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Clouston syndrome: case report and diagnostic approach to pachyonychia in pediatrics

Síndrome de Clouston: reporte de caso y abordaje diagnóstico de las paquioniquias en pediatría

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Abstract

Clouston syndrome or hypohidrotic ectodermal dysplasia is a rare autosomal dominant disorder caused by a mutation in the GJB6 gene. Its main clinical features include the triad of palmoplantar keratoderma, nail dystrophy, and hypotrichosis. A pedia- tric patient with nail and hair abnormalities was diagnosed clinically and genetically with this condition, and a diagnostic algorithm for approaching causes of pachyonychia in pediatric patients is presented. The importance of genetic counselling and appropriate differential diagnosis underscore the need for early clinical suspicion to initiate suitable therapeutic and supportive interventions.

Keywords: *Ectodermal dysplasia. Nail diseases. Hypotrichosis. Genetic counselling.*

Resumen

El síndrome de Clouston o displasia ectodérmica hidrótica es una rara enfermedad autosómica dominante, causada por una mutación en el gen GJB6. Sus principales hallazgos clínicos incluyen la tríada de queratodermia palmo-plantar, distrofia ungueal e hipotricosis. Se reporta el caso de una paciente pediátrica con alteraciones ungulares y del pelo, con diagnóstico clínico y genético de esta patología, y se presenta un algoritmo diagnóstico para el abordaje de las causas de paquioniquia en la edad pediátrica. La importancia de la consejería genética y el diagnóstico diferencial adecuado resaltan la necesidad de una sospecha clínica temprana para iniciar intervenciones terapéuticas y de apoyo adecuadas.

Palabras clave: *Displasia ectodérmica. Enfermedades de las uñas. Hipotricosis. Consejería genética.*

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Introduction

Hidrotic ectodermal dysplasia, or Clouston syndrome, is a rare autosomal dominant disorder caused by a mutation in the *GJB6* gene[1]. Its main clinical features include the triad of palmoplantar keratoderma, nail dystrophy, and hypotrichosis.

The nails typically become thicker and more dystrophic over time, which is an essential feature of the syndrome, and in approximately 30% of affected individuals, nail dystrophy may be the only suggestive sign[2]. Very often, such changes may be misdiagnosed as onychomycosis or pachyonychia congenita[1].

Case report

A 5-year-old girl from Cali, Colombia, with no relevant past medical history, born from a full-term first pregnancy to non-consanguineous parents. The patient was seen at a tertiary referral center pediatric dermatology service with a 2-year history of thickening of all fingernails and toenails. She had been managed by a primary care physician as a case of onychomycosis, without mycological studies, using oral antifungals without improvement. Additionally, the patient presented with diffuse hair loss on the scalp and eyebrows, with no treatment administered for this condition.

The clinical examination revealed phototype II, and involvement of all 20 nail plates as evidenced by thickening, subungual hyperkeratosis, and pincer nail deformity, particularly in the fingernails. Furthermore, sparse blond scalp hair and hypotrichosis of the eyebrows and eyelashes were observed (Fig. 1).

Initially, universal alopecia areata was considered as a differential diagnosis, but due to the clinical findings and chronic nature of the condition, a medical genetics evaluation was requested. A whole exome sequencing (NGS-WES) was performed, revealing a heterozygous variant related to the described symptoms in the *GJB6* gene, categorized as pathogenic according to the American College of Medical Genetics and Genomics criteria. Based on this result, a diagnosis of Clouston syndrome was established. Genetic counseling was provided, and treatment with keratolytics was initiated to reduce the thickening of the nail plates, resulting in an improved aesthetic appearance of the nails.

Discussion

Ectodermal dysplasias are genetic conditions that affect the development or homeostasis of 2 or more tissues of ectodermal origin, including hair, teeth, and certain glands, with or without involvement of other tissues and organs. Multiple genes and pathways involved in the development of complex molecular structures necessary for the formation, structure, and normal function of ectodermal derivatives are involved[3]. They are considered rare diseases, with an estimated incidence rate of 7 per 10,000 births and a prevalence of 1-9 per 100,000[4].

They can be categorized as hypohidrotic or hidrotic. Hypohidrotic ectodermal dysplasia is characterized by fine, sparse, or absent hair, missing or conical teeth, and marked reduction in sweating, along with normal nails[4]. In contrast, hidrotic ectodermal dysplasia or Clouston syndrome is a rare autosomal dominant disease caused by a mutation in the *GJB6* gene. This gene is located on the long arm of chromosome 13 and encodes connexin 30, which is part of a group of proteins that enable the transport of nutrients, ions, and signaling molecules, and is present in various tissues of the body, especially the palms, soles, hair follicles, and nails. The disease has complete penetrance but highly variable expressivity, even among affected individuals from the same family[5].

Clinical findings include the triad of palmoplantar keratoderma, nail dystrophy, and hypotrichosis. Palmoplantar keratoderma may develop during childhood and worsen with age, being a common but not universal finding[6]. The nails are typically thick and dystrophic over time, representing an essential feature of the syndrome and the only suggestive sign in up to 30% of patients. However, they can be mistaken for onychomycosis or congenital paronychia. Nail abnormalities reported include thickening or shortening (micronychia), onychorrhexis, or triangular nail plates that may resemble pachyonychia congenita. In fact, most cases of Clouston syndrome have thickened and hyperconvex nails. Pincer nails have also been described, as in the present case[7,8]. Hypotrichosis manifests as fine, slow-growing hair, sparse or absent eyebrows and eyelashes, as well as scant pubic and axillary hair[1,2].

Other ectodermal anomalies have also been reported, such as hyperpigmentation of the skin over large joints, ocular abnormalities, skeletal disorders, sensorineural hearing loss, and intellectual disability[2-9]. There are few reports linking this condition to benign neoplasms, such as eccrine syringocystadenoma, or malignant tumors, such as squamous cell carcinoma of the skin, nail bed, or trachea. One report describes a cuniculatum epithelioma associated with conditions involving palmoplantar keratoderma[5-10].

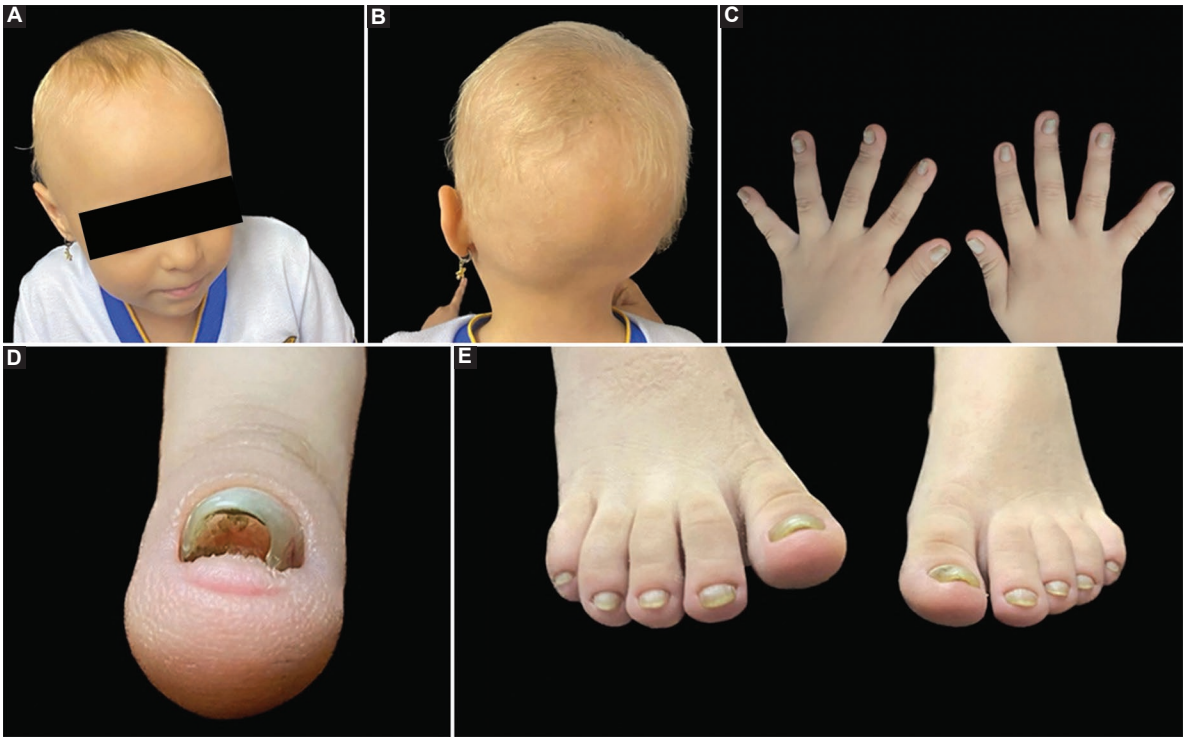

Figure 1. Clinical findings in the patient. **A:** hypotrichosis of the scalp, eyebrows, and eyelashes (frontal view). **B:** hypotrichosis of the scalp (posterior view). **C:** thickening and xanthonychia of all 10 fingernails. **D:** detail of pincer nail deformity and subungual hyperkeratosis on one finger. **E:** xanthonychia and thickening of all 10 toenails.

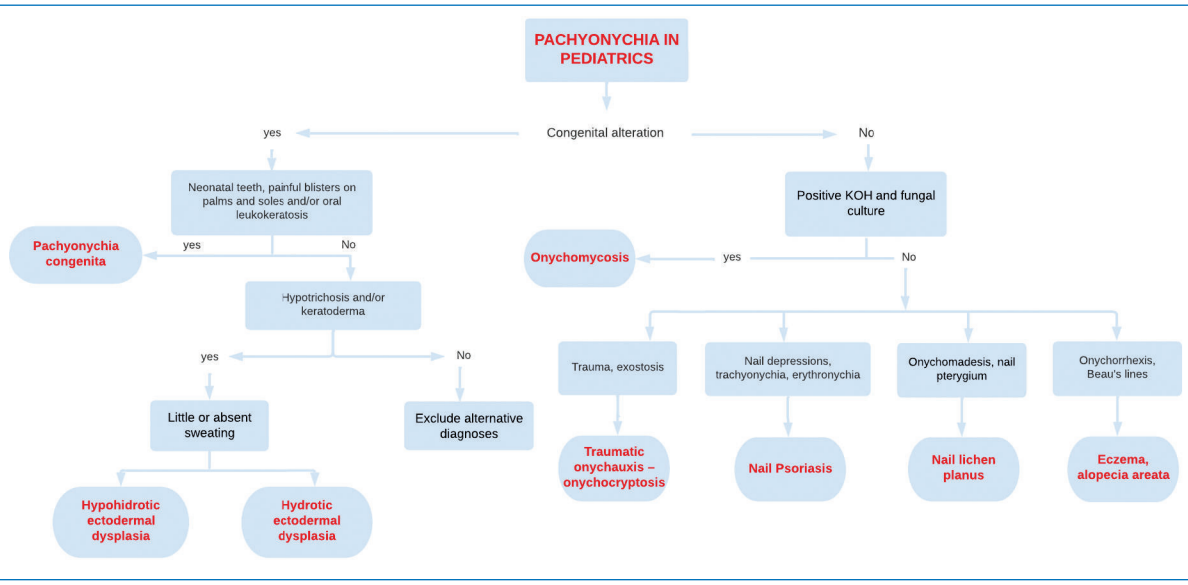

Figure 2. Diagnostic algorithm for pediatric patients with pachyonychia *(developed by the authors).*

The degree of alopecia and hyperkeratosis appears to vary, with some families described without the latter. Dental and eccrine gland functions are normal[1].

Diagnosis is clinical, supported by genetic testing to identify variants in the affected gene[2-11]. However, a methodical differential diagnostic process is essential

when evaluating pachyonychia associated with congenital abnormalities or genodermatoses. Figure 2 proposes a practical diagnostic algorithm for the initial assessment and study of pachyonychia in pediatric patients.

Currently, there is no cure for the disease, and management is primarily supportive. A multidisciplinary follow-up approach is important to monitor clinical features and provide emotional and psychological support, along with genetic counseling[2-12].

Treatment options for nail plates and palmoplantar hyperkeratosis include topical emollients and keratolytics (urea- or lactic acid-based), and nail matrix ablation. There are reports of topical minoxidil use with improvement in alopecia[13]. Physical and cosmetic options may also be proposed, such as wigs for scalp hair, eyebrow tattoos, and artificial nails[12-14].

Conclusions

This is a case of a rare disease known as Clouston syndrome, which may clinically resemble more common pediatric conditions such as alopecia areata, onychomycosis, and other conditions involving cutaneous appendages or genodermatoses. However, awareness of this condition enables dermatologists to suspect it and refer the patient to a geneticist in a timely manner for appropriate studies, allowing early supportive management to improve the patients' quality of life.

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The authors declare that this work was conducted with personal resources.

Conflicts of interest

The authors declared no conflicts of interest whatsoever.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments on humans or animals were conducted for this research.

Confidentiality, informed consent, and ethics approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from the patients, and have approval from the Ethics Committee. The recommendations of the SAGER guidelines have been followed according to the nature of the study.

Statement on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in writing this manuscript.

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