BJMG 23 (1), 2020 • 91-94
DOI: 10.2478/bjmg-2020-0012
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CASE REPORT

A NEW SPLICE-SITE MUTATION OF *SPINK5* GENE IN THE NETHERTON SYNDROME WITH DIFFERENT CLINICAL FEATURES: A CASE REPORT

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ABSTRACT

Netherton syndrome (NS) is a rare genodermatosis characterized by the triad of ichthyosiform erythroderma, hair shaft abnormality and an atopic diathesis. We report a case of a 20-year-old male patient presented with pruritus, decreased sweat secretion and generalized erythema on his body. Netherton syndrome is caused by mutations in the *SPINK5* gene that is a crucial role for epidermal barrier function in the skin. Different clinical and phenotypical features can occur based on various LEKTI-domains mutations. Diagnosis is made by the atopic story, hair shaft abnormality, cutaneous lesions and identification of the *SPINK5* gene mutation. In our patient, we detected a new splice site mutation in the *SPINK5* gene and pili annulati as hair abnormality. Affected patients are usually misdiagnosed because of cutaneous lesions such as atopic dermatitis. Therefore, each clinical finding should be evaluated together. We aimed to present a case with a new *SPINK5* gene mutation and different clinical features in NS.

Keywords: Hair shaft abnormality; Netherton syndrome (NS); *SPINK5* gene mutation.

INTRODUCTION

Netherton syndrome (NS) is a rare autosomal recessive genodermatosis of cornification characterized by the triad of congenital ichthyosiform erythroderma/ichthyosis linearis circumflexa, trichorrhexis invaginata (bamboo hair), and an atopic diathesis [1]. Netherton syndrome was clinically described in 1964 by Wilkinson *et al.* [2] and its incidence is estimated per 200,000 live births [3]. This disease, originates from mutations in the *SPINK5* gene (encoding the protease inhibitor lympho-epithelial Kazal type inhibitor, LEKTI), in a wide range from mild to severe. As a result of deficiency in the LEKTI function, the skin permeability increases and epidermal barrier function decreases. The clinical presentation may be quite different in affected people. The location, type and the size of genetic mutations (*SPINK5*), may affect the phenotypical findings and clinical presentations [4,5]. Here, we aimed to present a case with a new mutation in the *SPINK5* gene, different hair shaft abnormality and different clinical features in NS.

Clinical Presentation. A 20-year-old male patient was referred to our department with complaints of pruritus, decreased sweat secretion and generalized erythema on his body. Erythematous lesions have been repeated since birth. He was born at term and did not have any history of collodion membrane at birth. He did not have a family history for this illness and his parents were cousins. In the following years, hair loss and dental development disorders have been added. Dermatological examination showed generalized erythema, dryness affecting almost all the body surface and desquamation on some body areas, regression on frontal hair-line, loss of eyebrows and eyelash. Scalp hairs could not grow and the hair shaft was short and thin. The presence of a hair shaft abnormality called "pili annulati" was demonstrated by trichogram examination [Figure 1(a), 1(b), (c); Figure 2(a), (b), (c)]. We did not detect any changes in the nails, palms and mucosal surfaces. Serum IgE level was found to be elevated (>2000.0 UI/mL). The patient was a student at a university and his mental development was normal. A skin biopsy was performed on the trunk. The histological examination of the biopsy showed a mild hyperkeratosis, hypergranulosis, acanthosis and a perivascular lymphoplasmocytic infiltrate in the upper

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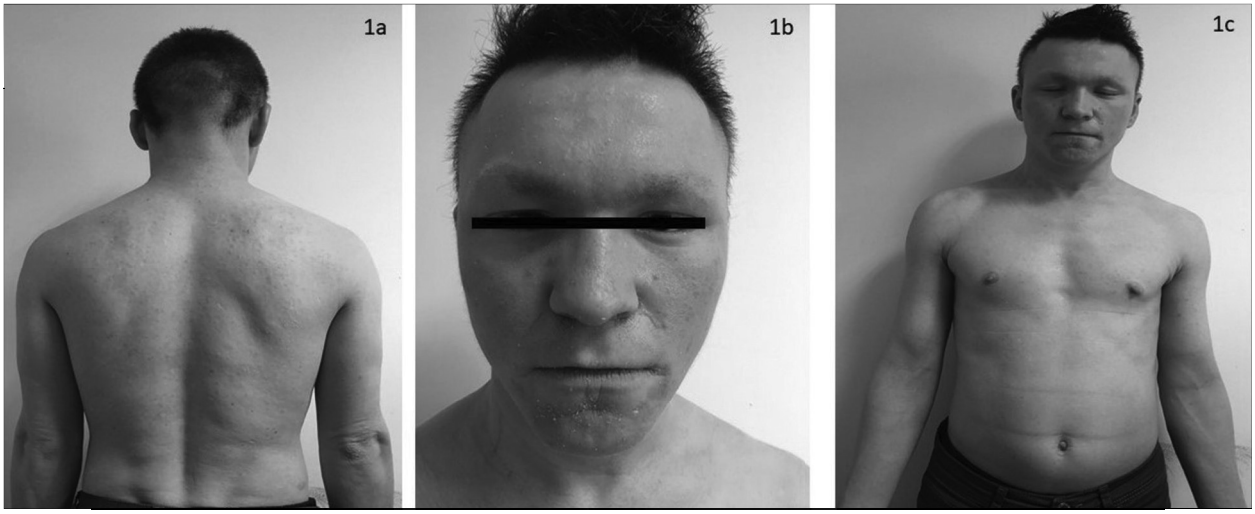

Figure 1. (a), (b), (c): There is showed erythema and desquamation on the trunk and face, regression in frontal hair-line, loss of eyebrows and eyelash.

Figure 2. (a), (b), (c): In the hair shaft examination, Pili annulati abnormality. (100X or 200X magnification under light microscobic.)

dermis. Molecular analysis detected a c.1608-1G>A splice site mutation in the *SPINK5* (NM_001127698.1) gene. The patient was considered to carry NS as a result of molecular analysis, clinical and histopathological findings.

Genetic Analysis. Clinical exome solution by Sophia Genetics® (Saint-Sulpice, Switzerland) was performed for molecular diagnosis of the patient. For the variant filtering process, we considered only nonsense and missense variants, insertions/deletions, and variants at canonical splice sites, excluding variants with minor allele frequency greater than 0.01 in different public and local resources. The c.1608-1G>A splice site mutation was detected in the *SPINK5* (NM_001127698.1) gene. Moreover, this variation has not been reported in GnomAD, Exac and inhouse databases, but it is listed as a 'disease causing' mutation at several *in silico* databases. Parenteral segregation was confirmed with Sanger sequencing. Informed consent was obtained from the patient included in this case report.

DISCUSSION

Netherton syndrome is caused by mutation in serine protease inhibitor, kazal type 5 gene, which is located on the long arm of chromosome 5q32. Lympho-epithelial Kazal type inhibitor (LEKTI) is expressed in epithelium, mucosa, thymus and produced by the *SPINK5* gene. Human tissue kallikreins (KLKs) are expressed in the skin including a serine-proteases family and secreted together with LEKTI. The balance of KLKs and LEKTI, including other serine proteases and their inhibitors, is important for regulation of a skin barrier. If KLKs activities increase in the skin, increased activity may break down a normal epidermal barrier.

Different clinical manifestation are derived from various LEKTI-domains mutations [4-7]. Hence, phenotypic features could be substantially different. Up to now, in patients with NS, 80 different mutations have been defined that are associated with the *SPINK5* gene [8-10].

A large proportion of patients with NS start erythematous lesions at birth or soon after, later develop polycylic patches with double edged scaling called ichthyosis linearis circumflexa and may persist throughout their lives [11]. In our patient, there were no typical lesions, but there was disseminated ichthyosiform erythema affecting almost all the body surface and desquamation on some body areas.

Hair shaft abnormalities usually occur later than skin lesions. In affected patients, hair shafts are short, thin and

do not grow. Trichorrhexis invaginata (TI) is most commonly seen form and happens to depend on invagination of the distal portion of the hair shaft into the proximal portion. The presence of this shaft abnormality can be demonstrated by trichogram or trichoscopy and provide the most particular clue for diagnosis. Trichorrhexis invaginata is just a supportive finding for diagnosis, but its absence does not rule out a diagnosis, as in our case. Our patient had pili annulati as a hair shaft abnomality. Pili annulati is a rare hair shaft disorder consisting of bright and dark sections. There are abnormal air spaces within the bright bands of hair cortex. In this hair shaft abnormality, the hair cannot grow and fragility is not commonly present. We detected other hair shaft abnormalities such as trichorrhexis nodosa and pili torti excluding TI in the literature research (pubmed database) [12,13]. However, we could not find any NS case with pili annulati.

We know that the *SPINK5* gene is expressed on epithelial surfaces. If there is a deficiency in the function of this gene, the penetration of many allergens will increase and it cannot provide a protective effect against these allergens. As a result, atopic manifestation or disorders (such as atopic dermatitis, asthma, allerjic rhinitis, urticaria, food allergies and increased serum IgE levels) will occur. As a matter of fact, it has been suggested that two-thirds of patients have allergic disorders [14,15]. Our patient had a high serum IgE level but did not have any atopic manifestation or food allergy.

Some patients can have recurrent infections, mental-motor retardation, metabolic imbalance and intestinal pathologies [10,16-18]. Although NS is a rare disease, some familial cases also have been reported [19,20].

The diagnosis is supported by the presence of finding such allergic or atopic story, hair shaft abnormality, ichthyosiform erythroderma and identification of a germline *SPINK5* mutation by DNA sequencing. Although, various treatment methods such as topical corticosteroids, topical calcineurin inhibitors, topical and systemic retinoids, phototherapy and infliximab are used; there is no cure for NS at this time [11].

Conclusions. As a result, NS can be presented in a manner that can range from mild clinical signs to life-threatening complications, especially in the neonatal period. If we evaluate these clinical presentations alone, we may cause a misdiagnosis or a delayed diagnosis. Therefore, it will be a more accurate approach to evaluate each clinical findings together. We presented a patient with NS who had different clinical features because of the presence of a previously unreported pili annulati abnormality and a new *SPINK5* gene mutation, the absence of mental retardation and frequent infections.

Declaration of Interest. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

REFERENCES

1. Netherton EW. A unique case of trichorrhexis nodosa; bamboo hairs. AMA Arch Derm. 1958; 78(4): 483-487.
2. Wilkinson RD, George HC, William AH. Netherton's disease: Trichorrhexis invaginata (bamboo hair), congenital ichthyosiform erythroderma and the atopic diathesis. A histopathologic study. Arch Dermatol. 1964; 89(1): 46-54. doi: 10.1001/archderm.1964.0159025005 2010.
3. Sarri CA, Roussaki-Schulze A, Vasilopoulos Y, Zafiriou E, Patsatsi A, Stamatis C, *et al.* Netherton syndrome: A genotype-phenotype review. Mol Diag Ther. 2017; 21(2): 137-152.
4. Fortugno P, Grosso F, Zambruno G, Pastore S, Faletra F, Castiglia D. A synonymous mutation in SPINK5 exon 11 causes Netherton syndrome by altering exonic splicing regulatory elements. J Hum Genet. 2012; 57(5): 311-315.
5. Zhang X-B, Zhang S-Q, He Y-Q, Luo Y-W, Luo Q, Li C-X. Netherton syndrome in one Chinese adult with a novel mutation in the SPINK5 gene and immunohistochemical studies of LEKTI. Indian J Dermatol. 2012; 57(4): 265-268.
6. Bitoun E, Chavanas S, Irvine AD, Lonie L, Bodemer C, Paradisi M, *et al.* Netherton syndrome: Disease expression and spectrum of SPINK5 mutations in 21 families. J Invest Dermatol. 2002; 118(2): 352-361.
7. Komatsu N, Saijoh K, Jayakumar A, Clayman GL, Tohyama M, Suga Y, *et al.* Correlation between SPINK5 gene mutations and clinical manifestations in Netherton syndrome patients. J Invest Dermatol. 2008; 128(5): 1148-1159.
8. Tüysüz B, Ojalvo D, Mat C, Zambruno G, Covaciu C, Castiglia D, *et al.* A new SPINK5 donor splice site mutation in siblings with Netherton syndrome. Acta Derm Venereol. 2010; 90(1): 95-96.
9. Fong K, Akdeniz S, Isi H, Taskesen M, McGrath JA, Lai Cheong JE. New homozygous SPINK5 mutation, p. Gln333X, in a Turkish pedigree with Netherton syndrome. Clin Exp Dermatol. 2011; 36(4), 412-415.
10. Nevet MJ, Indelman M, Ben-Ari J, Bergman R. A case of Netherton syndrome with intestinal atresia, a novel SPINK5 mutation, and a fatal course. Int J Dermatol. 2017; 56(10): 1055-1057.

11. Roda Â, Mendonça-Sanches M, Travassos AR, Soares-de-Almeida L, Metze D. Infliximab therapy for Netherton syndrome: A case report. JAAD Case Rep. 2017; 3(6): 550-552.
12. Srinivas SM, Hiremagalore R, Suryanarayan S, Budamakuntala L. Netherton syndrome with pili torti. Int J Trichology. 2013; 5(4): 225-226.
13. Mirmirani Paradi, Huang KP, Price VH. A practical, algorithmic approach to diagnosing hair shaft disorders. Int J Dermatol. 2011; 50(1): 1-12.
14. Śmigiel R, Królak-Olejnik B, Śniegórska D, Rozensztrauch A, Szafrańska A, Sasiadek MM, *et al.* Is c.1431-12G>A a common European mutation of SPINK5? Report of a patient with Netherton syndrome. Balkan J Med Genet. 2017; 19(2): 81-84.
15. Hovnanian A. Netherton syndrome: Skin inflammation and allergy by loss of protease inhibition. Cell Tissue Res. 2013; 351(2): 289-300.
16. Alpigiani MG, Salvati P, Schiaffino MC, Occella C, Castiglia D, Covaciu C, *et al.* A new SPINK5 mutation in a patient with Netherton syndrome: A case report. Pediatr Dermatol. 2012; 29(4): 521-522.
17. Itoh K, Kako T, Suzuki N, Sakurai N, Sugiyama K, Yamanishi K. Severe lethal phenotype of a Japanese case of Netherton syndrome with homozygous founder mutations of SPINK5 c.375_376delAT. J Dermatol. 2015; 42(12): 1212-1214.
18. Diociaiuti A, Castiglia D, Fortugno P, Bartuli A, Pascucci M, Zambruno G, *et al*. Lethal Netherton syndrome due to homozygous p.Arg371X mutation in SPINK5. Pediatr Dermatol. 2013; 30(4): e65-e67.
19. Emre S, Metin A, Demirseren DD, Yorulmaz A, Onursever A, Kaftan B. Two siblings with Netherton syndrome. Turkish J Med Sci. 2010; 40(5): 819-823.
20. Jones SK, Thomason LM, Surbrugg SK, Weston WL. Neonatal hypernatraemia in two siblings with Netherton's syndrome. Br J Dermatol. 1986; 114(6): 741-743.