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CASE REPORT

Netherton Syndrome: Case report

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Abstract

Introduction: Netherton Syndrome (NS), one of the most serious disorders of cornification, is an autosomal recessive disease characterized by a mutation in the SPINK5 gene on chromosome 5q32. Its incidence is estimated at 1: 100,000 to 1: 200.00 live births, with a variable phenotype among patients. The clinical picture is based on the congenital ichthyosiform erythroderma triad, invaginated trichorexis and atopic manifestations. Objectives: The purpose of this paper is to report the case of a patient with classic NS changes. **Methods:** The paper in question deals with a case report of a preschooler who presented, already in the neonatal period, clinical manifestations and complications resulting from the disease, associated with mutations of the SPINK5 gene. **Results and Discussions:** The case report highlights the various clinical manifestations that affected patients may present, demonstrating the criteria necessary to close the diagnosis for NS. **Conclusions:** NS is a rare disease. it has a highly variable phenotype among patients and has a potential risk for complications. Due to the variability of clinical presentations, the diagnosis can be difficult and take years to establish. This demonstrates the importance of early recognition of the clinical condition associated with greater access to specific diagnostic tests, which would enable an institution of early treatment adapted to the needs of patients.

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INTRODUCTION

Netherton Syndrome (NS) – OMIM number 256500-, is a rare autosomal recessive disease, characterized by the congenital ichthyosiform erythroderma, trichorhexis invaginata and atopic manifestations triad[1], due to mutations in the SPINK5 gene on chromosome 5q32[1,2].

NS is one of the most severe disorders of cornification, with manifestations at birth of generalized desquamative erythroderma, with a high risk of life-threatening complications, such as: hypernatremic dehydration, growth failure and sepsis. Older children may have a wide variety of allergic manifestations, including severe atopic dermatitis, asthma, hay fever, and markedly elevated serum levels of immunoglobulin E3.

The NS phenotype can be quite variable among patients, and there may be changes in the severity of the phenotype over time. Due to the variability of the clinical presentation and its change over time, the diagnosis can be difficult, a high index of suspicion is necessary for patients who manifest a mild or incomplete phenotype[4].

Clinical suspicion should be raised in all neonates and infants with ichthyosiform erythroderma, as approximately 20% will have NS. In older children, the presence of serpiginous erythematous plaques with typical double-edged scale (circumflex linear ichthyosis) on the trunk and extremities suggests NS. This diagnosis should also be considered in children with atopic eczema that does not respond to standard treatment[1,2].

Furthermore, both in children and in adults, the presence of sparse and fragile hair, associated with eczematous lesions similar to atopic dermatitis, should raise suspicion of NS and request a careful microscopic or dermoscopy examination of hair and eyebrows for invaginated trichorhexis[1,2].

Diagnosis is based on the presence of one or more criteria in addition to allergic disorders (atopic dermatitis, atopic diathesis, food allergies, hay fever, history of anaphylaxis, elevated IgE levels, eosinophilia): typical skin lesions, typical findings of hair - TI hairs, “t-golf” and “matchstick”, history of SN in a sibling, identification of a germline SPINK5 mutation by DNA sequencing[5].

CASE DESCRIPTION

Preschooler, 3 years and 1 month old, male, Caucasian, presented, during the neonatal period, thin, white, scaly plaques on a background of erythematous skin (Figure 1). In the first months of life, he evolved with recurrent hospitalizations due to respiratory tract infections, anemia, dehydration and malnutrition. During the introduction of complementary foods, the child had several episodes of anaphylaxis to common foods, such as beans; as a consequence, he presented delayed neuropsychomotor development and weight and height deficit. He has non-consanguineous parents and no family history of dermatological, congenital or autoimmune diseases.



Figure 1. Clinical manifestations of the patient.
***A, B, C, D, E - Desquamative erythroderma-type lesions, C - Desquamative erythroderma-type lesions and areas of thinning hair.

In the clinical examination there were: thick dermal scale-like lesions, significant xeroderma, ichthyosis, circumflex linear, rarefaction of hair and hypotrichia. In his laboratory workup, there was an increase in total serum levels of IgE and IgA, and his skin biopsy showed acanthosis with hyperkeratosis, foci of parakeratosis and spongiosis, dermis with lymphoid infiltrate and mutations in the SPINK5 gene on genetic examination, which added to the clinical picture enabling the diagnosis of NS. Currently, he is being followed up by the dermatology and allergy services and is using monthly immunoglobulin G and daily topical medications based on hyaluronic acid and glycerin.

DISCUSSION

NS, whose incidence is estimated at 1:100,000 to 1:200,000 live births, presents a highly variable phenotype among patients[1]. In a study published in 2002, which aimed to determine the causes of congenital erythroderma in a series of patients, reported that NS may happen in up to 18% of cases[2].

Clinical manifestations include generalized desquamative erythroderma; brittle, opaque hair with rarefaction areas, in addition to findings such as trichorexis invaginata, trichorexis nodosa and pilitorti, atopic manifestations associated with high levels of immunoglobulin E (IgE) and eosinophilia.

Manifestations of atopy may become apparent in the neonatal period and increase during childhood. They include atopic dermatitis, which can be serious; food allergies, often severe and multiple; hay fever and asthma. Angioedema and anaphylaxis, mainly to food, have also been reported. Among the extra-cutaneous manifestations, mild developmental delay, intellectual disability, recurrent cutaneous and systemic infections, short stature and growth hormone deficiency[1,2].

As mentioned above, the patient in question presented with typical symptoms of NS at an early age: desquamative erythroderma, rarefaction of hair, various atopies, serum IgE > 600 and delayed neuropsychomotor development.

The diagnosis of NS is based on (Figure 2)[1,6]:

Even though it has a very characteristic picture of NS, in view of its rarity, lack of knowledge of its existence and difficulty in accessing specific exams, the presented case was diagnosed after 2 years of symptoms, through genetic testing with the presence of the SPINK5gene mutation, which demonstrates the difficulty in recognizing this entity and, therefore, delay in diagnosis.

Currently, there is no specific treatment for this syndrome. Therapy is largely symptomatic and must be adapted to the needs of each patient, which includes antihistamines, topical corticosteroids and topical calcineurin inhibitors. Improvement has been described in some patients with severe NS conditions after intravenous immunoglobulin replacement therapy[2,7].

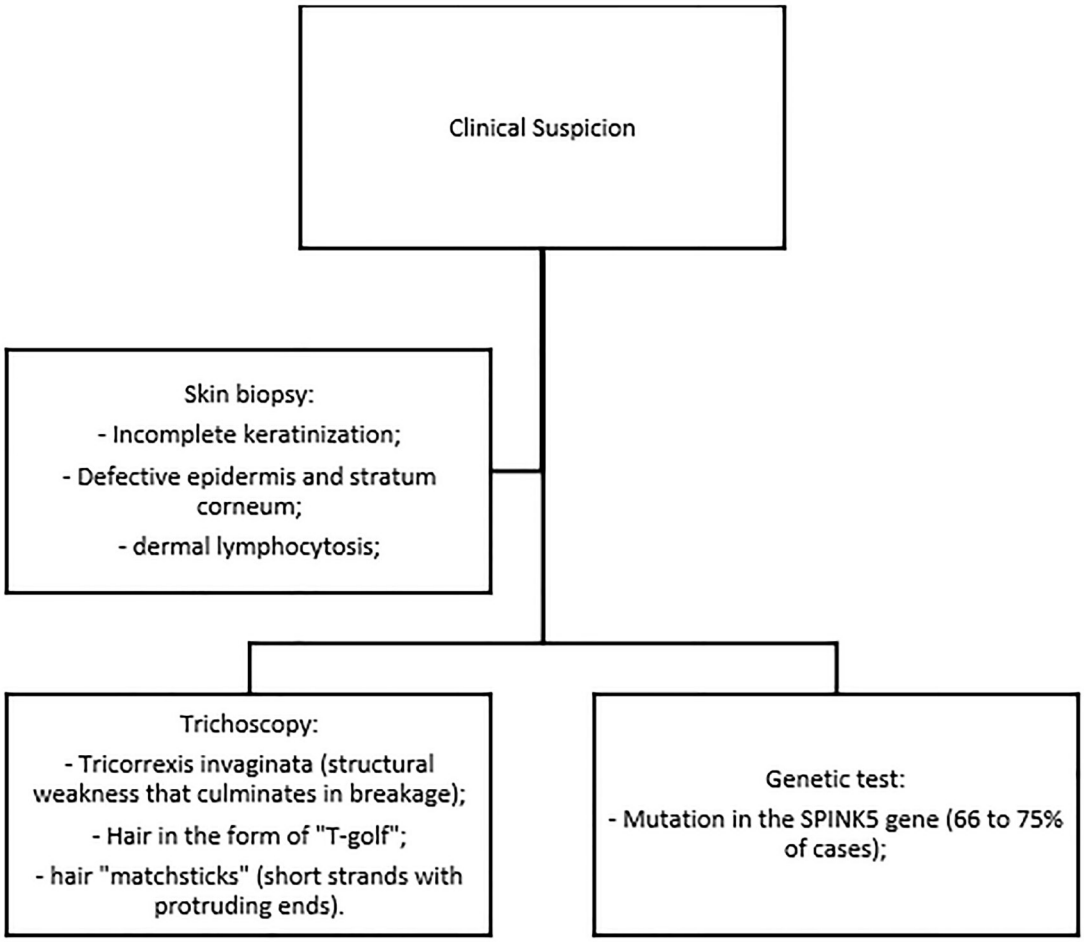


Figure 2. SN diagnosis flowchart.

Some reports have noted benefits for patients from narrowband ultraviolet B phototherapy. Furthermore, there are isolated reports of the successful use of tumor necrosis factor alpha inhibitors (eg, infliximab) for the treatment of inflammatory skin lesions in the NS. Kallikrein inhibitors are under investigation and development and appear to improve NS symptoms in animal models. Gene therapy using a lentiviral vector encoding the Kazal gene serine protease inhibitor type 5 (SPINK5) is also under investigation[8,9,10,11].

The patient initially underwent therapy with retinoids and cyclosporine, but he had gastrointestinal intolerance and there was no improvement after a few months of treatment.

Currently, he is using immunoglobulin G and topical medications, with partial improvement of symptoms, with persistent pruritus and intense desquamation.

It is known that the prognosis is favorable for patients with NS who evolve to a milder phenotype over time. Squamous cell squamous cell carcinomas and basal cell carcinomas can develop at an early age[2].

CONCLUSION

NS is a rare disease, presents a very variable phenotype among patients and has a potential risk of complications. Due to the variability of the clinical presentation, the diagnosis can be difficult and take years to be established. This demonstrates the importance of early recognition of the clinical picture associated with greater access to specific diagnostic tests, which would enable early treatment adapted to the needs of the patient.

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