectual disability, next generation sequencing, trichoscopy, genetic counseling

Introduction

Netherton syndrome is a rare autosomal recessive syndromic ichthyosis caused by mutations of the *SPINK5* gene, which encodes the lymphoepithelial Kazal-type-related inhibitor (LEKTI) protein. The clinical diagnosis is based on the simultaneous presence of ichthyosiform dermatitis, atopic diathesis, and hair defects. The skin appears with the particular appearance of ichthyosis linearis circumflexa. In several patients generalized erythroderma has been described; noticeable itching is often present and bamboo hair is a

particular sign on microscopic observation. Trichoscopic examinations, indeed, shows a swelling along the hair shaft, which looks like a fishing pole or a bamboo cane. A further optical microscopic analysis shows trichorrhexis invaginata, the pathognomonic sign of Netherton syndrome.

Case Synopsis

We present two siblings affected by Netherton/Comèl syndrome. The two were born to unrelated parents and two elder sisters were not affected.

A 13-year-old boy was referred to our center for a suspected genetic skin disease. At birth, the full-term infant presented with a reddish skin, as reported by the mother; at a very early age the child's skin tone was extremely erythematous. On physical examination, he was hyposomic and presented with generalized light erythroderma; he constantly scratched himself. His face was dysmorphic and characterized by the almost total absence of eyelashes and eyebrows, whereas scalp hair was short and thin (**Figure 1**). After obtaining consent, trichoscopic analysis was performed on a small sample of hair and genetic molecular testing on blood was carried out. The trichoscopic examination showed a swelling along the hair shaft, which looked like a bamboo cane (**Figure 2**), the pathognomonic sign of Netherton syndrome. A further investigation on scanning electron microscopic (SEM) showed, in some hair, exfoliations, fractures, and

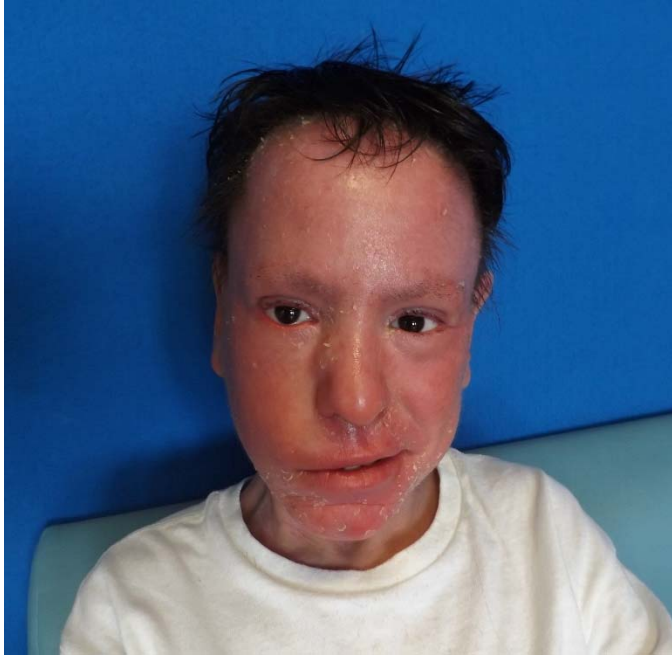


Figure 1. Peculiar dysmorphic face of the young patient. Few eyelashes and eyebrows.

intussusceptions of the shaft. Sometimes typical joints looked like a fishing pole (**Figure 3**). DNA was isolated from lymphocytes using the salt chloroform extraction method. *SPINK5* primers were designed using the AmpliSeq Designer software (Thermo Fisher Scientific), targeting the complete coding sequence of the *SPINK5* gene (transcript reference, NM_001127698.1). Next generation sequencing was performed using the Ion Torrent Personal Genome

Machine (Thermo Fisher Scientific). We identified a frameshift insertion homozygous variant c.238_239insG (p.Ala80fs) in the *SPINK5* gene, which has been never described before to our knowledge.

The second patient, the sister of patient 1, is a female student aged 20. She was referred to our Regional Reference Center for Genodermatosis with a previous diagnosis of congenital ichthyosis. Upon clinical examination, she appeared in a good general state of health, whereas the skin showed background erythema with fine desquamation. The hair was sparse and shaggy. Eyelashes and eyebrows were almost absent (**Figure 4**). After consent, a sample of hair was obtained and processed for examination and genetic molecular testing on blood was carried out. Trichoscopy revealed some bamboo hair, whereas light microscopy better demonstrated the shaft defects (**Figure 5**). On SEM the images were similar to those of her brother. We identified also the same frameshift insertion homozygous variant c.238_239insG (p.Ala80fs) in the *SPINK5* gene, as in her brother.

Case Discussion

In 1949, Comèl described a bizarre and figurate psoriasiform dermatopathy in a young adult woman and named it "ichthyosis linearis circumflessa [1]." In 1958 Netherton described a female with an

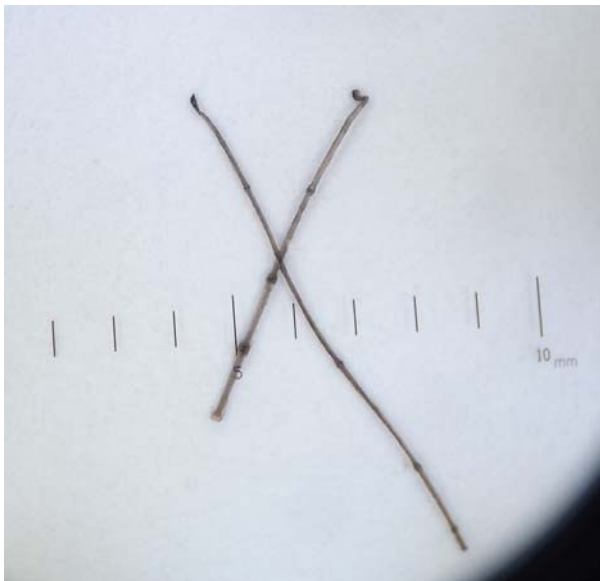


Figure 2. Two hairs that look like bamboo fishing poles on trichoscopy.

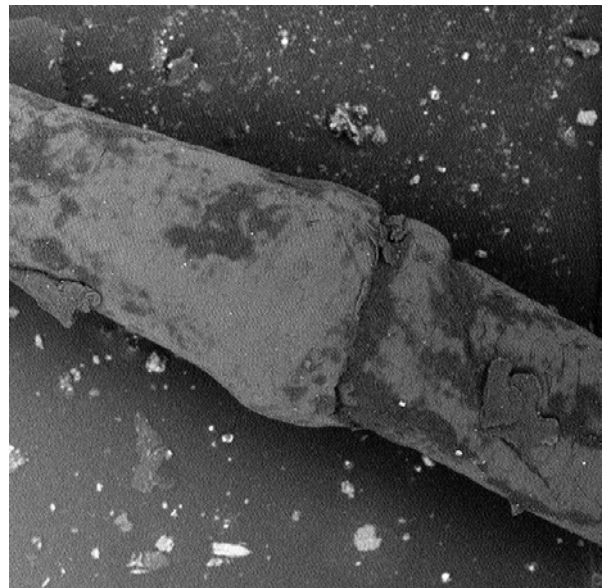


Figure 3. On scanning electron microscopy intussusceptions of the shaft (trichorrhexis invaginata).



Figure 4. Rare eyelashes and eyebrows on the second patient.

unknown abnormality of the hair shafts, which he then named as "bamboo hair [2]." The two conditions were not connected to each other until 1969 when Altman and Stroud found both anomalies in two males and concluded that it was a single clinical condition that also exhibited atopic dermatitis [3]. Only in 2000, a group of French-English researchers identified 13 families with several mutations in *SPINK5*, the encoding gene to serine protease inhibitor (LEKTI), as the cause of Comèl/Netherton syndrome, [4]. LEKTI deficiency plays a role in the barrier dysfunction of the skin and therefore in the pathogenesis of inflammation and the typical hair defect. Comèl/Netherton syndrome encompasses three main clinical findings: 1) ichthyosiform dermatitis and/or ichthyosis linearis circumflexa with peculiar "double-edged" scales, 2) hair shaft defects with peculiar "trichorrhexis invaginata (bamboo pole hair)," 3) atopic dermatitis.



Figure 5. Light microscopy showing a bamboo-like hair.

Intellectual disability, short stature, and tendency to develop food allergies are also reported [5]. Next generation sequencing analysis in our patients allowed a more precise clarification concerning the impact of the mutation on the structure of protein, predicted to be "strong" according to ACMG Standard Guidelines [6].

The use of dermoscopy and trichoscopy for the observation of the hair shaft has been introduced as an easy method for the observation of hair in Comèl/Netherton syndrome and in some genodermatosis with hair alterations similar to Netherton/Comèl syndrome [5, 7-9]. We have recently emphasized the role of trichoscopy as a useful first investigation when there is a suspicion of Comèl/Netherton syndrome. Obviously, SEM allows more detailed observations of the hair shaft and has been used in studies concerning the pathogenesis of bamboo hair [10-11].

Conclusion

A diagnostic pathway and the description of a new *SPINK5* variant have been discovered for these two patients. Genetically, a frameshift insertion, homozygous variant c.238_239insG (p.Ala80fs) in the *SPINK5* gene has been described for the first time in the literature to our knowledge. However, a compound heterozygosity of this variation with a hypothetical deletion could be possible, but the lack of parents' DNA did not allow us to make this determination. This is one of the few "target-gene" studies that has allowed the identification of additional mutations and to extend the clinical features associated with variants in the *SPINK5* gene.

Potential conflicts of interest

The authors declare no conflicts of interest.

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