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Successful treatment of Netherton syndrome with ustekinumab in a 15-year-old girl

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Netherton syndrome (NS) is a rare autosomal recessive ichthyosis syndrome, which manifests at birth or shortly thereafter, and is characterized by erythroderma, ichthyosis linearis circumflexa, trichorrhexis invaginata, immunodeficiency, failure to thrive and high serum IgE level.¹ Approximately 80 different mutations in exonic and intronic regions of the *SPINK5* gene have been reported, resulting in deficiency of lymphoepithelial Kazal type inhibitor (LEKTI), a serine protease inhibitor in epithelia, thymus, tonsils, parathyroid glands and trachea. Treatment of NS has always been challenging², but evidence is accumulating that i) an IL17-dominant inflammatory response is found in orphan ichthyoses³ and ii) that the inflammation may be targeted efficiently by anti-TNF and anti-IL12/23 antibodies.⁴

A 15-year old girl with erythroderma was admitted to our ward. She presented with generalized fine scaling and polycyclic plaques on the trunk (Figs 1a, b) and lower extremities. Psoriasis-like non-itchy patches were pronounced around the umbilicus and in the anal folds. She had “bamboo hair”, sparse eyelashes and retroauricular oozing eczematous lesions. She was 155cm tall, weighed 56kg and had signs of iatrogenic Cushing’s syndrome. Routine laboratory investigations were unremarkable except for highly elevated serum IgE (1.512 UI/ml). Bacterial culture of skin swabs was positive for *S. aureus*. NS had been diagnosed two years earlier by clinical symptoms,

histology and exome sequencing revealing two autosomal recessive mutations of the *SPINK5* gene, i.e. c.1431-12G>A in intron 15 and c2472_2473delAG in exon 26. For the first 13 years of her life she had been treated as severe atopic dermatitis with repeated episodes of bacterial superinfection. Prior therapies included both topical and systemic corticosteroids, antibiotics and various emollients.

In addition to antibiotic treatment with oral cephalexin 500 mg three times daily we initiated acitretin 25mg (0,45mg/kg bodyweight) daily and replaced topical steroids by emollients. After a brief improvement of erythroderma and scaling, the patient experienced a massive relapse. Therefore, acitretin was stopped and topical steroids re-initiated, tapered slowly and gradually replaced by topical tacrolimus. After four weeks the patient was re-admitted because of exacerbation with heavy colonization of the skin with *S. aureus*, *Streptococcus Group C*, *Serratia marcescens* and *Proteus mirabilis* and urinary tract infection with *E. coli*. Antibiotic treatment with oral cephalexin 500mg, three times daily, was restarted.

We then considered immunotherapy with biologicals as further therapeutic option. Although high-dose intravenous immunoglobulins (IVIG) have been reported to be beneficial¹ we decided to target the inflammatory cells more specifically because erythroderma with pronounced inflammation was continuously present in our patient. Recent publications point to a shared Th17/IL-23 immune profile in orphan ichthyoses such as NS.² However, neither IL-17 nor IL-23p19 inhibitors had been approved for children as yet. Three reasons spoke in favor of systemic off-label treatment with ustekinumab, i.e. the clinical similarities of single lesions with psoriasis, the approval in children with psoriasis from 12 years onwards and the reduced risk of developing infections. Contraindications for biological therapies including HIV, hepatitis and latent tuberculosis infection were ruled out and efficient contraception with three monthly subcutaneous injections of medroxyprogesteronacetate was introduced by the pediatric gynecologist after informed consent had been obtained from the mother. Subsequently, the patient was started on ustekinumab 45 mg s.c. corresponding to 0,75mg/kg. Two weeks after the second application of ustekinumab (week 4) the skin symptoms had improved substantially (Figs 1c, d), with only remnants of small eczematous areas retroauricularly and of the psoriasiform lesions. Signs of Cushing's syndrome had disappeared. After one year the patient is doing well on a three monthly ustekinumab treatment schedule with no signs of relapse (Figs 1e, f).

There have been few reports on the benefits of IVIG and TNF inhibitors in NS^{1,4}. Ustekinumab blocks the p40 partition of IL-12 and IL-23 and is established in psoriasis and psoriatic arthritis treatment. Recently, it has been shown to be effective in pityriasis rubra pilaris and other inflammatory skin diseases.⁵ Paller et al. found an IL-17 dominant immune profile and increased levels of TNF in patients with NS and other ichthyoses. They considered targeting the IL-17/IL-23 axis as a useful intervention strategy.³ Therefore, treatment with an IL-17 inhibitor may be the next choice for our patient, if ustekinumab fails in long-term use.

To the best of our knowledge, this is the first report of ustekinumab in a patient with NS. Considerable efficacy was observed. However, systematic clinical studies are needed to confirm our findings.

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FIGURE LEGEND

Figure 1 a-f. 15-year-old girl with erythrodermic, generalized fine scaling and localized, polycyclic plaques on the trunk (**A, B**). Substantial clinical improvement after two applications of ustekinumab (**C, D**). No relapse one year after initiation of ustekinumab treatment (**E, F**).



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