Nail involvement in pediatric patients with epidermolysis bullosa occurs in all disease subtypes

Implicación ungueal en pacientes pediátricos con epidermólisis ampollosa: prevalente en todos los subtipos

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ABSTRACT

Introduction: ungual alterations are extremely frequent in patients with epidermolysis bullosa (EB) and may even be associated with prognosis and outcomes. However, there are few studies characterizing nail involvement in EB.

Methods: we performed an observational cross-sectional descriptive study of children aged zero to 18 years with the diagnosis of EB cared for at the National Institute for Pediatrics, a tertiary referral center in Mexico City.

Results: we searched for nail involvement in 22 patients with EB (14 with recessive dystrophic EB, four with dominant dystrophic EB, two with EB simplex, one with junctional EB and one with Kindler syndrome) that attended our specialized multidisciplinary clinic. Patients had a median age of 9.2 years (range 0.4-17.5), and all had nail involvement. The most frequent nail changes across all subtypes were: anonychia (81.8%), hypotrophic/dystrophic nails (31.8%), pachyonychia (22.7%) and longitudinal ridging (4.5%).

Discussion/conclusion: we found all patients had nail alterations regardless of EB subtypes. Most of those with severe subtypes had anonychia at a young age. This descriptive study confirms nail changes are extremely frequent in all subtypes of EB. Further studies to characterize nail involvement in specific subtypes of EB and association with outcomes are needed.

Keywords: *epidermolysis bullosa, nail disease, nails malformed, pediatrics.*

RESUMEN

Introducción: las alteraciones ungueales son extremadamente frecuentes en pacientes con epidermólisis ampollosa (EB) e incluso pueden estar asociadas con el pronóstico y los resultados. Sin embargo, existen pocos estudios que caracterizan la afección ungueal en la EB.

Material y métodos: se realizó un estudio descriptivo observacional de corte transversal en niños de cero a 18 años con diagnóstico de EB atendidos en el Instituto Nacional de Pediatría, centro de referencia en Ciudad de México.

Resultados: se realizó exploración dirigida buscando afección ungueal en 22 pacientes con EB (14 con EB distrófica recesiva, cuatro con EB distrófica dominante, dos con EB simple, uno con EB de unión y uno con síndrome de Kindler) que asistieron a nuestra clínica multidisciplinaria especializada. Los pacientes tenían una mediana de edad de 9.2 años (rango 0.4-17.5) y todos tenían afección ungueal. Los cambios ungueales más frecuentes en todos los subtipos fueron: anoniquia (81.8%), uñas hipotróficas/distróficas (31.8%), paquioniquia (22.7%) y estrías longitudinales (4.5%).

Discusión/conclusión: Encontramos que todos los pacientes tenían alteraciones ungueales independientemente del subtipo de EB. La mayoría de los pacientes con subtipos graves tenían anoniquia en todas las uñas desde una edad temprana. Este estudio descriptivo confirma que los cambios ungueales son extremadamente frecuentes en todos los subtipos de EB. Se necesitan más estudios para caracterizar la afección ungueal en subtipos específicos de EB y su asociación con los resultados.

Palabras clave: *epidermolisis ampollosa, distrofia ungueal, uña malformada, pediatría.*

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Introduction

Epidermolysis bullosa (EB) is a rare genodermatosis with skin and mucous membrane fragility leading to blisters, erosions and systemic involvement. It is divided into four major types according to different genetic mutations that give rise to altered structural proteins at distinct levels of the dermoepidermal junction. The prevalence of EB is estimated at 11.1 cases per one million live births, and its incidence is 19.57 cases per 1 million live births. There is no predominance of gender.[1,2]

There are four major subtypes of EB caused by different altered structural proteins in the dermoepidermal junction. These subtypes are simplex (EBS), junctional (JEB), dystrophic (DEB), Kindler syndrome (KS).[2] They are further subclassified by mode of inheritance, phenotype, immunofluorescence antigen mapping and genetic analysis findings.[3]

Nail involvement is a common characteristic in EB patients, resulting in abnormalities of the nail matrix and bed associated with diminished cohesion secondary to the pathogenic alterations of the dermoepidermal junction.[4,5] Nail abnormalities may be the first or the only symptom of EB, for example, in the nails-only dominant DEB and EBS subtypes.[4,6]

There is scarce literature about the nail alterations patients with different subtypes of EB present. Therefore, we decided to perform this study with the objective of describing nail involvement in patients cared for at our multidisciplinary EB clinic.

Materials and methods

We conducted a cross-sectional descriptive observational study of EB patients aged zero to 18 years that attended a specialized multidisciplinary clinic at the National Institute for Pediatrics, a tertiary referral center, during the period between 2019 and 2020. This study protocol was reviewed and approved by the National Institute for Pediatrics' Ethics in Research and Research Committees, approval number C022-2019. Written informed consent was obtained from participants (or their parent/legal guardian/next of kin) to participate in the study. We evaluated nail involvement by a medical interview and targeted physical examination searching for nail dystrophies like pachyonychia (nail thickening), anonychia (nail loss), hypotrophic/atrophic nails (nails that lose normal architecture and become small and/or thin), nail blistering, onychogryphosis (thickened nails with increased curvature) or any other alterations. Descriptive statistics were used with dispersion measurements for continuous variables, percentages and frequencies for categorical variables.

Results

We included 22 patients with a median age of 9.2 years (range 0.4-17.5), 14 were boys (63.6%). Eighteen had DEB (14 recessive and four dominant), two had EBS, one JEB and one KS. All patients had nail involvement: 63.6% had only one alteration, 31.8% two abnormalities, and the rest three different types of nail abnormalities. The median number of absent nails was 20 (range 1-20). The nail abnormalities found were: anonychia (81.8%) (**figure 1**), hypotrophic/atrophic nails (31.8%) (**figure 2**), pachyonychia (22.7%) (**figure 3**) and longitudinal ridging (4.5%) (**table 1**).

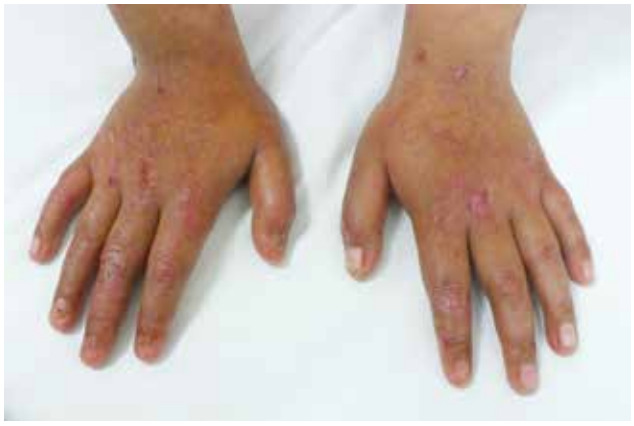

Figure 1. Anonychia of all fingernails in a patient with RDEB.

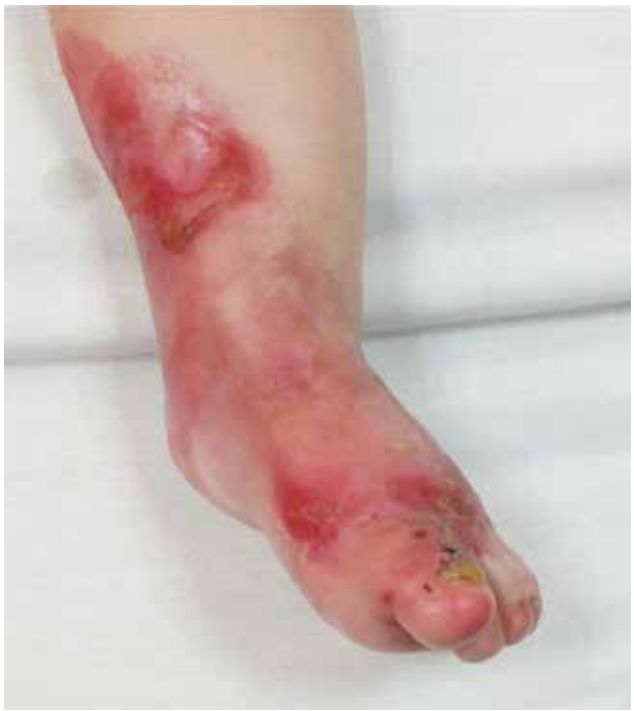

Figure 2. Hypotrophic/atrophic nails in right 1st, 2nd, 3rd and 4th fingernails and left 2nd fingernail in a patient with DDEB.

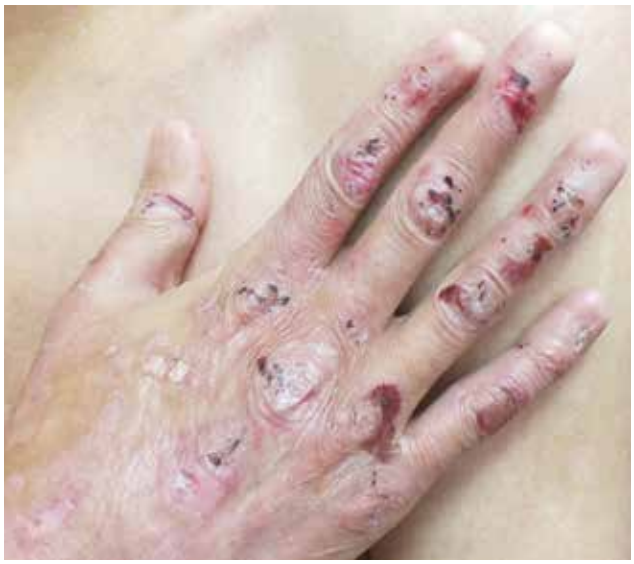

Figure 3. Pachyonychia of right 1st toenail in a patient with RDEB.

The most severely damaged nails were observed in patients with recessive DEB (RDEB) and JEB, as 15 of 15 patients had a median of 20 nails with anonychia**.** The two patients with EBS had hypotrophic/atrophic nails**.** Our one patient with KS had longitudinal ridging as only manifestation**.**

Discussion/conclusions

There are few studies of nail changes in EB worldwide[4,6] even though they are extremely common and are part of the criteria used in scoring tools for EB severity.[7] In this study, we found all patients cared for at our EB clinic have nail alterations.

Almost all 14 patients with RDEB, at a median age of 5.5 years, had anonychia of all nails. This has been described previously in this subtype, probably due to destruction of the nail matrix secondary to repeated extensive sub-basement membrane blistering and scarring.[5,8] Three patients also had hypotrophic/atrophic nails, which is an infrequent finding.[9]

The two patients with EBS studied both had hypotrophic/atrophic nails and one each had anonychia and pachyonychia. The latter finding has been well described both in EBS localized and generalized.[4,10] Nail findings in patients with this subtype are common, even though absence of nail abnormality was used in the past to exclude the diagnosis of EBS.[8]

Patients with DDEB had less nails involved than the other children included in the study, and were older. The most frequent finding was anonychia in ¾. In this subtype of EB, there have been a wide range of nail alterations described, from minor dystrophy to complete nail loss. There is even a nails-only DDEB variant in which patients only have nail dystrophy without blistering in other areas.[11,12]

We included one patient with JEB (generalized intermediate), who had all 20 nails absent. This has been described as the most frequent finding in this subtype.[5] Other frequent findings in JEB are granulation tissue and nail blisetering with severe nail dystrophy.[4,8]

The most common nail abnormality described in patients with KS are diverse and include onychogryphosis or parrot beak deformity, thin nail plates, onycholysis, subungual hyperkeratosis, yellow nails, dystrophic nails and long cuticles.[4,13] The one patient we included had longitudinal ridging in four nails, however she was six years of age and could eventually present other manifestations.

Nail changes can be caused by the specific pathogenic mechanisms underlying each EB subtype, or by secondary abnormalities. The antigenic expression of the basement

Table 1. Characteristics of pediatric patients with epidermolysis bullosa

	All subtypes N = 22 (100%)	JEB N = 1 (4.5%)	DDEB N = 4 (18.1%)	RDEB N = 14 (63.6%)	EBS N = 2 (9%)	KS N = 1 (4.5%)
Age in years, median (range)	9.2 (0.4-17.5)	16.9	15.5 (9.4-17.5)	5.5 (0.4-14.7)	6.6 (0.9-12.3)	6.5
Female gender, n (%)	8 (36.3%)	0	1 (25%)	5 (35.7%)	1 (50%)	1 (100%)
Number of nails involved, median (range)	20 (2-20)	20	11.5 (6-15)	20 (2-20)	16.5 (13-20)	4
Anonychia, n (%)	18 (81.8%)	1(100%)	3 (75%)	13 (92.8%)	1 (50%)	0
Hypotrophic/atrophic nails, n (%)	7 (31.8%)	0	2 (50%)	3 (21.4%)	2 (100%)	0
Pachyonychia, n (%)	5 (22.7%)	0	2 (50%)	2 (14.2%)	1 (50%)	0
Other nail abnormalities, n (%)	1 (4.5%)	0	0	0	0	1 (100%)

JEB: junctional epidermolysis bullosa; DDEB: dominant dystrophic epidermolysis bullosa; RDEB: recessive dystrophic epidermolysis bullosa; EBS: epidermolysis bullosa simplex; KS: Kindler syndrome.

membrane zone components in the normal nail apparatus is similar to that of normal skin, which explains why nail abnormalities are a feature of most EB subtypes. Also, secondary trauma, chronic inflammation and scarring of the nail matrix are considered contributory factors. Repeated and extensive nail blistering followed by scarring leads to nail bed and matrix damage and eventual destruction causing pachyonychia, onychogryphosis, nail erosions with granulation tissue, nail hypotrophy/atrophy, parrot beak nail deformity, longitudinal ridging, and/or permanent anonychia. Trauma undoubtedly contributes to the development of nail dystrophy as well, this being the reason for more severe involvement of great toenails.

Disease severity and progression, especially in patients with JEB and RDEB, may be correlated with early nail abnormalities, such as nail dystrophy and loss, and with more severe systemic involvement, like esophageal stenosis, malnutrition and contracture of the hands and feet.[2]

Although this was a small observational study, we found nail alterations in all included patients with all four major subtypes of EB. This is relevant because nail examination is not always done and even patients with milder subtypes may have severe involvement of many nails. As expected, patients with more severe subtypes (JEB and RDEB) had all nails involved and almost all had anonychia. Further studies to characterize nail involvement in specific subtypes and association with outcomes are needed.

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