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EPIDERMOLYSIS BULLOSA: LITERATURE REVIEW

Sara Pereira da Costa
Universidade de Gurupi (UnirG) - Campus Gurupi, Tocantins – Brazil
Gurupi – Tocantins
http://lattes.cnpq.br/9063399111618009

Ananda Lobo Pedreira Costa
Universidade de Gurupi (UnirG) - Campus Gurupi, Tocantins – Brazil
Gurupi – Tocantins
http://lattes.cnpq.br/0313224856671660

Blenda Ariadne Pereira Mendes
Universidade Federal de Santa Maria (UFSM) - Campus Santa Maria, Rio Grande do Sul - Brazil - Santa Maria - RS
http://lattes.cnpq.br/3786960171548081

Karoline Alves Pereira
Universidade de Gurupi (UnirG)
Campus Gurupi, Tocantins-Brasil;
Bacharelado em Odontologia pela Universidade de Brasília(UnB - 2014)
Brasília – DF
http://lattes.cnpq.br/2913631865644093

Taynara Fonseca Abreu
Universidade de Gurupi (UnirG) - Campus Gurupi, Tocantins – Brazil
Gurupi – Tocantins
https://lattes.cnpq.br/4977988325230986

Vitória Raposo Bonfim
Universidade de Gurupi (UnirG) - Campus Gurupi, Tocantins – Brazil
Gurupi – Tocantins
http://lattes.cnpq.br/0194519203901413

Abstract: Introduction: Epidermolysis Bullosa (EB) is a rare, non-contagious hereditary or acquired genetic disease, which affects the skin and mucous membranes, generating a defect in the adhesion mechanisms between epithelial cells or the underlying connective tissue. **Objective**: Understand the genetic and immunological alterations that lead to the development of the disease. **Methodology:** Literature review through bibliographical research based on the survey of scientific articles published in the last 12 years (2010-2022) in the Lilacs, Pubmed and Scielo databases. **Results and discussion:** It was found that the disease is caused by a mutation that affects the production of proteins by the skin in the junction between the epidermis and the dermis, which weakens the tissue and causes the formation of blisters. Recent research has led to the identification of 18 different genes in human DNA that characterize the clinical picture of EB. It is currently classified into four main types: Simple (EBS), Junctional (EBJ), Dystrophic (EBD) and Kindler Syndrome (KS), in addition to having different subtypes. Furthermore, EB can be acquired, being associated with the interaction of skin structures and autoantibodies. **Conclusion:** It is noticed that the treatment and follow-up of the patient with EB varies according to the type. Because it is a genetic and immunological disease, there is no cure. However, early diagnosis is possible to assist in family planning and genetic counseling of affected families.
Keywords: Autoimmune disease. Mutations. Heredity.

INTRODUCTION

Epidermolysis Bullosa (EB) is a rare, non-contagious genetic condition, first described by Koeber in 1886, characterized by the presence of blisters and erosions on the skin or on the mucous membranes (STEINBERG et al., 2014). They may arise spontaneously or with minor trauma due to the fragility of the epithelial tissue, causing a disfiguring impact on the patient (FINE et al., 2014).

According to the Ministry of Health (2019), the disease is caused by a mutation in genes responsible for the production of proteins necessary for the formation of the dermal-epidermal junction zone, leading to a decrease in skin resistance. EB can be hereditary - with autosomal dominant or recessive transmission - in addition to the acquired form (EBA).

Hereditary forms of EB are classified into 4 major groups: Epidermolysis Bullosa Simplex (EBS), Junctional Epidermolysis Bullosa (EBJ), Dystrophic Epidermolysis Bullosa (EBD) and Kindler Syndrome (KS), in addition to having different subtypes related to changes in 18 genes (KELMANN, 2022). Its severity is related to the mutated protein (type) and its degree of mutation (subtype) (STEINBERG et al., 2014).

Hereditary EB was better differentiated after the introduction of transmission electron microscopy first described by Pearson (1962). A posteriori, they used monoclonal antibodies for better characterization of the phenotypes. Bonifas, in 1991, was a pioneer in demonstrating molecular alterations in simple EB. Subsequently, the molecular basis of the other subtypes of EB were established (OLIVEIRA et al., 2010).

The acquired EB form is rarer than the genetic and hereditary form, caused by the autoimmune reaction of autoantibodies against type VII collagen in the basal membrane zone of the dermal-epidermal junction of the stratified squamous epithelium, developing the wounds in the skin and mucosa that are characteristics of EB (MINISTRY OF HEALTH, 2019).

Mariath (2020) states that hereditary EB occurs worldwide and affects both sexes, with a prevalence close to 11 cases per million

inhabitants and an incidence of approximately 20 cases per million live births. However, there are still no surveys of epidemiological data on its occurrence in Brazil.

It is important to point out that the incidence rate of EB, by subtype, is approximately eight per million live births for simple EB, three per million live births for junctional EB, two per million live births for dystrophic dominant EB and three per million live births due to recessive dystrophic EB (MARIATH, 2020).

In their study, Intong and Murrell (2012) argue that the diagnosis of EB is clinical and laboratory - through skin biopsy, through immunofluorescence, genetic mapping and specific monoclonal antigens, in addition to electron microscopy, the latter being the gold standard exam in the diagnosis of this genodermatosis. Furthermore, for Bega (2015), another indispensable factor in the diagnostic process is the investigation of the family history and the consanguinity of the parents, which are also important for genetic counseling.

The subclassification of the types of EB is essential to determine the risks of mucosal involvement, the development of neoplasms and premature death, in addition to publicizing and raising awareness among the affected population about the different forms of manifestation of the disease, still serving as a guide for professionals in the diagnosis. and the treatment (MARIATH, 2020).

The treatment of the disease involves nutritional therapy, pain management, prevention of lesions with sterile dressings to avoid possible infections, in addition to psychological support for the patient and his family. The greatest difficulty is preventing the appearance of blisters, since chronic injuries can lead to the development of tumors, one of the main causes of death in these patients (TEIXEIRA et al., 2021).

Therefore, this bibliographic review aims to understand the main genetic and immunological alterations that lead to the development of epidermolysis bullosa.

METHODOLOGY

This is a literature review, conducted through a comprehensive bibliographical research, with the aim of obtaining information about Epidermolysis Bullosa (EB), its classification, focusing on genetic and immunological alterations, as well as the diagnosis and treatment of this condition. dermatological condition. Inclusion criteria were: studies published in the last 12 years (2010 – 2022), in Portuguese and English and availability of full text in electronic media. On the other hand, exclusion criteria included book chapters and articles that did not meet the study theme, studies published in different languages and outside the determined period, as well as texts that were not available in full.

The scientific articles were chosen through an active search carried out in the Lilacs, Pubmed and Scielo databases. The descriptors used in the search were "Epidermolysis bullosa", "Autoimmune disease", "Dermo-epidermal junction", "Mutation", "Genetic inheritance" and "Gene therapy". In addition, manuals, book chapters and other articles were used as a basic reference for the discussion of the subject. At the end of the selection, six articles were analyzed for the composition of this work.

RESULTS

The information on the selected studies is organized in Table 2, where the inclusion and exclusion criteria were applied through thorough reading to carry out the selection of publications.

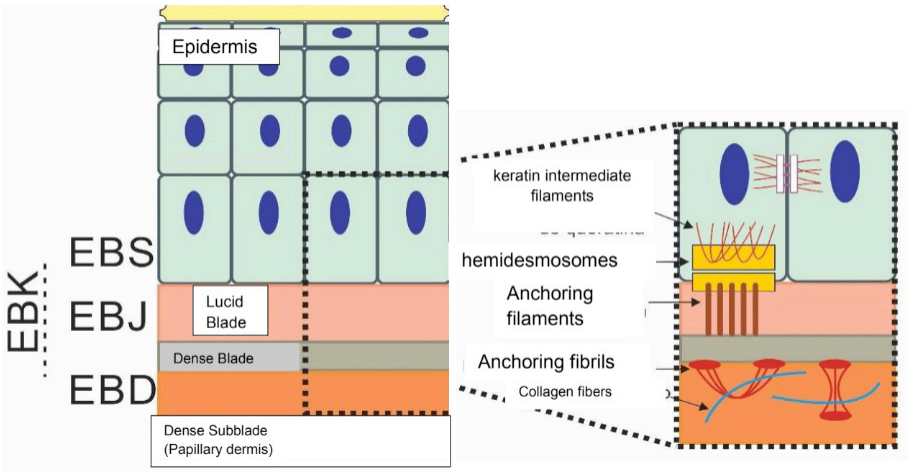

Figure 1 – Representation of the skin layers associated with the types of Epidermolysis Bullosa (EB)

Source: Mariath (2020)

Data base	Descriptors	Works included
Lilacs, Pubmed and Scielo	"Autoimmune disease", "Dermo-epidermal junction", "Mutation", "Gene inheritance", "Gene therapy"	6

Table 1– Database search process.

Source: Authors

Author(s)	Year	Title
SAWAMURA D., NAKANO H., MATSUZAKI Y	2010	**Overview of epidermolysis bullosa**
MOSQUEIRA, C. B. et al.	2010	**Immunomapping in hereditary epidermolysis bullosa**
LOPES L. et. al.	2015	**Newborn with non-herlitz junctional epidermolysis bullosa: the importance of prenatal diagnosis**
SILVA, R. A.	2019	**The experience of family care in the rare illness caused by Epidermolysis Bullosa**
HAS et al.	2020	**Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility**
MARIATH, L. M. et al	2020	**Hereditary epidermolysis bullosa: update on clinical and genetic aspects**

Table 2– Bibliography consulted to carry out the bibliographic review.

Source: Authors

Type	Heritage	Dermis cleavage level	Main mutations
EBS	Autosomal Dominant Autosomal Recessive	Intradermal	KRT5 e KRT14
EBJ	Autosomal Recessive	Lamina lucida of the basement membrane zone	LAMB3, COL17A1, LAMC2 e LAMA3
EBD	Autosomal Dominant Autosomal Recessive	dense subblade	COL7A1
SK	Autosomal Recessive	Varied in basement membrane zone (intraepidermal or subepidermal)	FERMT1
EBA	Acquired	subepidermal	Production of autoantigen that identifies collagen VII

Table 1. Types, inheritance, level of dermal cleavage and main mutations

Source: Adapted from PERAZA (2022)

DISCUSSION

Epidermolysis Bullosa (EB) is a rare genetic, hereditary or acquired disease, whose main characteristic is skin fragility. It belongs to one of the main groups of genodermatoses, with disfiguring impact on the affected individual, due to the formation of blisters and erosions on the skin and mucosa (LOPES et. al., 2015).

The research by Sawamura, Nakano and Matsuzaki (2012) showed that the pathogenesis of this disease involves mutations in genes that encode any of the structural components of the dermal-epidermal junction and keratinocytes, which anchor the skin. Mosqueira (2010) also discusses that, with the absence or decrease of these proteins, the skin becomes fragile, the layers are not fixed and, consequently, come loose at the slightest friction, forming spaces between them that are filled by fluids rich in proteins., giving rise to blisters that evolve into a wound.

EB can be classified as hereditary - with autosomal dominant or recessive transmission - in addition to the acquired form (EBA). Hereditary EB is the most common form related to the mutation of 18 genes, being divided into four major groups: Epidermolysis Bullosa Simplex (EBS), Junctional Epidermolysis Bullosa (EBJ), Dystrophic Epidermolysis Bullosa (EBD) and Kindler Syndrome (KS). Each of these four groups is divided into other subtypes according to the mutated protein (type) and its degree of mutation (subtype) (KELMANN, 2022).

Epidermolysis Bullosa Simples (EBS) is the most common form, as described by Mariath (2020), associated with the formation of intradermal blisters and milder clinical manifestations. It appears that the blister pattern mainly affects the hands and feet, with a more common transmission in the autosomal dominant form and rarely in the autosomal recessive form, which originates the different EBS subtypes (HAS et al., 2020).

For Has et al. (2020), cleavage of this type occurs within basal keratinocytes at keratin genes 5 (gen KRT5) or 14 (gen KRT14), which lead to structural modifications of hemidesmosomes, keratin intermediate filaments, and cellular vesicle transport. In addition, mutations in plectin (PLEC1 gene), a component of the inner plate of the hemidesmosome, also lead to intraepidermal cleavage.

Epidermolysis Bullosa Simplex - EBS	
Heritage	**Subtypes**
Autosomal Dominant	Localized EBS (Weber-Cockayne) Generalized intermediate EBS (Koebner) Generalized severe EBS (Dowling-Meara)
Autosomal Recessive	EBS with muscular dystrophy autosomal recessive EBS superficial EBS lethal acantholytic EBS EBS with plakophilin 1 deficiency EBS with pyloric atresia EBS migratory circinata

Table 3 – Subtypes of Epidermolysis Bullosa Simplex (EBS)

Source: Adapted from Ministry of Health (2019)

Junctional Epidermolysis Bullosa (EBJ) occurs within the lamina lucida, with the main proteins associated with junctional epidermolysis bullosa being α6β4 Integrin, collagen XVII and Laminin-332, which interact to allow the binding of keratin intermediate filaments to the fibrils anchorage (formed by collagen type VII) in the upper part of the dermis (MARIATH, 2020).

As a result of the complexity of the basement membrane zone, alterations in the genes lead to the detachment of basal keratinocytes in the lamina lucida, due to the dysfunction of adherence between these and the lamina Densa (ALMEIDA, 2002). Parentes (2020) also describes that the blisters are deep, resulting in skin atrophy, which affects a large part of the body surface, being a severe form

of EB.

Junctional Epidermolysis Bullosa - EBJ		
Heritage		**Subtypes**
Autosomal Recessive	Localized	EBJ located inverse EBJ EBJ laryngo-onycho-cutaneous syndrome
	Wides-pread	Generalized severe EBJ (Herlitz) Generalized intermediate EBJ (non-Herlitz) EBJ with pyloric atresia

Table 4 – Subtypes of Junctional Epidermolysis Bullosa (EBJ)

Source: Adapted from Ministry of Health (2019)

Dystrophic Epidermolysis Bullosa (EBD) occurs in the part of the dense sublamina, in the upper portion of the dermis (papillary dermis), and the separation takes place on the dermal side of the cutaneous basement membrane (OLIVEIRA et al., 2010). Has et al. (2020) adds that this type can be autosomal dominant or autosomal recessive, however, all types of EBD are caused by mutations in only one gene, the COL7A1 gene, the main component of anchoring fibrils, producing cleavage below the lamina Densa, which encodes type VII collagen, which forms the anchoring fibrils for the basement membrane of the epidermis. The blisters resulting from EBD are even deeper than the other subtypes, generating scars and even more severe mutilations (MARIATH, 2020).

In Kindler Syndrome (KS), cleavage can occur in basal keratinocytes, in the lamina lucida or below the lamina Densa, thus, the alteration in a gene determines its phenotypic demonstration (MARIATH, 2020). Kindler syndrome (KS) is an autosomal recessive type of EB caused by mutations in the FERMT1 gene, which encodes the homologous focal adhesion protein 1 of the fermitin family, also called kindlin-1, resulting in tissue cleavage at varying levels in the basement membrane zone (INTONG; MURRELL, 2012). In addition, according to the Ministry of Health (2019), it is a rare form, as it presents characteristics of all other types of EB, in this sense, the formation of blisters can occur in different regions: intradermal, in the lamina lucida and below the dense blade.

As for the acquired form, it was verified that it is a disease that starts in adulthood, regardless of race or gender, however, it usually settles in adulthood (higher incidence at 50 years of age), being related to the HLA-DR2 allele (MOSQUEIRA, 2010). Accordingly, the study by Silva (2020) revealed that people with this phenotype are more susceptible to the deposit of IgG and C3 in the basement membrane (occasionally IgA and IgM are also present). Thus, autoantibodies bind to type VII collagen, which alters dermoepidermal adhesion, forming blisters.

The diagnosis of EB can be performed in the prenatal period, through fetal skin biopsy or fetal DNA analysis - little used in Brazil due to the lack of specific materials for its realization, in addition to the high cost (LOPES et. al. 2015).

The clinical diagnosis can be performed after birth according to the evolution and characteristics of the lesions. In order to confirm the types and subtypes of EB, it is necessary to perform a skin biopsy for immunohistological and ultrastructural investigation with transmission electronic microscopy and immunofluorescence mapping, with mapping being the gold standard in the diagnosis of epidermolysis bullosa (INTONG; MURRELL, 2012).

The clinical course of the disease depends on the type and subtype of EB, its evolution can be mild - with mild epithelial fragility and without major systemic involvement - or severe - compromising several organs, which can lead the individual to death (SIMIONI;

UGRINOVICH, 2021). Silva (2019) points out that complications may appear from birth, which will vary according to their severity, and may compromise all body systems such as the respiratory, gastrointestinal, genitourinary, ophthalmological tract, as well as a greater predisposition to the development of dermatological and malignant neoplasms. encapsulation of hands and feet as a result of wound healing. Furthermore, the bearer of EB is at daily risk of dehydration, growth retardation, anemia, infectious conditions, chronic inflammation and sepsis.

It is worth noting that pain is the most debilitating symptom in the life of individuals with EB, compromising their daily activities. Bathing and changing dressings represent a great challenge, being considered the most painful activities (SILVA, 2019).

Silva (2019) also states that the treatment of this genodermatosis aims to provide pain control, prevent the formation of blisters and minimize associated complications, improving the quality of life of affected individuals. To achieve these results, it is necessary to have individualized therapeutic approaches for each case, with a multidisciplinary approach and a multidisciplinary team. Through this collaborative action, the aim is to offer comprehensive care, which goes beyond just symptom relief, also encompassing the general well-being of each individual.

That said, Simioni and Ugrinovich (2021) argue that for an assertive treatment, it is essential to identify the type of EB. In milder cases, care for the lesions is local, with or without the use of topical antibiotics for larger blisters. While in the most severe cases, intensive treatment is required. Unfortunately, despite all medical assistance, many patients die as a result of infectious complications.

Thus, it is clear that the treatment and follow-up of patients with epidermolysis varies according to the type. Because it is a genetic and immunological disease, there is no cure. However, early diagnosis is possible, through special tests that can be performed during the prenatal period (chorionic villus sampling, amniocentesis or genetic mapping) to assist in family planning and genetic counseling of affected families (LOPES et al. al. 2015).

CONCLUSION

Epidermolysis bullosa is a rare medical condition that encompasses genetic and autoimmune aspects, and its main clinical manifestation is the formation of blisters that appear due to minimal trauma to the skin and mucous membranes. The severity of the lesions varies according to the genetic mutation and the level of cleavage of the dermoepidermal junction.

In view of this, it is essential that the patient with epidermolysis undergo treatment and follow-up according to the type. In milder cases, treatment is directed at local lesions, with or without the use of topical antibiotics for larger blisters. In the most severe cases, intensive treatment is required. Unfortunately, as discussed, many patients die as a result of complications from infections despite all medical care and because it is a disease of a genetic nature, there is no cure, only prevention and remediation actions as soon as possible. Thus, it is indicated and essential that there be an early diagnosis, through prenatal care, to assist in family planning and genetic counseling of affected families to avoid complications of the disease.

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