Netherton Syndrome: A Case-Based Review of Diagnosis, Management, and Emerging Treatments

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SUMMARY Netherton syndrome (NS) is a rare autosomal recessive disorder caused by SPINK5 mutations, leading to LEKTI deficiency and skin barrier dysfunction. It manifests as ichthyosis, trichorrhexis invaginata (bamboo hair), and atopic diathesis, including food allergies, asthma, and elevated IgE levels. Early genetic testing is key for accurate diagnosis and treatment. We report a case of a two-year-old girl initially diagnosed with atopic dermatitis, presenting with severe, persistent skin issues from infancy. The symptoms included dry, scaly, and inflamed skin, along with elevated IgE levels and polysensitization to food allergens. Trichorrhexis invaginata was identified, and genetic testing confirmed NS. Despite treatments with corticosteroids and emollients, the patient continued to experience flare-ups, leading to the use of biological therapy, specifically secukinumab, due to persistent skin barrier dysfunction. NS is often misdiagnosed due to its overlap with atopic dermatitis, especially in early stages. Mutations in SPINK5 vary in severity, influencing treatment outcomes. Current therapies, including corticosteroids, emollients, and immunomodulators, provide limited relief. New treatments like IVIG, retinoids, and biologics (e.g., secukinumab, dupilumab) show promise in managing inflammation and restoring the skin barrier, with secukinumab targeting IL-17A showing significant improvements. The psychosocial impact of NS affects the patient's quality of life, causing anxiety, social withdrawal, and family stress. Early genetic testing, targeted therapies, and psychosocial support are crucial for managing NS. Future research should focus on improving genetic testing accessibility, optimizing combination therapies, and addressing psychosocial challenges.

KEY WORDS: Netherton syndrome; atopic dermatitis; SPINK5 gene; genetic testing; secukinumab

INTRODUCTION

Netherton syndrome (NS) is a rare autosomal recessive disorder affecting epidermal maturation and keratinization [1]. It is characterized by ichthyosiform dermatosis, a distinctive hair abnormality known as trichorrhexis invaginata ("bamboo hair"), and atopic diathesis, including food allergies, asthma, allergic rhinitis, eosinophilia, and elevated IgE levels [1-2]. The syndrome results from pathogenic mutations in the SPINK5 gene, located on chromosome 5q31-32, leading to a loss of function in the serine protease inhibitor Kazal type 5, which encodes the lymphoepithelial Kazal-type related protease inhibitor (LEKTI). LEKTI

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inhibits kallikrein-associated peptidases and cathepsin G and is found in the thymus and epithelium. Loss of LEKTI function disrupts skin barrier integrity, resulting in excessive desquamation, inflammation, and increased susceptibility to infections [3-4]. Despite advances in genetic screening, Netherton syndrome remains underdiagnosed or misdiagnosed as severe atopic dermatitis or ichthyosis linearis circumflexa, delaying appropriate management [5]. This review aims to provide a comprehensive overview of diagnostic challenges, therapeutic options, and future perspectives in the management of Netherton syndrome.

CASE PRESENTATION

A two-year-old girl presented with severe, persistent atopic dermatitis, characterized by widespread dry, scaly, erythematous, and inflamed skin with intense pruritus, significantly affecting her quality of life (Figure 1). Symptoms began in early infancy as erythema and desquamation on the hands. She has a family history of atopic diseases on both sides, and her mother has psoriasis. Initially diagnosed with atopic dermatitis, she had IgE levels of 211 IU/mL and polysensitization to multiple food allergens. She showed temporary improvement with topical corticosteroids and emollients. Her hair was short, brittle, and thin, without growth or developmental delays. Laboratory tests later revealed a significantly elevated IgE level (9439 IU/mL) and polysensitization to nutritional allergens, with mild sensitization to inhalants. Immunophenotyping ruled out immunodeficiency. Dermatoscopy identified trichorrhexis invaginata, confirming Netherton syndrome. Genetic testing detected two pathogenic SPINK5 variants: c.891C>T, p.(Cys297=) and c.1431-12G>A. Skin biopsy results are pending. The patient had been breastfed until 18 months, and dietary elimination of allergens improved her skin condition. Despite various treatments, including emollients, corticosteroids, montelukast, and antihistamines, severe skin exacerbations persisted. Due to ongoing inflammation and skin barrier dysfunction, biological therapy with secukinumab, available in our healthcare system, is planned. Multidisciplinary care is in place, and topical immunomodulators were delayed due to her compromised skin barrier. Genetic counseling was recommended for her parents to assess hereditary risks.

DISCUSSION

Average Age of Diagnosis and Diagnostic Delays

The age of NS diagnosis varies, ranging from infancy to late childhood [2-9]. In neonates, it is often identified due to severe complications such as failure to thrive, feeding difficulties, hypernatremia, dehydration, and erythroderma with extensive desquamation [9]. In our case, symptoms resembling atopic dermatitis were present from birth, worsening after weaning and the introduction of complementary feeding, alongside significantly elevated IgE levels and polysensitization. NS is frequently misdiagnosed as atopic dermatitis due to overlapping eczematous lesions and a family history of atopy. Additionally, distinctive features such as ichthyosis linearis circumflexa, brittle hair, and trichorrhexis invaginata may not appear until later in childhood. Elevated serum IgE levels and variable skin presentations further complicate differentiation [5]. Some cases remain undiagnosed until adulthood, as seen in two sisters initially treated for ichthyosiform erythroderma but later diagnosed with NS following genetic testing [8]. Concomitant SPINK5 and FLG2 mutations can further complicate clinical presentation, mimicking severe atopic dermatitis [10]. Delayed diagnosis increases the risk of malnutrition, infections, and long-term skin barrier dysfunction [11]. Limited access to genetic testing in some regions contributes to misdiagnosis and treatment delays.

GENETIC VARIABILITY AND DISEASE SEVERITY

In our case, genetic analysis confirmed the clinical suspicion, revealing the mutations SPINK5 c.891C>T (p.Cys297=) and SPINK5 c.1431-12G>A in heterozygosity, localized on chromosome 5q32. The c.891C>T variant is a synonymous mutation close to an exon-intron boundary and may potentially interfere with RNA splicing. This variant has been observed in several individuals affected by Netherton syndrome [12-13]. Additionally, the c.1431-12G>A variant, which also lies near an exon-intron boundary, has been identified in individuals with NS and is predicted to affect normal RNA splicing, though this has not yet been confirmed by functional studies [14-

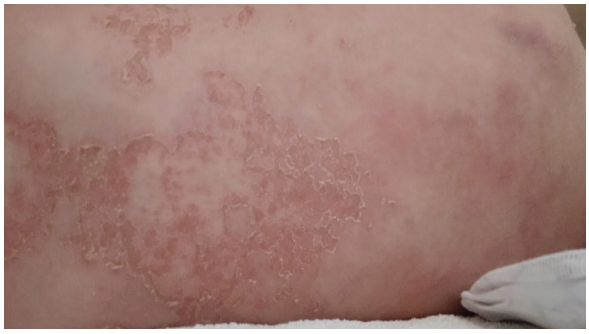

Figure 1. Dry, scaly and erythematous skin of our patient.

16]. The synonymus genetic variant SPINK5 c.891C>T (p.Cys297=) and intron variant SPINK5 c.1431-12G>A is associated with conditions of erythroderma, ichtyosis linearis complexa and increased concentration of circulating IgE [17-18]. Different SPINK5 mutations have been associated with variable disease severity, influencing treatment response [9]. Over 108 pathogenic variants have been identified in NS, with over 80 being nonsense mutations and small deletions/insertions, leading to truncated, nonfunctional proteins. Splicing and missense mutations have also been reported [4, 19]. SPINK5 mutations affect the organ-specific expression of LEKTI isoforms, with upstream mutations generally causing more severe NS phenotypes. Mutations occurring earlier in the LEKTI gene result in a more severe phenotype compared to those located closer to the 3′ region [9]. Specific truncating mutations may lead to more severe skin barrier defects and increased infection risk, while missense mutations might result in a milder phenotype [19]. This highlights the potential role of genotype-phenotype correlations in predicting disease course and therapeutic response [1].

Psychosocial Impact and Quality of Life

Patients with Netherton syndrome experience chronic pruritus, recurrent infections, and visible skin lesions. These symptoms lead to psychosocial distress and reduced quality of life. Children may develop anxiety, social withdrawal, and school absenteeism due to persistent symptoms and visible skin changes. Family burden is also significant, it requires continuous medical care, dietary modifications, and psychological support. Stigma and emotional distress related to severe skin manifestations further contribute to diminished self-esteem and mental health challenges [20].

Current and Emerging Therapeutic Approaches

In our case, the available therapy was mostly symptomatic, with a good response to local or intravenous corticosteroid administration but with occasional exacerbations. There is no standardized protocol for the treatment nor ideal treatment, therapy is mainly supportive. Current available treatments include topical emollients, antihistamines, corticosteroids, and calcineurin inhibitors which provide symptomatic relief but do not address the underlying cause [4]. Systemic corticosteroids are not a primary treatment for Netherton syndrome but may help during flare-ups. Cyclosporine, used in autoimmune and skin disorders, has shown no documented effectiveness in NS, with reported cases failing to demonstrate improvement. Due to limited and inconclusive data, its efficacy remains uncertain [1]. During exacerbations antibiotics and intravenous immunoglobulins (IVIG) can also be used. Intravenous immunoglobulin acts on opsonization of bacteria and phagocytosis and consequently reduces inflammation and incidence of infections [4]. Immunoglobulin therapy has shown clinical improvement in 13 out of 15 reported NS patients, likely due to immunomodulatory effects rather than IgG deficiency. Most treated patients were children, experiencing reduced inflammation, erythema, scaling, infections, and improved quality of life, with some showing growth improvements. Data on adults are limited, with only one case reporting mild improvement after six months of IVIG treatment [1]. Retinoids, synthetic vitamin A analogs, have shown mixed results in NS, primarily reducing scaling through their anti-keratinizing effects. Some patients improved, while others worsened, suggesting lower doses may be beneficial, though inconsistent reporting limits conclusions. Their effectiveness may depend on scaling severity versus erythroderma, but no standardized assessments confirm this. Retinoids remain a secondary treatment option compared to immunoglobulins and biologics [1]. Oral retinoids, acitretin and isotretinoin have been used, but their efficacy is inconsistent, some patients experiance worsening and side effects such as bone toxicity, teratogenicity, growth retardation and hepatotoxicity are limiting their use and outweight the benefits of their use [4]. The key challenge in NS is finding treatments that restore the skin barrier and control chronic inflammation. Biologic therapies show promise as targeted treatments, addressing Th2/Th17 pathway upregulation, high TNF-α, and elevated IgE levels. Seven biologicals have been studied, with dupilumab and secukinumab being the most frequently used [1]. Patients with NS exhibit increased IL-17A signaling, making IL-17 blockade a potential therapeutic target. Secukinumab, a monoclonal antibody that binds IL-17A and prevents its interaction with its receptor, has shown promising results in case reports, particularly in pediatric patients. Studies have reported improvements in skin condition, reduced pruritus, decreased use of topical steroids, and, in some cases, enhanced growth rates without significant adverse effects. By targeting IL-17A, secukinumab helps modulate inflammation and may contribute to restoring the skin barrier, making it a promising option for managing NS [6]. Dupilumab is also effective in NS as it blocks the IL-4 receptor alpha subunit, inhibiting IL-4 and IL-13 signaling, which are key drivers of the TH2 inflammatory response. Case reports on dupilumab show

improved skin condition, reduced pruritus, inflammation, IgE, and eosinophil levels, along with lower disease severity scores. Patients experienced better ichthyosis, hair growth, and reduced need for immunoglobulin therapy. By targeting IL-4 and IL-13, dupilumab helps regulate immune dysregulation and may aid in skin barrier restoration in Netherton syndrome [21]. Infliximab, a chimeric antibody that blocks both circulating and transmembrane TNF-α, was used in one case report. Elevated TNF-α levels contribute to disease severity in NS. A pediatric case showed significant skin improvement after infliximab treatment, with decreased disease severity during the use [22]. Ustekinumab is a monoclonal antibody that blocks the p40 subunit shared by IL-12 and IL-23, inhibiting both TH1 and TH17 immune responses involved in inflammation [21]. A case report of a 15-year-old patient with uncontrolled skin lesions showed significant improvement after the second dose, with sustained remission after one year of treatment [23]. Biological therapy appears to be a promising and generally safe option for pediatric NS, though larger controlled trials are needed for definitive conclusions. Given its consistent clinical benefits, IL-17A blockade with secukinumab or ixekizumab is the preferred choice for patients with severe inflammatory and pruritic skin manifestations. Dupilumab, targeting IL-4 and IL-13, may be beneficial for patients with a strong Th2-driven immune profile, while ustekinumab, which inhibits IL-12 and IL-23, could be considered in cases resembling psoriasis. TNF-α inhibitors like infliximab have shown efficacy but carry a higher risk of serious infections, requiring close monitoring. Regardless of the chosen therapy, pre-treatment vaccination, infection surveillance, and individualized treatment plans based on immune and clinical profiles are essential for optimizing outcomes [21]. Additionally, emerging therapies targeting IL-36 and Th9 pathways are currently being explored as additional treatment strategies [24].

Future Directions and Research Recommendations

By increasing availability and affordability of genetic testing, more patients could be accurately diagnosed at an earlier stage, allowing for timely medical intervention and potentially better clinical outcomes [4]. Further research should explore the potential of combination therapy strategies, particularly the concurrent use of IL-17 and IL-4/IL-13 inhibitors. Current reports suggest that some patients respond well to secukinumab, while others benefit more from dupilumab, raising the possibility that a combined approach could yield better disease control [4]. Long-term studies on the safety, efficacy, and accessibility of biologic treatments are essential. Given that NS is a lifelong condition, assessing the sustained benefits and risks of biologic agents in pediatric and adult populations is necessary. Prospective trials and real-world evidence could provide valuable data to guide clinical decision-making, particularly in determining which patients are most likely to benefit from specific biologic therapies [25]. Beyond treatment, addressing the psychosocial burden of Netherton syndrome is crucial. Future research should focus on psychological counseling, social support programs, and caregiver education to enhance patient and family well-being [20].

CONCLUSION

Netherton syndrome is a severe dermatological disorder requiring early diagnosis, multidisciplinary management, and personalized treatment approaches. Genetic testing is crucial for accurate diagnosis and intervention. Advances in biological therapies such as secukinumab and dupilumab offer new hope, though accessibility remains a challenge. This case underscores the need for improved genetic screening, early intervention, and a holistic approach to care. Future research should focus on optimizing treatment strategies, improving genetic testing access, and addressing the psychosocial burden of Netherton syndrome.

Parental Consent

Written informed consent was obtained from the patient's parents for the publication of this case report, in accordance with ethical guidelines.

References

1. Nouwen AEM, Schappin R, Nguyen NT, Ragamin A, Bygum A, Bodemer C, *et al.* Outcomes of systematic treatment in children and adults with Netherton syndrome: A systematic review. Front Immunol. 2022;13:864449.
2. Sun C, Chen Y. Treatment of Netherton syndrome in pediatrics with upadacitinib. Altern Ther Health Med. 2025;31:266-9.
3. Herz-Ruelas ME, Chavez-Alvarez S, Garza-Chapa JI, Ocampo-Candiani J, Cab-Morales VA, Kubelis-López DE. Netherton syndrome: Case report and review of the literature. Skin Appendage Disord. 2021;7:346-50.
4. Kostova P, Petrova G, Shahid M, Papochieva V, Miteva D, Yordanova I, *et al.* Netherton syndrome-A therapeutic challenge in childhood. Clin Case Rep. 2024;12(4):e8770.

5. Leung AKC, Barankin B, Leong KF. An 8-year-old child with delayed diagnosis of Netherton syndrome. Case Rep Pediatr. 2018;30:9434916.
6. Inaba Y, Kanazawa N, Muraoka K, Yariyama A, Kawaguchi A, Kunimoto K, *et al.* Dupilumab improves pruritus in Netherton syndrome: A case study. Children (Basel). 2022;9(3):310.
7. Saleem H, Shahid M, Shahbaz A, *et al.* Netherton syndrome: A case report and review of literature. Cureus. 2018;10(7):e3070.
8. Martin-García C, Godoy E, Cabrera A, *et al.* Report of two sisters with Netherton syndrome successfully treated with dupilumab and review of the literature. Int J Immunopathol Pharmacol. 2023;37:1-5.
9. Di Nora A, Consentino MC, Messina G, Timpanaro T, Smilari P, Pavone P. Severe hypernatremia as presentation of Netherton syndrome. Glob Med Genet. 2023;10(4):335-8.
10. Moar A, Bruni M, Schena D, Rigotti E, Colato C, Novelli A, *et al.* Netherton syndrome plus atopic dermatitis: Two new genetic mutations in the same patient. Clin Case Rep. 2021;9(11):e05108.
11. Luchsinger I, Knöpfel N, Theiler M, *et al.* Secukinumab therapy for Netherton syndrome. JAMA Dermatol. 2020;156(8):907-11.
12. Lacroix M, Lacaze-Buzy L, Furio L, Tron E, Valari M, Van der Wier G, *et al.* Clinical expression and new SPINK5 splicing defects in Netherton syndrome: unmasking a frequent founder synonymous mutation and unconventional intronic mutations. J Invest Dermatol. 2012;132(3 Pt 1):575-82.
13. 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):311-5.
14. Raghunath M, Tontsidou L, Oji V, Aufenvenne K, Schürmeyer-Horst F, Jayakumar A, *et al.* SPINK5 and Netherton syndrome: novel mutations, demonstration of missing LEKTI, and differential expression of transglutaminases. J Invest Dermatol. 2004;123(3):474-83.
15. Sitek JC, Kulseth MA, Rypdal KB, Skodje T, Sheng Y, Retterstøl L. Whole-exome sequencing for diagnosis of hereditary ichthyosis. J Eur Acad Dermatol Venereol. 2018;32(6):1022-7.
16. Ilias C, Evgenia B, Aikaterini P, Asimina GT, Constantina S, Maria L, *et al.* Netherton syndrome in a neonate with possible growth hormone deficiency and transient hyperaldosteronism. Case Rep Pediatr. 2015;2015:818961.
17. National Center for Biotechnology Information. ClinVar; [VCV000374066.17]. Available from: https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV000374066.17 (accessed Feb. 24, 2025).
18. National Center for Biotechnology Information. ClinVar; [VCV000372516.43]. Available from: https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV000372516.43 (accessed Feb. 24, 2025).
19. Moltrasio C, Romagnuolo M, Riva D, Colavito D, Ferrucci SM, Marzano AV, *et al.* Netherton syndrome caused by heterozygous frameshift mutation combined with homozygous c.1258A>G polymorphism in SPINK5 gene. Genes (Basel). 2023;14(5):1080.
20. Versteegh JJ, Dulfer K, Stuvel K, Pasmans SG, Utens EM. Netherton syndrome; neuropsychological and psychosocial functioning of child and adult patients and their parents. J Health Psychol. 2020;25(13-14):2296-316.
21. Pontone M, Giovannini M, Filippeschi C, Oranges T, Pedaci FA, Mori F, *et al.* Biological treatments for pediatric Netherton syndrome. Front Pediatr. 2022 Dec 23;10:1074243.
22. Cicek F, Cekic S, Kilic SS. Infliximab therapy in an infant with Netherton syndrome. Pediatr Dermatol. 2021;38(3):714-6.
23. Volc S, Maier L, Gritsch A, Aichelburg MC, Volc-Platzer B. Successful treatment of Netherton syndrome with ustekinumab in a 15-year-old girl. Br J Dermatol. 2020;183(1):165-7.
24. Barbieux C, Bonnet des Claustres M, Fahrner M, Petrova E, Tsoi LC, Gouin O, *et al.* Netherton syndrome subtypes share IL-17/IL-36 signature with distinct IFN-α and allergic responses. J Allergy Clin Immunol. 2022;149(4):1358-72.
25. Barbati F, Giovannini M, Oranges T, Lodi L, Barni S, Novembre E, *et al.* Netherton syndrome in children: Management and future perspectives. Front Pediatr. 2021;9:645259.