CUTANEOUS AND EXTRA CUTANEOUS MANIFESTATIONS AND FAMILY HISTORY AMONG PATIENTS WITH EPIDERMOLYSIS BULLOSA IN MISRATA - LIBYA

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ABSTRACT

Epidermolysis bullosa refers to a group of rare genetic disorders marked by recurrent blister formation and fragility of the skin and can affect any epithelial tissues in the body. The aim of the paper to presents the cutaneous as well as the extracutaneous manifestations of epidermolysis bullosa among Libyan patients, and highlights the association between extracutaneous manifestation and family history. A retrospective single-center case-control study on patients diagnosed with epidermolysis bullosa registered in the genodermatosis outpatient clinic of the dermatology department at Misrata Medical Center. Ethical approval was obtained. Data were collected from patients' files into an excel sheet and then analyzed using SPSS software. Seventy-three patients were included. Mean age was 5.7 years and male to female ratio is 1:1.6.
The most common skin manifestations were bullae with erythema, crusts, and erosions. 69.8% of patients (51 patients) developed extracutaneous manifestations, such as oral blisters, dental hypoplasia, nail dystrophy, alopecia, constipation, dysphagia, or corneal opacities. Among which, 42 patients have a positive family history of epidermolysis bullosa. The odds ratio is 2.6667 and the P-value is 0.0884. Although, 42 patients (75%) with a positive family history of epidermolysis bullosa have extracutaneous manifestations. Statistical analysis did not show a strong association. Further studies with a bigger sample size are required.

KEYWORDS: Epidermolysis Bullosa, Genetic Disorder, Cutaneous.

INTRODUCTION

There are many types and subtypes of this genetic disorder, all of which are considered rare. The overall incidence of all types of epidermolsis bullosa in England and the USA are 67.8 and 19

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The actual prevalence of epidermolysis bullosa worldwide is unknown. But, an estimated 50 in 1 million live births and 9 in 1 million people worldwide are diagnosed with this genetic disorder [3]. The major types of epidermolysis bullosa are simplex (EBS), junctional (JEB), Dystrophic (DEB), and Kindler

syndrome. This classification is based on the ultrastructural level within which blisters develop within the skin. Moreover, these major types of epidermolysis bullosa are further classified into subtypes. Other classifications for epidermolysis bullosa have been developed. For example, classification according to the mode of inheritance, Antigenic alterations in the skin, or mutational analyses [4]. The clinical features and severity of the disease vary greatly between different types and subtypes. The hallmark cutaneous features of all epidermolysis bullosa subtypes are fragile skin and the formation of blisters or erosions [1]. According to the type of epidermolysis bullosa, the extension of skin involvement may range from occasional mild blistering of the hands and feet to severe and widespread formation of large bullae [5]. When the mechanical trauma or friction is recurrent, the skin lesions may become chronic resulting in scarring in most cases. Any epithelial surface may be affected in epidermolysis bullosa. Such as the mucus membrane of the oral cavity, esophagus, trachea, genitourinary tract, and the eye [6]. Many epidermolysis bullosa subtypes are associated with clinically significant extracutaneous (EC) manifestations or complications, which in turn lead to morbidity and, in some cases, death [7]. For example, Recurrent painful erosions and blisters are severe complications within the external eye and may lead to scarring and progressive visual impairment. Furthermore, gastrointestinal complications include esophageal blistering, strictures, and web formation, gastroesophageal reflux disease, and constipation [8,9]. Moreover, partial or complete occlusion of the upper airway is considered one of the most severe otorhinolaryngeal complications. This severe stricture formation within or near the level of the vocal cords may lead to death if left untreated [10,11]. The diagnosis is dependent on correlating clinical presentation with immunohistological features or electron microscopic findings or mutational analyses [12]. Typically, a Skin biopsy from an induced blister site for immunofluorescence mapping is sufficient for the diagnosis. as it can identify the level of cleavage in most severe cases. If immunofluorescence mapping fails to demonstrate the level of cleavage, then the diagnosis can be made with either transmission electron microscopy or mutational analysis.

Epidermolysis bullosa has many modes of inheritance, it can be autosomal dominant, autosomal recessive, or even arise as a new mutation in the affected person. mutational analysis is the greatest test of determining the mode of inheritance and the precise sites and types of molecular mutation present in a patient. According to the 2014 classification system, the major types of epidermolysis bullosa were found to be caused by pathogenic variants in 18 different genes [13]. More than 30 different phenotypes of epidermolysis bullosa have now been illustrated, each one resulting from molecular mutations within genes encoding for proteins within the skin [14].

OBJECTIVES

In this study, we will present clinical features of Libyan patients diagnosed with epidermolysis bullosa including extracutaneous manifestations. In addition, we will highlight the association between the presence of (EC) features of epidermolysis bullosa and the presence of positive family history.

METHODS

This is a retrospective single-center case-control study among Libyan patients diagnosed clinically with epidermolysis bullosa. After getting ethical approval from Medical Affairs Office at Misrata Medical Center, we collected the data from patients' files at the dermatology department of Misrata Medical Center.

The inclusion criteria were any Libyan patients diagnosed with epidermolysis bullosa from October 2010 until October 2021 regardless of their age, gender, or social class. the exclusion criteria were any patient who has other dermatological conditions that might contribute to his skin manifestations. From each file, we collected patient age, gender, city, cutaneous and (EC) manifestations, and family history. For those patients who have a positive family history of epidermolysis bullosa, we collected the relative degree, whether first degree, second degree, or third degree. First-degree relatives include parents or siblings. Second degree relatives include grandparents, aunt, uncle, niece, or nephew. Third-degree relatives or more include Cousins or any family member not from the first or the second degree. Patients' names were not collected to ensure their privacy. all data was collected into an excel sheet and then underwent statistical analysis using the SPSS software version 24. We used file numbers instead of patient names to remove the duplicated data. for numerical data we used mean and mode and standard deviation. for categorical data, we used frequencies and percentages. we split the patients into two groups, the case group include all patients with skin and (EC) features. The control group includes patients with cutaneous features only. For the association between variables, we used the Odds ratio. Further analytical tests were used such as confidence interval (CI), Z score, and p-value. P-value of < 0.05 is considered statistically significant.

RESULTS

The total number of files reviewed was 393 files. Out of them 73 patients were diagnosed as epidermolysis bullosa. The study included 45 females (61.64%) and 28 males (38.36%). The male to female ratio was 1:1.6. The vast majority of cases were from Misrata and just four (5.8%) cases were from outside Misrata. The mean age was 5.7 years, the median 2.5, and the standard deviation 5.87. All patients have skin findings related to epidermolysis bullosa.

The most common skin manifestations were bullae, erythema, crusts, and/or erosions (Table 1).

Fifty-six patients (76.71) had a positive family history of the disease, and 17 (23.28%) patients did not have a family history of epidermolysis bullosa.

For those patients with positive family history, 42 (75%) cases developed (EC) manifestations, and 14 (25%) cases did not show any evidence of systematic involvement (Table 2).

Table 2 : The association between EB and family history

	+ ve	- ve	Total
Cutaneous and (EC) manifestations	42	9	51
Cases with cutaneous manifestation only	14	8	22
Total	56	17	73

Table 1: Skin manifestation

	The lesion	No.	%
1	Erythema	42	57.5
2	Crusts	37	50.7
3	Scales	11	15.1
4	Bullae	46	63
5	Hyperpigmentation	5	6.8
6	Nodules	2	2.7
7	Erosions	25	34.2
8	Vesicle	13	17.6
9	Papule	4	5.5
10	Hypopigmentation	5	6.8
11	Ulcer	2	2.7

Fifty percent of cases have first-degree relatives suffering from epidermolysis bullosa (Table 3).

Table 3: Family history of EB

	No.	%
First degree	28	50
Second degree	11	19.6
Third degree	11	19.6
NO data	6	10.7

Regarding the association between (EC) manifestation and positive family history.

The odds ratio is 2.6667. However, further statistical analysis did not show a strong association (table 4)

Table 4: Statistical tests Results

Odds ratio	2.6667
Confidence interval (95%)	0.8629 to 8.2405
z-score	1.704
P-Value	P = 0.0884

Among the 73 patients, 51 (69.86%) patients had (EC) manifestations. The oral cavity was the most common site to be affected followed by nails. Other organs affected by the disease are the eyes, ears, hair, and many organs within the gastrointestinal system (Table 4).

DISCUSSION

The fact that epidermolysis bullosa is a rare disorder, made data collection about this disease take time. Over the last 11 years, we could retrieve only 73 cases.

Unfortunately, there is no national registry in Libya that provide the prevalence and the incidence of epidermolysis bullosa. According to our knowledge, this is the first study in Libyan that provides clinical data from Libyan patients diagnosed clinically with epidermolysis bullosa.

Our study did not show any significant gender privilege regarding the disease onset or clinical manifestations, supporting previously published data in the literature. Moreover, the onset of the disease can vary, but most patients in this study had the onset during the first year of life.

Table 4: Extracutaneous manifestations

Organ or system	No. & %	Clinical findings or symptoms
Nail apparatus	36 (70.6%)	Pitting, dystrophy, avulsion, hyperkeratosis
Oral cavity	39 (76.5%)	Mucosal blistering and ulcers, Tongue and gingival redness, Dental pitting or hypoplasia
Eye	6 (11.8%)	Conjunctival redness, corneal opacities
Hair	4 (7.8%)	Alopecia
Gastrointestinal	8 (15.7%)	Dysphagia, constipation, diarrhea anal fissure
Ear, nose, and throat	2 (3.9%)	Uricular blistering, crusts, and erosions, Trachea or laryngeal erosions
Musculoskeletal	5 (9.8%)	Abnormal gait, Fingers contracture

Regarding pathogenesis;

Epidermolysis bullosa is caused by mutations involving many genes encoding proteins. The type (homozygote or heterozygote), number (monogenic, digenic inheritance), and location of mutation(s) within the gene, resulting in marked genetic heterogeneity with complex genotype-phenotype correlations. For instance, mutations in the same gene may be inherited in an autosomal dominant or recessive manner and result in different phenotypes. In contrast, mutations in different genes, with either dominant or recessive inheritance, may underlie similar phenotypes. Besides the primary structural-functional defect, other genetic, epigenetic, and even nongenetic factors contribute to the significantly variable phenotype of epidermolysis bullosa [15-17], such as socioeconomic and environmental factors or differentially regulated expression of other genes involved in the induction of inflammatory cascades. As a result, the clinical finding will depend greatly on the type or subtype of epidermolysis bullosa. Skin findings can range from simple localized blisters to enormous bullae which cover a large surface area. In this study, the most common skin findings are bullae, erythema, crusts, and erosions. Other less common skin findings are hypopigmented or hyperpigmented macules, papules, or ulcers. This wide range of clinical findings could be explained by the presence of different genetic subtypes of epidermolysis bullosa among our patients.

In terms of systemic involvement, more than two-thirds of our patients developed (EC) manifestations. Therefore, epidermolysis bullosa should be a multisystemic disease associated with significant morbidity and mortality and require a multidisciplinary approach for management. The most common site for (EC) manifestations is the oral cavity. Different parts of the oral cavity were involved such as teeth, tongue, palate, lips, or buccal mucosa. These findings have been reported in the literature [7]. The second most common site for (EC) manifestations is the nail apparatus. our patients have a wide range of clinical findings, such as nail pitting, nail dystrophy nail avulsion, or subungual hyperkeratosis. It has been reported that early nail

dystrophy and nail avulsion correlate with disease severity and progression, particularly in junctional epidermolysis bullosa and recessive dystrophic epidermolysis bullosa [18]. For the gastrointestinal system, some of our patients suffer from dysphagia, constipation, diarrhea, or fissure. involvement of Gastrointestinal system organs can lead to serious complications [8,19]. None of our patients had clinical findings related to the genitourinary system. even though it is published that epidermolysis bullosa can affect the Genitourinary tract [20].

The fact that (EC) manifestation is associated with serious complications and mortality raises our concern. It is worth mentioning that in this study, patients with positive family history were 2.6 times more likely to have systemic involvement of epidermolysis bullosa compared to patients with negative family history. however, the further stoical analysis did not show a strong association. The result of statistical analysis may be an actual result or a type 2 error. More studies are required with a bigger sample size to prove the association between (EC) manifestations and mode of inheritance.

As with any study, this research is subjected to limitations. The Fist limitation is the sample size in this study is small. this is mainly because the incidence of epidermolysis bullosa is low worldwide. Also, the data in this study is subjected to recall bias and missed information because it is a retrospective study. In addition, due lack of resources for genetic analysis, we were not able to classify the cases according to the genetic subtypes. Lastly, most of these cases were from Misrata city and they don't represent all cases in Libya.

The risk of death from epidermolysis bullosa varies markedly by subtype in terms of specific cause and magnitude of risk. Infants and children with epidermolysis bullosa, particularly those with Junctional epidermolysis bullosa, are at significant risk of death as a result of disease complications [21]. It is highly recommended to raise awareness about this disease and modes of inheritance in our community. moreover, genetic counseling and family planning are excellent approaches to reducing the incidence of this disorder in our community. For example, the incidence of Junctional epidermolysis bullosa, which is inherited by Autosomal recessive mode, can be reduced by family planning. and this applies to any type inherited by autosomal recessive modes such as Dystrophic, Simplex, or Kindler epidermolysis bullosa.

CONCLUSIONS:

Seventy-three patients diagnosed with epidermolysis bullosa in the last 11 years at Misrata Medical Center. The average age was 5.7 years, the Standard deviation was 5.8 and the male-to-female ratio is 1.6. All cases developed skin findings and the most common skin manifestations were bullae with erythema, crusts, and erosions.

Fifty-one patients (69.8%) developed extracutaneous manifestations. the most common site for (EC) manifestations among our patients was the oral cavity. different signs were observed such as blisters in the buccal mucosa, tongue, and palate. in addition to dental pitting and hypoplasia. Besides the oral cavity,

the nail apparatus was affected and some cases suffered from nail dystrophy, nail avulsion, or hyperkeratosis. Other systems were affected such as gastrointestinal, musculoskeletal, and ENT. 42 patients (75%) with a positive family history had (EC) manifestations. The odd ratio is 2.66, Confidence interval 955% is 0.8629 to 8.2405, and P-value is 0.088.

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