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ORIGINAL ARTICLE

Pediatric epidermolysis bullosa – psychosocial impact and the importance of palliative care based on 5 clinical cases

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Abstract

Introduction and Objectives: Epidermolysis bullosa (EB) is a rare genodermatosis caused by pathogenic variants in several genes leading to epithelial fragility with blisters, erosions and ulcerations following minor trauma. Given the affection of any epithelial-lined organ, it can result in several complications. Our aim was to describe this disease's psychosocial impact in pediatric patients. **Methods:** Case series of pediatric epidermolysis bullosa patients in a tertiary hospital between 2008-2023. Data collection was conducted retrospectively and quality of life assessment was obtained with a cross-sectional questionary. **Results:** We identified five unrelated patients, three of the female gender, aged 3 to 22 years old. All with neonatal symptoms. Genetic testing revealed pathogenic variants characteristic of dystrophic EB subtype in four and junctional EB subtype in one patient. Three patients were followed in psychology and psychiatry consultations. Four patients received pediatric palliative consultations. Three patients responded to quality-of-life questionnaires, two of them with a median score of PedsQL of 47% and one with a DLQI score of 17. Regarding complications, all patients had microcytic anemia requiring iron supplementation. Gastrointestinal symptoms included epigastric pain in three patients and esophageal stenosis needing gastrostomy in one patient. Poor weight gain was detected in four patients. **Discussion and Conclusions:** EB is a complex and heterogeneous disease. Pediatricians should be aware of the complications associated to this disease in order to provide early guidance. Palliative care with social, psychological and spiritual support for patients and their family are essential for the management of this disease.

Keywords: Dermatology. Epidermolysis bullosa. Genetics. Palliative care.

Epidermólise bolhosa em idade pediátrica – impacto psicossocial e a importância dos cuidados paliativos, baseado em 5 casos clínicos

Resumo

Introdução e Objetivos: A epidermólise bolhosa (EB) é uma genodermatose rara causada por variantes patogénicas num dos várias genes que causam fragilidade dos tecidos epiteliais com a formação de bolhas, vesículas e úlceras após trauma *minor*.

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Dado poder afetar qualquer órgão epitelial, resulta numa variedade de complicações. O nosso estudo tem como objetivo descrever o impacto psicossocial desta doença em idade pediátrica. **Métodos:** Série de casos de doentes com epidermólise bolhosa diagnosticada em idade pediátrica, num hospital terciário, entre 2008 e 2023. A colheita de dados foi realizada de forma retrospetiva e a avaliação da qualidade de vida foi obtida através da aplicação de um questionário. **Resultados:** Foram identificados cinco pacientes, três do sexo feminino, com idade à data de colheita de dados: 3 a 22 anos. Todos apresentaram sintomas no período neonatal. O estudo genético revelou variantes patogénicas, características to subtipo distrófico em quatro pacientes e característica do tipo juncional num paciente. Três doentes eram seguidos em consulta de psicologia e psiquiatria. Três doentes responderam a questionários de qualidade de vida, dois com score mediano de PedsQL de 47% e um com score de DLQI de 17. Quatro doentes tinham seguimento em cuidados paliativos pediátricos. Relativamente a complicações, todos os doentes apresentaram anemia microcítica com necessidade de ferro suplementar. Sintomas gastrointestinais incluíram dor epigástrica em três doentes e estenose do esófago com necessidade de gastrostomia num doente. Foi identificada má evolução ponderal em quatro pacientes. **Discussão e Conclusão:** A EB é uma doença complexa e heterogénea. Os pediatras devem ter presente as várias complicações associadas à doença de forma a garantir o seu tratamento precoce. A abordagem holistica dos cuidados paliativos integrando o apoio social, espiritual e psicológico do doente e familiares, são essenciais na abordagem da doença.

Palavras-chave: Cuidados paliativos. Dermatologia. Epidermólise bolhosa. Genética.

Keypoints

What is known
- Epidermolysis bullosa is a heterogeneous entity with a broad genetic and phenotypic spectrum.
- Given that any epithelial-lined organ can be affected several complications can arise from this disease.
- There is no curative treatment - symptom control and complications' prevention and management are the main objective of these patient's management.

What is added
- Patients with epidermolysis bullosa had low quality of life scores.
- The majority of our patients received psychological and psychiatric support, and some of them needed treatment with antidepressants.
- Regular follow-up by palliative care specialists should be ensured from the moment of diagnosis, enabling not only pain management, but also guaranteeing a holistic and integrated approach, from pediatric age onwards.

Introduction

Epidermolysis bullosa (EB) is a rare genodermatosis, clinically and genetically heterogeneous[1]. A research group on EB in the United States estimated the incidence (from 1986 to 2002) to be 19.57 per 1,000,000 individuals[2].

EB is characterized by mechanical fragility of the epithelial tissues giving rise to mucocutaneous blistering, erosions and ulcerations secondary to minor trauma[3]. Pathogenic variants in more than 30 genes that encode proteins influencing cellular integrity and adhesion have been associated with EB. Depending on the gene involved, a specific subtype might be expected[3]. There are different subtypes of EB according to the layer of the skin affected: bullosa simplex epidermolysis (intra-epidermal), junctional epidermolysis bullosa (lamina lucida of the basement membrane) and dystrophic epidermolysis bullosa (below the basement membrane). Kindler syndrome, a genodermatosis with a mixed skin cleavage pattern is also an important differential diagnosis to keep in mind. Depending on the phenotypic spectrum, patients can be mildly to severely affected and symptoms can present from birth to early childhood[4].

Any epithelial-lined organ can be involved resulting in a vast array of complications. Depending on the subtype, musculoskeletal system, heart, bone marrow, and oral and esophageal mucosa can also be affected[5]. Regarding epithelial tissues, squamous cell carcinoma and cutaneous infections, which can lead to sepsis, are important causes of morbidity and mortality in these patients[6].

Several studies have showed that chronic dermatologic conditions have an important psychosocial impact on patient's life. In fact, EB patients struggle with altered perception of the body, lack of self-esteem and depression[7,8]. Quality of life (QoL) scores have been reported to be lower in these patients, including studies in children and their caregivers[9], given the challenges that this disease raises. Since there is no curative therapy for EB, an holistic palliative care approach, with wound care and pain management, as well as psychosocial support, is of crucial importance for these patients[10-12].

Although several studies have focused on the adult population, literature regarding challenges in the pediatric EB population is still lacking. Our study aims to describe the psycho-social impact of EB in young patients.

Methods

This article presents a case series of patients with history of epidermolysis bullosa followed diagnosed in pediatric age, in a tertiary hospital between 2008-2023. Data collection was conducted retrospectively and quality of life assessment was obtained with a cross-sectional questionary.

We identified all patients who had a diagnosis of EB from birth to 18 years of age based on ICD9 and ICD10 diagnosis coding (ICD9: 694.8; 694.9; 757.39 and ICD10: Q81 (Q81.0; Q81.1;Q81.2; Q81.8; Q81.9) and L12 (L12.8; L12.9; 2l; L12.30; L12.31; L12.35). After screening, these patients were included if they had a genetic test result compatible with EB.

Clinical data including age, sex, genetic analysis, hospitalizations, hospital consultations, emergency visits and usual medication was collected from paper and electronic clinical records.

Regarding genetic testing, three patients underwent Next Generation Sequencing (NGS) gene panel for genes related to EB, with different number of genes testes depending on the date of the test. Patient 5 underwent targeted Sanger sequencing for the genes *LAMA3, LAMB3, LAMC2, COL7A1 and COL17A1.*

Quality of life (QoL) was assessed by tele-consultation using the Pediatric Quality of Life 4 (PedsQL-4) score for patients under 16 years old and the Dermatology Life Quality Index (DLQI) for patients over 16 years old. Both questionaries are validated for the Portuguese population[13,14]. We did not use the C-DLQI score for younger children because it is not validated for our population. For the PedsQL score, higher results mean a higher quality of life. For the DLQI score, 0-1 meant no effect on patient's life; 2-5 small effect on patient's life; 6-10 moderate effect on patient's life; 11-20 very large effect on patient's life and 21-30 extremely large effect on patient's life[15].

Results

Sample characteristics

A total of five patients were identified (numbered 1-5 in Table 1), 60% (n = 3) of the female gender. All of the patients presented with symptoms during the neonatal period and underwent genetic testing (number of genes discriminated in Table 1). For patient 2, the original genetic report was not found, but clinical records refer to a *COL7A1* pathogenic variant. In four patients, *COL7A1* pathogenic or likely pathogenic variants were identified, compatible with the dystrophic epidermolysis bullosa (DEB) subtype. Personal and family history and genetic testing of patients 1 and 3 is suggestive of an autosomal recessive phenotype, patient 4 can either have autosomal dominant DEB or recessive DEB with second variant not found. The allelic status of the variants in patient 1 could not be confirmed. Patient 5 has a homozygous *COL17A1* pathogenic variant, compatible with autosomal recessive junctional epidermolysis bullosa (JEB). None of the patients performed copy number variation analysis in the EB genes. None of the patients had family history of EB.

EB multi-systemic complications

We identified several complications of EB, further described in table 1. All the patients presented with chronic anemia and required iron supplementation. Four patients had gastrointestinal involvement with epigastric pain: three patients were treated with proton pump inhibitors and one patient (patient 3, with DEB) had esophageal stenosis with the need for gastrostomy and posterior parenteral feeding. The same four patients showed poor weight gain with the need for nutritional supplementation. Two patients, with DEB, had corneal leucoma. One of them presented with corneal neo-vascularization and underwent treatment with bevacizumab. Both of them maintained treatment with eye lubricant. Three patients had oral and dental complications with the need for treatment and intervention by stomatology specialists.

One patient, with DEB, had bilateral digital synechia requiring plastic surgery. The first surgery was at 5 years of age and he needed two re-interventions. The median number of hospitalizations for cutaneous infections was 1.5 (0-4).

One death was registered: patient 3, at five years of age, had a prolonged hospitalization due to multiple cutaneous infected lesions and posteriorly developed an infection of the central venous catheter. He died of sepsis in this context (two agents were identified in blood culture: *Acinetobacter baumannii* and *Enterococcus faecalis*).

We did not find any case of squamous cell carcinoma.

EB iatrogenic complications

One patient developed adrenal insufficiency resulting from the prolonged use of topical corticotherapy. This patient was then chronically treated with oral prednisolone.

Table 1. Characteristics and clinical complications of patients with epidermolysis bullosa

	Dystrophic subtype				Junctional subtype
Patients	1	2	3	4	5
Age at the time of data collection (years)	22	12	†	3	18
Sex	M	F	F	M	F
Genetic analyses	NGS panel (21 genes)	NA	NGS panel (8 genes)	NGS panel (22 genes)	Targeted sequencing (5 genes)
Gene	*COL7A1*	*COL7A1*	*COL7A1*	*COL7A1*	*COL17A1*
Genetic variant (s) (hg19)	c. 6527dup p. (Gly2177Trpfs*113)/c. 5009G > A p. (Gly1670Asp)	NA	c. 7006G > A p.(Gly2336Arg)	c. 325_326insCG p.(Glu109Alafs*39)	c. 505 > T p. (Arg169*)
Allelic status	Double heterozygous†	NA	Homozygous†	Heterozygous	Homozygous†
ACGM variant classification	P/LP	NA	LP	P	P
Symptoms in the neonatal period	+	+	+	+	+
Chronic anemia (n = 5)	+	+	+	+	+
Gastrointestinal symptoms (n = 4) Epigastric pain (n = 3) Esophageal stenosis (n = 1)	 + -	 + -	 + +	 - -	 + -
Poor weight gain (n = 4)	+	+	+	-	+
Corneal leucoma (n = 2)	-	+	-	+‡	-
Digital synechia (n = 1)	+	-	-	-	-
Psychology/psychiatry consultations (n = 3)	+	+	-	-	+
Oral/dental complications	+	+	-	-	+
Pediatric palliative care consultation	+	+	-	+	+§
QoL score	-	36%¶	-	58%¶	17**
Number of hospitalization for cutaneous infection	4	1	3	0	1
Iatrogenic complications	+	-	-	-	-
Deaths (n = 1)	-	-	+	-	-

*Non applicable, patient 3 died at 5 years of age, prior to data collection.
†Apparent, since segregation in parents was not performed.
‡Patient also presented with corneal neo-vascularization.
§Chronic pain consultation
¶PedsQL.
**DLQI.
NA: not available; M: male; F: female; P: pathogenic; LP: likely pathogenic.

EB QoL scores; psychological support and palliative care

One patient chose not to participate the QoL questionary. The remaining presented with a median PedsQL score of 47% and a DQLI score of 17. Three patients were followed in psychology and psychiatry consultations, two of them were being treated with antidepressants. Three patients were followed in palliative care consultations since pediatric age and one patient was followed in chronic pain consultation. All of them were medicated with fentanyl or tramadol with paracetamol in case of pain.

Discussion

As previously stated, EB is a heterogeneous entity with a variety of complications. All of our patients presented with symptoms in the neonatal period, which highlights the importance of pediatric care since birth in these patients.

Inevitably, EB's clinical manifestations with different degrees of severities, take a toll on patient's QoL. Although we were only able to analyze 3 of our patients, all of them had an impact on the QoL. Younger patient's PedsQL score was lower than the general population[13] and patient's 5 DLQI score showed that the disease had a very large effect on his life[15]. The majority of our patients were followed in psychology and psychiatry consultations, some of them needing treatment with antidepressants. These findings are a result of the particular combination of a rare disease, with a lifelong hereditary nature, and its disfiguring impact on the skin[8]. Similar to our results, Francesco Margari et al., studied a cohort of 25 patients with EB, including children and adults with different types of EB, and found a high frequency of psychiatric symptoms, in 80% of the population, and a severe impairment of the QoL. This study did not find a correlation between the clinical severity of the condition and the intensity of the psychological disturbances[16]. On the other hand, a cross-sectional study in adult patients with DEB did not show differences in anxiety and depression between patients with DEB and healthy individuals[17]. These apparently conflicting results may be explained by the fact that QoL, emotional and social functioning of patients with EB is not only influenced by the disease itself, but also by the family's support and emotional state as well as the patient's ability to develop coping strategies to accept and overcome EB's challenges[9].

Besides the impact that EB has on patients' wellbeing, it is also important to consider the disease's burden on caregivers and family members. Caregivers of EB patients are faced with the uncertainty of a chronic disease with no definitive treatment and are often concerned about their child suffering pain and being different[18]. Therefore, patients, as well as caretakers, should be given the adequate psychological support at the time of diagnosis. In addition, genetic counseling is also essential to predict prognosis and plan future pregnancies within the family.

Another important result we found was the importance of pain management and palliative care in this population. Almost all of our patients were followed in palliative or chronic pain consultation and follow-up was guaranteed from the time of diagnosis, in pediatric age. Routine management of patients with EB has several painful events. These episodes of pain may trigger the need for pharmacological intervention. Nevertheless, physicians must take into account that these medications may lead to a level of sedation that impairs patients' daily functioning. It is important to discuss the patients' options, which should include pharmacological as well as non-pharmacological approaches such as psychological support, as we mentioned before[19]. In terms of pain medication, in accordance to recent guidelines published on pain management of patients with EB[20], our patients were treated in the outpatient setting with tramadol and fentanyl for acute pain management. Patient 4 used the latter during his hospitalization, in the first months of life, for pain management during the procedures, given its practical intranasal formulation with a rapid onset of action[21]. Along with pain management, palliative consultations guaranteed proper wound management which, in our patients, included home care. Improvement in wound management has lead to a decrease in wound infections as well as systemic infections in patients with EB[6]. In accordance, our cohort had a low median hospitalization of 1.5 (0-4). We encountered a case of iatrogenic adrenal insufficiency due to prolonged topical corticotherapy for skin lesions treatment. This reminds us that the choice to use corticosteroids should be judicious, because even in the topical formulation it can have permanent secondary effects. In fact, treatment should be based essentially on disinfection and wound care[12].

Regarding other complications, chronic anemia was a common feature in our patients, in accordance to previous literature[22,23]. This complication is mainly caused by iron insufficiency due to feeding difficulties and impaired absorption caused by chronic denudation of the epithelial tract. Gastrointestinal ulcerations may also lead to blood loss. In addition, these patients are under a chronic inflammatory state, which contributes to anemia. Treatment should rely on iron supplementation, which can be given orally. In EB patients, this formulation seems to be less efficient due to decreased absorption and secondary gastrointestinal symptoms which affect treatment adherence. Alternatively, intravenous iron supplementation seems to have good results[24]. A. Reimer et al. found that anemia and iron deficiency correlated with low weight in patients with RDEB ($p < 0.001$)[23]. In line with these findings, poor weight gain was also a frequent complication in our group of patients. This results from a variety of factors, namely nutrients' malabsorption and oral cavity lesions which affect chewing and swallowing. In addition, caloric and protein requirements can be up to 50% and 100% higher, respectively, compared with

other children of the same age[6]. In order to provide a holistic and integrated approach to EB patients, treatment of anemia and poor weight gain were also guaranteed in our patient's palliative care consultations. Hemoglobin and iron study analysis, as well as anthropometric evaluations, were performed routinely. It is imperative that these patients are given adequate nutritional supplementation, in order to prevent failure to thrive, poor wound healing and delayed puberty.

Due to the requirement for ongoing chronic care, this disease also carries a significant social and economic impact. A Portuguese ictiosis/rare diseases working group, in a parliamentary hearing in 2014, estimated that direct health treatment costs of the most severe patients could reach 650 € per month, which can be unaffordable for most family budgets[25]. A more recent study with DEB in Europe showed that besides the direct health costs of EB, there are also high direct non-healthcare costs resulting from informal care needs and loss of patient and caregiver's labour productivity[26]. Although in our country, some hospitals co-participate with wound treatment and outpatient care, there is still a lack of specific legislation that protects this disease group which leads to healthcare asymmetry in EB. There is a need to create reference centers and regulations that detail treatment access for this group of patients.

This was a nonrandomized, single-center study, with its inherent limitations. Although we were able to identify variants in genes related to the main subtypes of EB, parental testing was not performed to confirm biallelic status of the recessive forms and accurately determine the inheritance pattern. Additionally, the NGS panel with all the genes reported to date and copy number variation of analyses in these genes could further enlighten the genotype of patients 2 and 4. On the other hand, when assessing patient's QoL we were not able to use the same instrument for different age categories, given the lack of validated pediatric dermatological questionaries for the Portuguese population. Nevertheless, we were able to gather a significant number of patients affected with this rare disease and analyze its vast array of complications and therapeutic approaches.

Conclusion

EB is a complex and heterogeneous disease. Pediatricians should be aware of the vast array of complications associated to this disease in order to provide early guidance. Palliative care consultations are indispensable to manage pain and guarantee multidisciplinary care tailored for these patients. It is essential to provide social, spiritual and psychological support to both patients and their caretakers. Studies of variants segregation in the parents are mandatory to carry out family studies and eventually reproductive options.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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