

Netherton's Syndrome with a 20-year follow-up*

*Síndrome de Netherton com 20 anos de acompanhamento**

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Abstract: Netherton's syndrome is a recessive autosomal skin disease, characterized by congenital erythroderma, hair anomalies such as trichorrhexis invaginata, and atopic manifestations. The case of a female patient with a 20-year follow-up is described, with an important improvement of hair alterations after use of oral acitretine.

Key words: Ichthyosis; Mutation; Retinoids

Resumo: A síndrome de Netherton é doença cutânea autossômica recessiva caracterizada por eritrodermia congênita, anormalidade específica dos pêlos denominada tricorrexe invaginada e manifestações atópicas. Os autores relatam acompanhamento de mais de 20 anos de paciente com essa doença e a melhora importante do cabelo com o uso de Acitretina.

Palavras-chave: Ictiose; Mutação; Retinóides

INTRODUCTION

Netherton's syndrome is a rare autosomal disease, characterized by diffuse erythema with polycyclic and migrating desquamation areas, atopy and a specific alteration of the hair, called *trichorrhexis invaginata*. The authors hereby present the case of a patient who was followed up for 20 years, and who had a significant improvement in hair alterations after use of acitretine.

CASE REPORT

The case is of a 43-year-old white female patient, who, ever since birth, had presented diffuse skin desquamation, constant pruritus and, from her second year of life on, intense alopecia in the temporal and occipital regions. She came to our department over 20 years ago, accompanied by her sister, who also displayed the same signs and symptoms,

and received the diagnosis of Netherton's syndrome. Back then, the cases were published, and the patients presented, upon initial examination, typical alterations, such as bamboo hair, atopy with pruritic eczematous lesions, some of them exudative, and located mainly on skin folds, leading to the aforementioned diagnosis.¹

Family history: consanguineal parents, cousins-siblings.

On the course of these two decades, the patients received topic treatment with emollients and steroids, and presented a moderate and temporary improvement of the eczematous lesions, with relapses after a few days of treatment interruption. After a year, only of them remained in the follow-up schedule.

During the 20 years, the patient exhibited a

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mild improvement in hair alterations, which was not true for desquamation and pruritus, which had no alterations.

Upon examination, polycyclic erythematic-serpiginous lesions with borders presenting double-edge scales (Figure 1), important xeroderma and mild lichenification on cubital and popliteal folds were noted. Also present were madarosis and hair rarefaction affecting mainly the nuchal and frontal regions.

Clinical examinations had no alterations.

Skin histopathology revealed hyperkeratosis with focal parakeratosis, follicular hyperkeratosis and acanthosis with psoriatic pattern.

Optic microscopy of hairs, with 100x magnification, showed a typical bamboo hair alteration, thus characterizing *trichorrexis invaginata* (Figure 2).

Treatment was initiated with only 25mg/day of acitretine, with an important improvement of cutaneous lesions 15 days later, great reduction of erythema, desquamation, pruritus and mainly with an improvement of hair alterations, which grew with good aspect and no fracture.

Figures 3 and 4 show the improvement of the hair and eyebrows after use of acitretine.

DISCUSSION

In 1949, Comèl described linear circumflex ichthyosis (LCI) with linear, migrating and circumflex ichthyosiform cutaneous alterations for the first time.² In 1982, Netherton described the same cutaneous alteration associated to hair alteration in a patient presenting erythematic ichthyosiform rash ever since birth. Later, Wilkinson and collaborators gave the eponym “Netherton’s disease” to the combination of congenital ichthyosis, bamboo hair and atopy.³

Netherton’s Syndrome (NS) is a recessive autosomal disease, characterized by the classic triad of dif-



FIGURE 1: Polycyclic erythematic-serpiginous lesions, with borders presenting double-edge scales on the patient’s leg



FIGURE 2: Microscopic examination of the hairs showing typical bamboo alteration, characterizing *trichorrexis invaginata*. 100x

fuse erythema, with usually migrating, polycyclic desquamation areas – LCI; *trichorrexis invaginata*, which consists of the invagination of the distal part into the proximal hair shaft, also called bamboo hair; and atopic manifestations. Most often, the first manifestation takes place in the neonatal period, in the form of erythroderma.^{4,5}

Another characteristic finding in childhood is hypotrichosis, which can also be present in other skin diseases. Short hairs owing to pillous alterations are the rule in the first years of life of a patient with NS. However, hairs can progressively reach larger lengths along the years.²

In a retrospective study carried out at the Dermatology department at Necker-Enfants Malades Hospital in Paris, France, 51 erythrodermic new-born were evaluated, and NS was the third main cause of neonatal erythrodermas, making up 18% of the cases.⁶

This same study assessed some characteristics of these patients, namely: all presented severe alopecia, 55% of them presenting also eye brows and lashes alopecia; eight out of nine patients with the disease had consanguineal parents; and only one third had relatives with history of atopy. As to laboratorial findings, only one did not display an increase in eosinophil count in peripheral blood, and 78% of them presented increased seric IgE.⁶

Diagnosis of NS is a difficult one, for several reasons: family history of the disease may not be present, there is no characteristic lesion, hypotrichosis and atopic stigmas are found in many of the erythrodermic new-born with other diseases, and not all hairs present *trichorrexis invaginata*, making it necessary to evaluate hairs several times, in different occasions.⁷

Among NS manifestations, the most specific is



FIGURE 3: On the left, patient 20 years ago; on the right, recent photograph showing important improvement, especially of the eyebrows.

the hair alteration, which should be always investigated in erythrodermic children. Assessment of eyebrow hairs should also be performed, as bamboo alterations are 10 times more common in them, when compared to head hairs.⁸

There is no specific atopic alteration related to NS. Nevertheless, eczematous lesions, pruritus, high fever, angioderma, urticaria, high levels of seric immunoglobulin E and hypereosinophilia have been described.^{9,10}

Anatomopathological examination shows unspecific psoriasis-like alterations with parakeratosis, acanthosis and deposit of eosinophilic material right below the horny stratum, which are little helpful for diagnosis.² Ultra-structural and histological studies reveal incomplete keratinization of the epidermis and a hornification defect, with lymphocytic infiltrate in the dermis.⁹

Electron microscopy studies suggest that *trichorrexis invaginata* occurs because of the presence of a transient defect of keratinization in the kerato-



FIGURE 4: On the left, patient 20 years ago; on the right, recent photograph showing important improvement of the alopecia, especially after initiation of acitretine.

genic zone.

Such defect occurs in the inner radicular sheath, which is keratinized, unlike the hair shaft, which is not. Weakness of the cortical region of the hair is suggested to be due to an incomplete conversion of sulphhydryl into disulphide bonds in the cortical region. Cortical tonophylaments exhibit a marked zig-zag pattern.

The distal keratinized region is involved by the proximal region of the hair, in a calyx-like aspect, because the interior, which is softer, is not completely keratinized yet, which causes invagination.¹¹

Although cited in many textbooks and articles, hair alteration is not pathognomonic of Netherton's syndrome, but is frequent. This alteration may occur due to trauma of the hair shaft, in normal or abnormal hairs.¹¹

The only advocated treatment, as in other keratinization disturbances, is the use of systemic retinoids. There are reports of cutaneous lesion control with low doses of acitretine, such as 5mg a day,

and of hair alteration improvement with this therapy.^{12,13} Eczematic alterations can be controlled with topic steroids.

There is an associated genetic defect, described in gene SPINK 5, which codes for a seric protease inhibitor, namely LEKT 1. It is expressed in the skin and lymphoid tissue. This is why there is an association between a keratinization deficit and an atopic picture, for the absence or dysfunction of these inhibitors deregulates cellular differentiation. Like in other genetic skin diseases, it is possible to make genetic-phenotypic correlations, and cases in which LEKT 1 is absent have more severe pictures.¹⁴

Netherton's syndrome is a rare and complex disease, which often presents serious complications during the neonatal period, due to hypernatremic dehydration, hypothermia, marked weight loss, respiratory infection and sepsis. In general, the response obtained with systemic retinoids in ichthyoses is well known, and an important improvement in the hair was described twice in the international literature.

The twenty-year follow-up of this patient is exceptional, and up to the moment we did not observe development multiple cutaneous neoplasms, as it has already been reported.¹⁵ □

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