Sibling Pair with Incomplete Feature of Netherton Syndrome: A Case Report*

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ABSTRACT

Introduction: Netherton Syndrome (NS) is characterized by a triad of congenital ichthyosiform erythroderma, trichorrhexis invaginata, and atopic diathesis. Diagnosis of NS poses a challenge due to its variable presentation and overlap with other dermatological conditions. Herein, we report a case of NS in a sibling pair, underscoring the challenges in diagnosis and genetic implications of this condition.

Case Summary: We present a case of an 8-year-old female and a 7-year-old male sibling pair, with Netherton Syndrome, who initially presented with atopic dermatitis and erythroderma without hair shaft abnormalities. Further investigation and genetic testing revealed homogeneous SPINK5 gene mutations in both patients, leading to the diagnosis of NS.

Conclusion: Early recognition and diagnosis of Netherton Syndrome are essential for proper management. In patients with early-onset atopic dermatitis resistant to treatment and recurrent erythroderma, further investigation is needed to exclude other diagnoses like Netherton Syndrome.

Keywords: Netherton Syndrome, hair shaft abnormalities, atopic diathesis, case report, sibling pair

INTRODUCTION

Netherton Syndrome (NS), first described by Comèl in 1949, is a rare genetic disorder with an estimated incidence of 1 in 200,000 live births.[1] It is caused by mutations in the serine protease inhibitor of the Kazal type 5 (SPINK5) gene on chromosome 5q32, encoding the lympho-epithelial Kazal-type-related inhibitor (LEKTI), a serine protease inhibitor of the epidermis, instrumental in maintaining skin barrier function.[2]As pathogenic autosomal recessive homozygous or compound heterozygous variants of the SPINK5 gene occur, a continual breakdown of the skin barrier with secondary inflammation occurs.[2] The deficiency of LEKTI in hair follicle inner root sheaths and the epidermal granular layer results in a loss of inhibition of serine proteinases and unopposed activity of kallikrein-related peptidase 5 (KLK5).[2] Unopposed KLK5 activates KLK7, KLK14 and elastase 2, leading to desmosomal cadherin component desmoglein 1 and other corneodesmosomal protein degradation, resulting in cell adhesion loss desquamation, and early stratum corneum detachment, and ultimately severe skin barrier impairment.[2] KLK5 also triggers the secretion of proinflammatory proallergic cytokines through proteinase-activated receptor 2 (PAR2) signaling in keratinocytes.[2] Increased mediators, such as tumor necrosis factor-α (TNF-α), intracellular adhesion molecule 1 (ICAM-1), interleukin-8 (IL-8) and thymic stromal lymphopoietin (TSLP), heighten allergic predisposition and secondary inflammation.[2] Marked upregulation of T helper type 17 (TH17)/IL-23 pathway and IL-1β expression is also seen in NS patients.[3]

NS is clinically characterized by a triad of manifestations, including congenital ichthyosiform erythroderma, trichorrhexis invaginata (TI) (bamboo hair), and atopic diathesis.[4] Diagnosis of NS poses a challenge due to its variable presentation and overlap with other dermatological conditions. In this paper, we report a case of NS in a sibling pair, highlighting the challenges in diagnosing and managing this condition.

Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.

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CASE REPORT

We present the case of an 8-year-old female and a 7-year-old male sibling, born to non-consanguineous parents, who both presented with atopic dermatitis and frequent erythroderma since infancy. The younger sibling was born to a then 24-year-old G2P2 mother. Both pregnancies and deliveries were unremarkable, and both had normal results for Newborn screening.

At birth, both siblings presented with erythematous papules, patches, and plaques on the bilateral cheeks without scaling. In the first few weeks of life, these initial lesions evolved to include the face, trunk, back, axilla, and bilateral extremities. The siblings were noted to be irritable, probably due to pruritus. They were initially diagnosed with Atopic Dermatitis and managed with topical steroids, moisturizing lotion, and petrolatum, which afforded temporary improvement of the lesions.

Both siblings developed recurrent exfoliative dermatitis during infancy up to early childhood, occurring at least twice a year. They had frequent admissions for "skin infection," where antibiotics and petrolatum would be prescribed.

Due to the chronicity and recurrence of the disease, the mother decided to seek a second opinion at our institution when the female sibling was 8 years old and the male sibling was 7 years old. The review of systems for both siblings was unremarkable. Past medical history revealed atopic diathesis in both siblings. Family history was positive for atopic dermatitis on the maternal side (see genogram).

On physical examination, both presented with generalized well-defined erythematous to hyperpigmented annular patches and plaques topped with polycyclic scales, more pronounced on the flexural areas. For the younger male sibling, there was yellow discoloration of the nails with onycholysis, while the elder female sibling had no nail changes. Neither presented with the characteristic bamboo hair, even under close examination through dermoscopy and light microscopy.

The siblings were clinically diagnosed as a case of Ichthyosis, probably epidermolytic ichthyosis versus Netherton Syndrome, due to the presence of atopic diathesis and Ichthyosis. However, hair shaft abnormalities were absent. Biopsies on both siblings revealed: 1) psoriasiform epidermal hyperplasia, 2) thin strands of parakeratosis (1-2 layers), 3) loss of most of the stratum corneum, some sections showing focal basketweave ortho-hyperkeratosis, 4) with normal granular layer, and no signs of epidermolytic hyperkeratosis, 5) widened intercellular spaces of keratinocytes in the epidermis without blistering, and 6) sparse to moderate superficial perivascular infiltrate of lymphocytes and histiocytes. The assessment given was Psoriasiform Dermatitis with the differential diagnosis of Netherton Syndrome. Molecular genetic work-up was suggested.

Patients were referred to a tertiary pediatric institution for genetic counseling. A congenital ichthyosis panel was recommended and performed. Genetic testing confirmed homozygous mutations in the SPINK5 gene (Exon 10, c.880_882del (p.Val294del)) and heterozygous mutations in the CYP4F22 gene (c.470G>A (p.Arg157His)) in both siblings, confirming the diagnosis of Netherton Syndrome [see **Figure 8**].

Both patients were treated with antihistamines, mineral oil for the scalp, tar shampoo, isotretinoin, emollients, and bleach baths, which afforded improvement of the symptoms. Prior to initiation of oral isotretinoin treatment, baseline laboratory tests (skeletal survey, complete blood count, urinalysis, kidney and liver function tests, lipid profile, fasting blood sugar, and serum cortisol) were performed, with regular follow-up tests. Due to chronic use of topical steroids, referral to Pediatric Endocrinology for evaluation for endocrine disorders and for co-management was done. The service recommended no further diagnostics and treatments, suggesting assessments to include growth velocity, weight, blood pressure, and general well-being, as the patients showed no signs of adrenal insufficiency. Regular teledermatology follow-up showed good compliance and tolerance to prescribed medications, with no significant adverse effects. Follow-up after 6 months of isotretinoin treatment [**Figure 9 and 10]** showed a decrease in the number and erythema of the previous erythematous patches and plaques topped with polycyclic scales. A trial of biologic, an IL-17A inhibitor, was recommended as a treatment option; however, due to financial constraints, it was not given.

DISCUSSION

Netherton Syndrome presents with a spectrum of clinical manifestations ranging from mild to severe.[4] The congenital ichthyosiform erythroderma, characterized by generalized erythema and fine scales, typically manifests at birth and may resemble other forms of congenital ichthyosis, necessitating a thorough differential diagnosis.[5] Trichorrhexis invaginata (TI), resulting from abnormal formation of hair shafts, is pathognomonic for NS.[6] Atopic diathesis, including allergic rhinitis, asthma, and atopic dermatitis, is commonly observed in NS patients, reflecting immune response dysregulation.[7] Genetic testing plays a crucial role in confirming the diagnosis, with SPINK5 mutations identified in the

majority of cases.[8] NS is typically diagnosed upon the presence of allergic manifestations, with the presence of: history of NS in a sibling, identification of SPINK5 mutation by DNA sequencing, scaling erythroderma or hair shaft abnormalities.[9]

In diagnosing NS, a thorough history and physical exam is pertinent. Leung, et.al., presented a case report of an 8-year-old male with sparse hair and erythematous serpiginous patches topped with scales since childhood who was assessed with severe atopic dermatitis.[10] A careful physical exam in another institution revealed the triad of NS, clinching the diagnosis.[10] The presentation of NS in this sibling pair, however, highlights the importance of genetic testing in cases of incomplete features of a possible Netherton Syndrome. In cases presenting with chronic atopic diathesis and erythroderma not responsive to conventional treatment, further molecular testing should be considered for Netherton Syndrome. For dermatologists who encounter numerous pediatric patients, the differential of NS may be kept in mind when assessing patients with the diagnosis of chronic, recurrent, and severe atopic dermatitis[9] [see **Figure 11**]. In a case report by Saleem, et. al, the authors note that NS is usually misdiagnosed as atopic dermatitis due to the presence of allergic manifestations and eczematous skin lesions.[9] It is important to note that we should still include NS in our differentials even if the TI is not observed, as in our case. A similar case of a 2-year-old with NS did not have the pathognomonic symptom of TI.[9] In another case report by Guerra et al., two siblings who first presented with cheek erythema, and later with sparse Ichthyosis linearis circumflexa lesions on the face, trunk and proximal extremities, had the absence of both atopy and TI.[11] The diagnosis of NS was only determined upon genetic testing.[11] In our patients, the presence of skin lesions at birth, which is not a usual presentation of Atopic Dermatitis, should also prompt dermatologists to consider Netherton Syndrome and other genetic skin diseases. Misdiagnosis or delays in diagnosis can occur when the specific features of NS are not evident.

Genetic testing plays a crucial role in confirming the diagnosis, identifying causative mutations, facilitating genetic counseling and guiding family planning.[12] Management of NS involves a multidisciplinary approach focusing on symptomatic relief, prevention of complications, improving quality of life, and genetic counseling for affected families.[4] For this sibling pair, there was close collaboration with the patient's pediatrician who co-managed frequent systemic infections. Due to their rural location, access to pediatric subspecialties was unfortunately limited, but the family was referred to geneticists who provided genetic counseling as part of their management. A recommendation for referral to Family Medicine for holistic care, addressing not only physical but also social, emotional, and overall well-being, was also made.

In the case of the sibling pair diagnosed genetically with NS, treatment strategies must be tailored to address the diverse manifestations and needs of each patient. Treatments include: emollients, topical therapies, topical corticosteroids, topical calcineurin inhibitors, UV phototherapy, systemic therapies such as oral retinoids and immunomodulators, supportive care, and multidisciplinary management.[4]

Natural and synthetic retinoids derived from vitamin A have been the primary treatment for ichthyosis in newborns to adults for decades.[13] They have shown efficacy in NS by modulating keratinocyte differentiation, proliferation, and reducing tissue inflammation, leading to less thickening, scaling, and erythema.[14] For NS, four retinoids (acitretin, alitretinoin, isotretinoin, and etretinate) have been utilized as therapy with varied outcomes.[14] A systematic review by Nouwen, et. al, noted six patients with NS improving with retinoids, with a reduction in the need for topical corticosteroids.[14] The authors noted retinoids were effective in NS patients in which scaling is more pronounced than erythema, suggesting that the benefits of such treatment may be suited for certain subtypes of NS, leaving retinoids as second-line treatment.[14]

Current investigation into the use of biologics for Netherton Syndrome is being done. Allergic and inflammatory pathways are upregulated in patients with NS as a result of SPINK5 gene mutation and LEKTI deficiency, particularly with both Th2 and Th17 pathways amplified and high levels of TNF-α and IgE present.[15] Seven biologicals have been investigated, including those that target IgE (omalizumab), TNF-α (adalimumab, infliximab), IL 12 and IL-23 (ustekinumab), IL-4 and IL-13 (dupilumab), and IL-17 (secukinumab, ixekizumab).[14] In 18 previous cases, these treatments led to clinical improvement, reducing inflammatory lesions, desquamation, and pruritus. Quality of life, hair condition, and sleep improved, while the need for topical corticosteroids and infections decreased.[14] However, studies have shown that different cases of NS have responded to different biologic drugs available, with investigators suggesting that clinical phenotype, and presumably differences in pathway activity between patients, could lead to individual NS patients benefiting from different treatments.[14] For this sibling pair, secukinumab, an IL-17A inhibitor, was offered as a

treatment option; however, consent to begin treatment was not obtained due to financial constraints. As such, oral isotretinoin, antihistamines, mineral oil, tar shampoo, topical corticosteroids, urea solution, emollients, and bleach baths were used, leading to symptom improvement, fewer admissions, and no significant side effects.

CONCLUSION

Netherton Syndrome is a rare genetic disorder characterized by congenital ichthyosiform erythroderma, hair shaft abnormalities, and atopic diathesis. The management of Netherton Syndrome requires a multifaceted approach encompassing topical therapies, phototherapy, systemic agents, and supportive care. Early recognition and diagnosis are crucial for appropriate management. In patients who present with early-onset atopic dermatitis recalcitrant to treatment and frequent erythroderma, Netherton Syndrome should be considered, and further investigation is warranted. Individualized treatment plans should be tailored to address the specific needs and manifestations of each patient, with a focus on optimizing symptom control, preventing complications, and improving long-term outcomes. Close collaboration between healthcare providers and ongoing research efforts is essential to advance our understanding and management of this rare genetic disorder. Further research into the pathophysiology of NS and the development of targeted therapies is warranted to improve outcomes for affected individuals.

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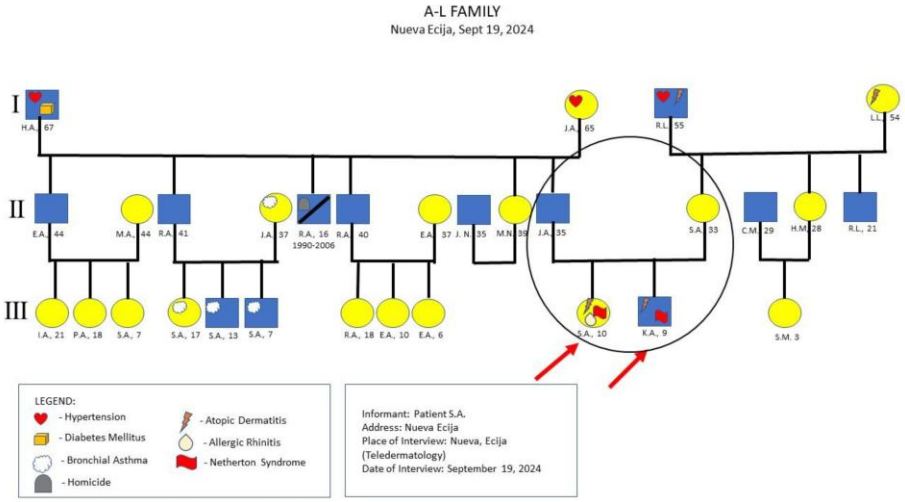

Figure 1: Genogram of the male and female sibling pair showing a family history of maternal Atopic Dermatitis, with Hypertension on both sides and Diabetes Mellitus on the paternal side. Consent on personal and family information was obtained.

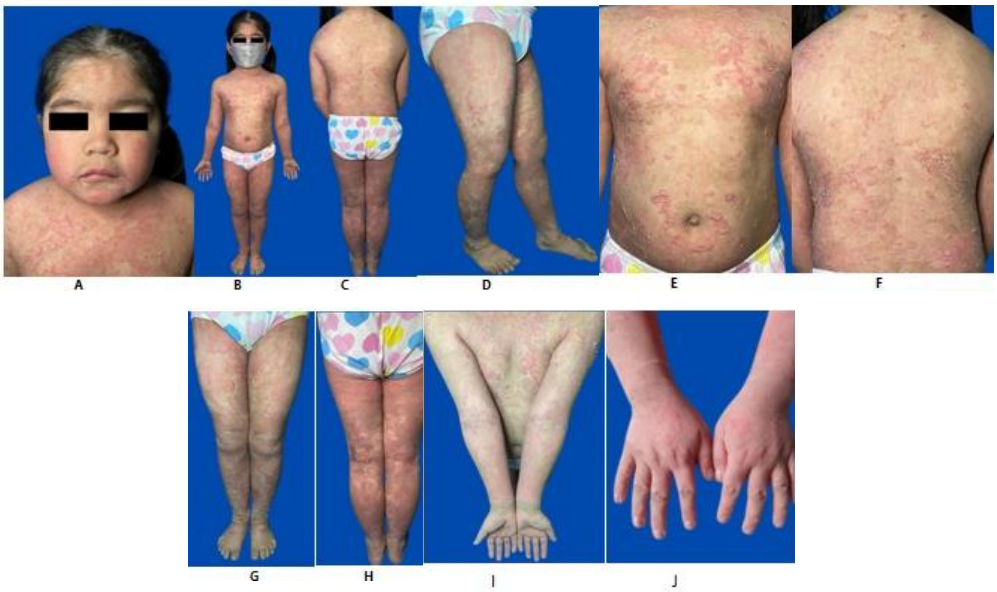

Figure 2: Images of the 8 year old female sibling diagnosed with Netherton Syndrome. The patient presented with generalized, well-defined erythematous to hyperpigmented annular patches and plaques topped with polycyclic scales. There was involvement of the face and scalp (A), trunk and abdomen (E, F), and bilateral upper and lower extremities, with more pronounced polycyclic scales on the flexural areas (H, I). Nail findings were unremarkable (J).

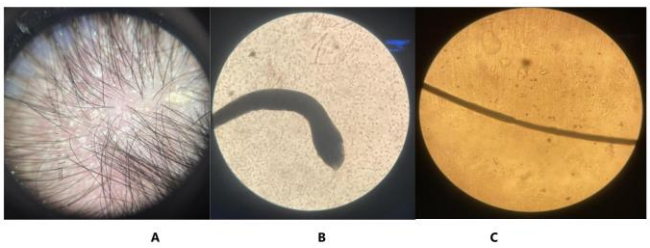

Figure 3: Hair examination of the 8 year old female sibling. While examination revealed erythematous patches topped with scales, sparse, brittle hair was not seen (A). Closer examination of the hair root (B) and hair shaft (C) did not reveal trichorrhexis invaginata.

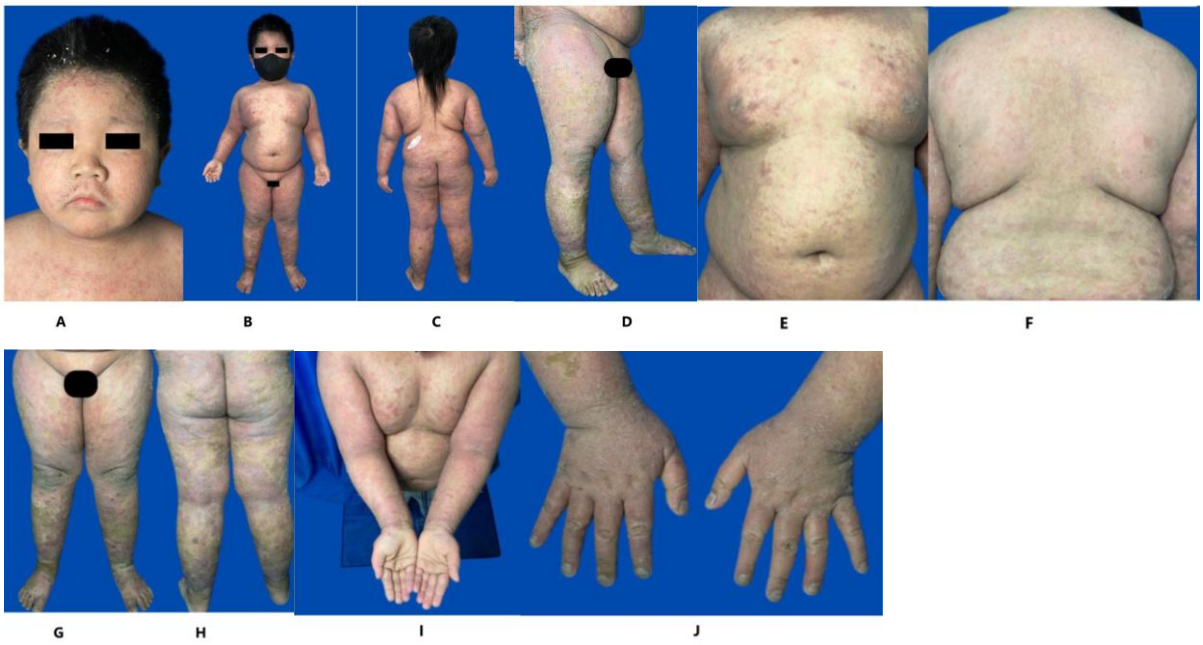

Figure 4: Images of the 7 year old male sibling diagnosed with Netherton Syndrome. The patient also presented with generalized, well-defined erythematous to hyperpigmented annular patches and plaques topped with polycyclic scales. There was involvement of the face and scalp (A), trunk and abdomen (E, F), and bilateral upper and lower extremities (G, H), with more pronounced polycyclic scales on the flexural areas (H, I). Nail findings revealed yellow discoloration with onycholysis (J).

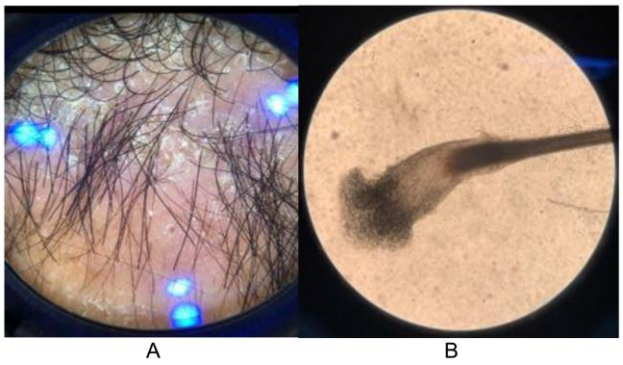

Figure 5: Hair examination of the male sibling. Hair examination showed the absence of the classic trichorrhexis invaginata (A, B)

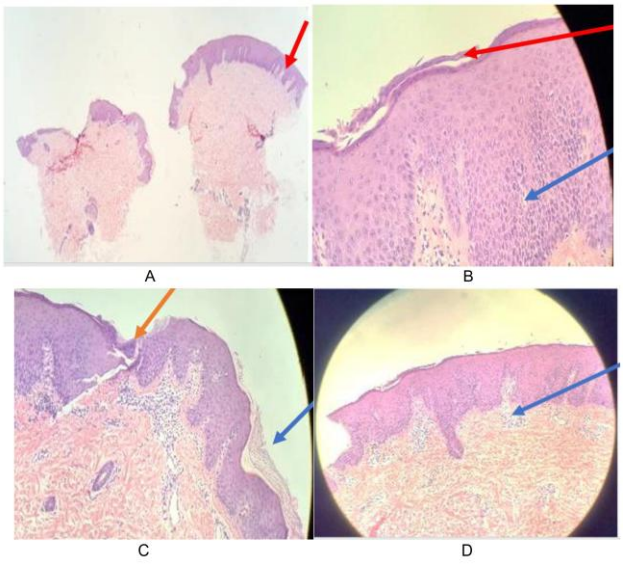

Figure 6: Biopsy report of the female sibling revealing 1) psoriasiform epidermal hyperplasia (A), 2) thin strands of parakeratosis (1-2 layers) (B, red arrow), 3) loss of most of the stratum corneum (C, red arrow), one section showing focal basketweave ortho-hyperkeratosis (C, blue arrow), 4) granular layer normal and showing no signs of degeneration or epidermolytic hyperkeratosis, 5) widened intercellular spaces of keratinocytes in the epidermis without blistering (B, blue arrow), and 6) sparse to moderate superficial perivascular infiltrate of lymphocytes and histiocytes (D).

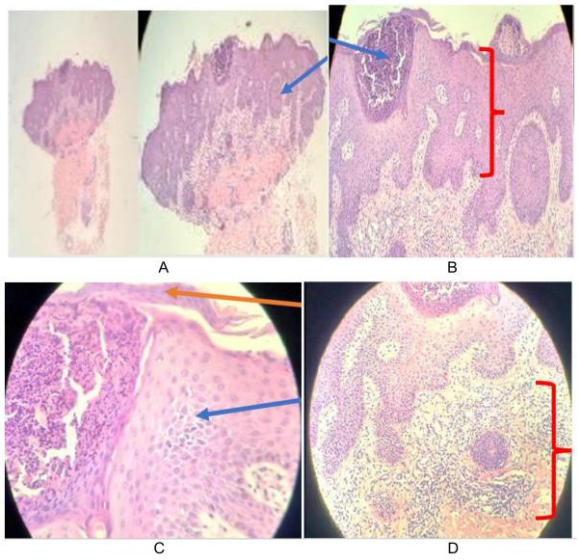

Figure 7: Biopsy report of the male sibling, revealing 1) psoriasiform hyperlapsia (A), subcorneal pustule (B, blue arrow) and ortho-hyperkeratosism (B, red bracket), 2) clusters of neutrophils, some forming small superficial pustules beneath thin parakeratotic strands (C, red arrow), 3) widened intracellular spaces without blister formation in the spinous layer (C, blue arrow) and 4) moderately dense superficial perivascular infiltrate of lymphocytes, histiocytes, eosinophils and melanophages; dilated small blood vessels (D, red bracket).

A

Variant details

CYP4F22, Exon 6, c.470G>A (p.Arg157His), heterozygous, Uncertain Significance

- This sequence change replaces arginine, which is basic and polar, with histidine, which is basic and polar, at codon 157 of the CYP4F22 protein (p.Arg157His).
- This variant is present in population databases (rs199641250, gnomAD 0.03%).
- This variant has not been reported in the literature in individuals affected with CYP4F22-related conditions.
- ClinVar contains an entry for this variant (Variation ID: 1030320).
- Algorithms developed to predict the effect of missense changes on protein structure and function are either unavailable or do not agree on the potential impact of this missense change (SIFT: "Deleterious"; PolyPhen-2: "Probably Damaging"; Align-GVGD: "Class C0").
- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

SPINK5, Exon 10, c.880_882del (p.Val294del), homozygous, Uncertain Significance

- This variant, c.880_882del, results in the deletion of 1 amino acid(s) of the SPINK5 protein (p.Val294del), but otherwise preserves the integrity of the reading frame. This variant also falls at the last nucleotide of exon 10, which is part of the consensus splice site for this exon.
- This variant is present in population databases (rs750225476, gnomAD 0.003%).
- This variant has been observed in individual(s) with Netherton syndrome (PMID: 16601670).
- This variant is also known as c.882+1_882+3del.
- Variants that disrupt the consensus splice site are a relatively common cause of aberrant splicing (PMID: 17576681, 9536098). Algorithms developed to predict the effect of sequence changes on RNA splicing suggest that this variant may disrupt the consensus splice site.
- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

B

Variant details

CYP4F22, Exon 6, c.470G>A (p.Arg157His), heterozygous, Uncertain Significance

- This sequence change replaces arginine, which is basic and polar, with histidine, which is basic and polar, at codon 157 of the CYP4F22 protein (p.Arg157His).
- This variant is present in population databases (rs199641250, gnomAD 0.03%).
- This variant has not been reported in the literature in individuals affected with CYP4F22-related conditions.
- ClinVar contains an entry for this variant (Variation ID: 1030320).
- Algorithms developed to predict the effect of missense changes on protein structure and function are either unavailable or do not agree on the potential impact of this missense change (SIFT: "Deleterious"; PolyPhen-2: "Probably Damaging"; Align-GVGD: "Class C0").
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- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

Figure 8: Genetic Testing Result for the female sibling (labeled A) and male sibling (labeled B). Results show homozygous variant c.880_882del (p.Val294del) for the SPINK 5 gene and heterozygous variant c.470G>A (p.Arg157His) of the CYP4F22 gene for both siblings.

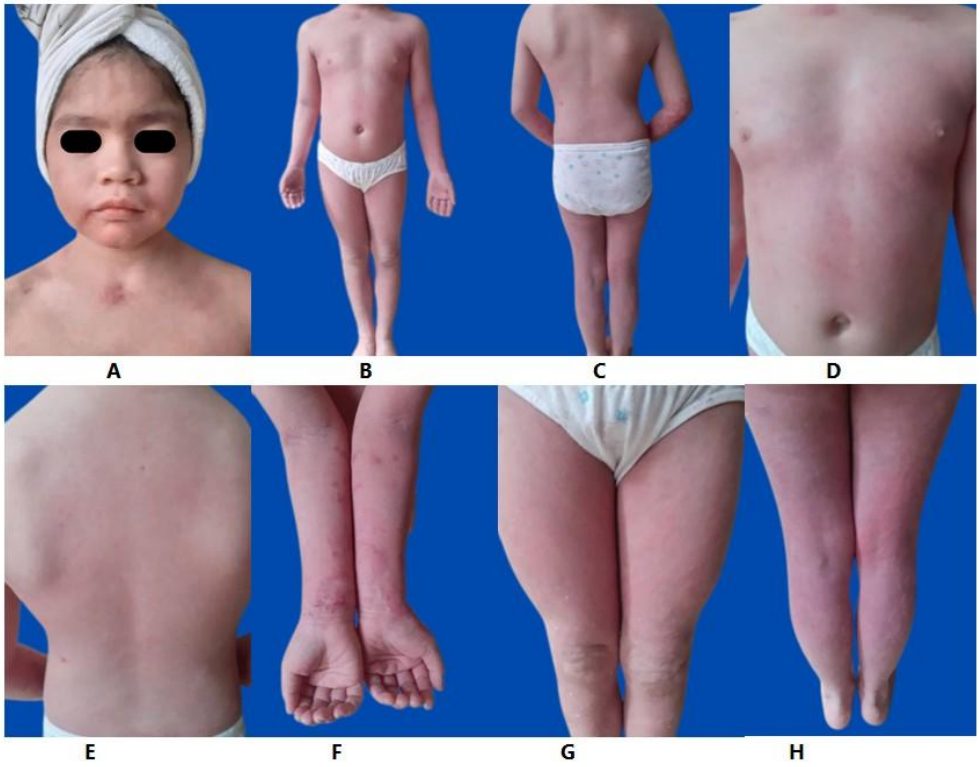


Figure 9: Follow up image through teledermatology of the female Netherton Syndrome sibling after 6 months initiation of Isotretinoin. There was a noted decrease in the multiple erythematous patches and plaques, topped with scales over the face and scalp (A), trunk (D, E), upper extremities (F) and lower extremities (G, H).

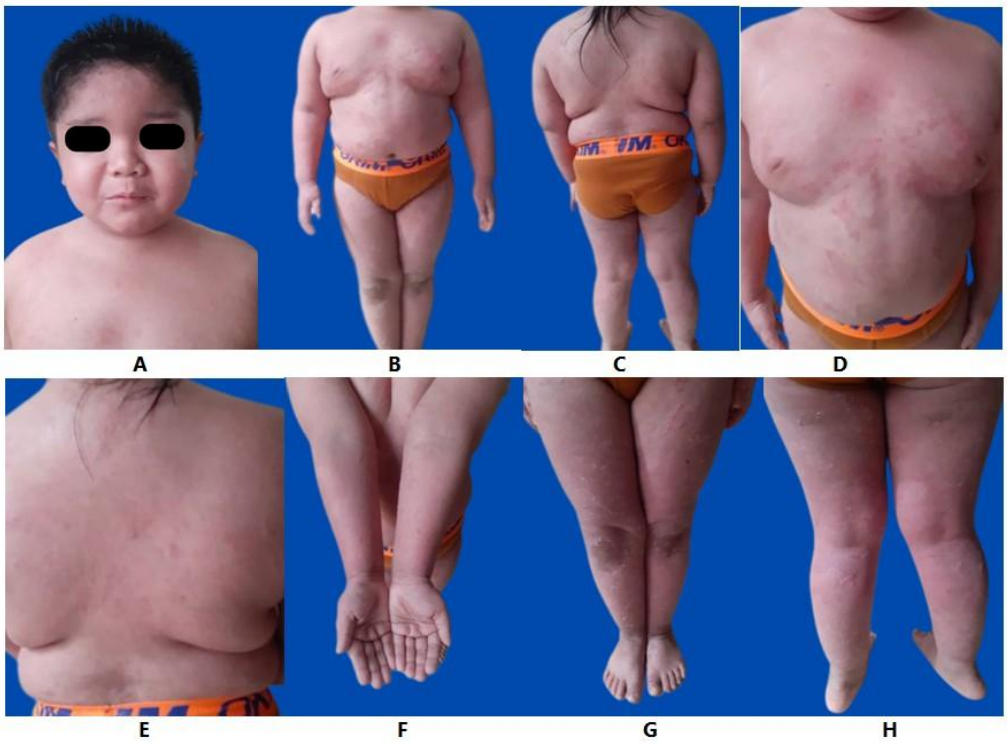
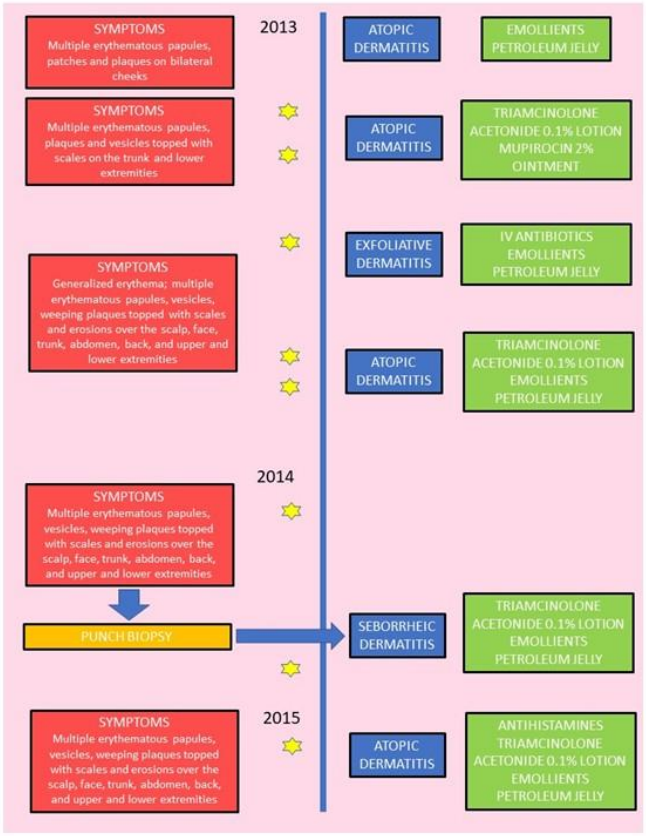


Figure 10: Follow up image through teledermatology of the male Netherton Syndrome sibling after 6 months initiation of Isotretinoin. There was a noted decrease in the multiple erythematous patches and plaques, topped with scales over the face and scalp (A), trunk (D, E), upper extremities (F) and lower extremities (G, H).



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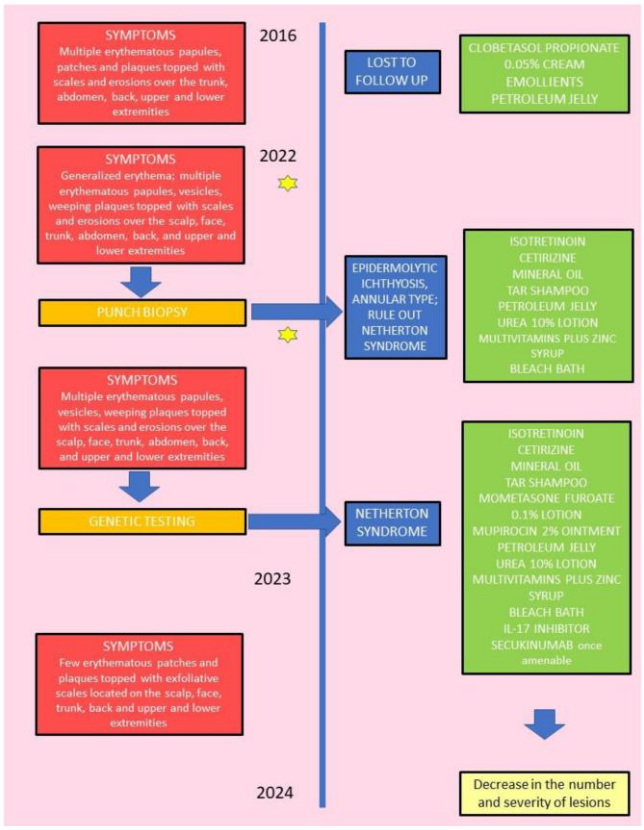

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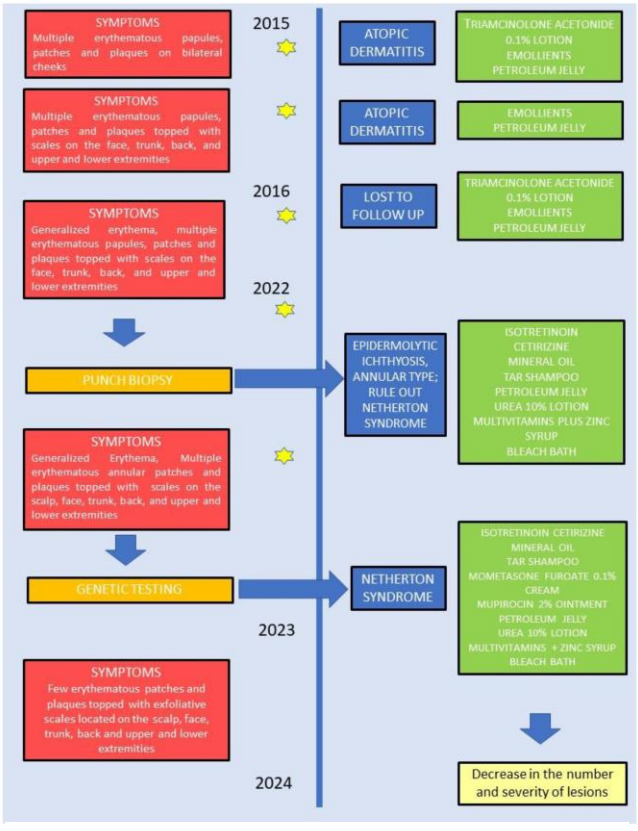

B

Figure 11: The diagnostic dilemma of the two siblings with Netherton Syndrome presented with the female sibling (A1 and A2) and male sibling (B) from birth to consultation, highlighting the symptoms (red boxes), diagnostics (orange boxes), working diagnosis (blue boxes) and treatment (green boxes). Both patients also had several hospitalizations and consultations for episodes of erythroderma, often associated with respiratory or urinary infections (denoted with a yellow *). The female sibling had a punch biopsy done in a previous institution which gave the assessment of seborrheic dermatitis.