International Journal of Women's Dermatology 1 (2015) 37–40

Contents lists available at ScienceDirect

International Journal of Women's Dermatology

Original Research

Prevalence of anemia in patients with epidermolysis bullosa registered in Australia

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ARTICLE INFO

Article history:
Received 15 September 2014
Received in revised form 1 December 2014
Accepted 13 December 2014

Keywords:
Epidermolysis bullosa
Bullous disease
Anemia
Prevalence
Epidemiology
Retrospective study

ABSTRACT

Background: Anemia is a common complication of epidermolysis bullosa (EB). To date, no extensive data on the prevalence of anemia in EB patients have been well characterized worldwide.
Objective: To determine and to characterize the prevalence of anemia in the Australian EB population by conducting a retrospective cross-sectional study.
Methods: All ($n = 368$) EB patients registered in the Australasian Epidermolysis Bullosa Registry (AEBR) from 2006 to 2012 were reviewed for pathological evidence of anemia. Patients with EB without anemia and those without hematological parameters were excluded from the study. Patients' particulars were separated into pediatric (<18 years old) and adult (≥18 years old) male and female subgroups.
Results: One-hundred sixty-nine out of 368 EB patients had eligible blood results to be analyzed, as milder forms of EB did not routinely have laboratory testing; 27.8% ($n = 47/169$) of EB patients were anemic at any time point in their lifetime. All generalized severe junctional EB (JEB-GS) cases (100%, $n = 4/4$); 68.0% ($n = 17/25$) of recessive dystrophic EB (RDEB); and 37.5% (n = 6/16) of generalized intermediate JEB (JEB-I) patients were anemic.
Limitations: As EB is an orphan disease, the limited sample size may have affected the significance of the study result.
Conclusion: The high prevalence of anemia seen in RDEB and JEB generalized severe (JEB-GS) patients in our cohort is similar to those reported in case series.

Introduction

Epidermolysis bullosa (EB) is a heterogeneous group of genodermatoses, which affects the skin, mucous membranes, and sometimes, internal organs. It is characterized by cutaneous blistering, bullae, and erosions that result from slight mechanical trauma and impaired wound healing (Haber et al., 1985; Kuo et al., 2006; Mitsuhashi & Hashimoto, 2003). EB is a rare disease with a reported prevalence of all dominant types together estimated to be at 1:50,000 and the recessive forms to be 1:300,000 (Kuo et al., 2006). Patients may develop a host of complications, from skin infections, to skin cancers, anemia, and renal failure, to mention a few with high mortality. EB has no sex predilection and occurs worldwide. The prevalence is estimated to be approximately 8.22 per million in the United States (Fine & Hintner, 2009) and 12.78 per million in Australia (Kho et al., 2010).

Four major types of EB are recognized following the Third and Fourth International Consensus Meeting on Diagnosis and Classification of EB: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler syndrome (Fine et al., 2008, 2014; Samad et al., 2004). The classification is based on the main clinical features and differences in the ultrastructural level within which blisters develop in EB skin (Fine et al., 2008; Mitsuhashi & Hashimoto, 2003; Samad et al., 2004). In this study, major types of EB have been further divided into major subtypes of EB as characterized in [5]. These are EBS, JEB-GS, JEB-I, dominant dystrophic EB (DDEB), recessive DEB (RDEB), and Kindler syndrome (Fine et al., 2008, 2014).

Anemia commonly occurs in patients with severe types of EB, particularly in RDEB and JEB, but also to a lesser extent in some other subtypes (Antunes et al., 1999). Patients with RDEB often present with severe anemia, becoming dependent on multiple blood transfusions (Antunes et al., 1999; Fine & Hintner, 2009).

Although anemia in EB patients is a well-known entity, no epidemiological studies had been previously conducted worldwide to show associations that exist between anemia and subtypes of EB. Therefore, this study will be the first retrospective cross-sectional study that addresses this correlation in the Australian EB population.

We report the prevalence of anemia in major subtypes of EB in both pediatric and adult EB populations living in Australia, any gender difference, and the mean hemoglobin value in different EB subtypes. We also recommend directions to future studies with regard to early screening and prompt treatment of anemia in EB patients.

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http://dx.doi.org/10.1016/j.ijwd.2014.12.001

Methods

Ethics statement

This study was a part of a project with ethics approval, "Development of an EB registry including rates of complications and severity of symptoms in EB patients within Australasia." In August 2006, the ethics approval for the project was granted from the South Eastern Sydney and Illawarra Area Health Service Human Research Ethics Committee (reference number 06/89). The project was also approved by the Bellberry Ethics Committee. (201202-683, 2012) and by the University of New South Wales ethics committee in January 2010.

Study population

Patients with subtypes of EB were diagnosed by EB expert dermatologists across Australia based on clinical assessment, light microscopic examination of a skin biopsy, immunofluorescence antigenic mapping, and transmission electron microscopy (Fine & Mellerio, 2009). Patients from the Australasian Epidermolysis Bullosa Registry (AEBR) in the period 2006–2012 were included in the study. The AEBR was established on November 8, 2006, at St George Hospital in Sydney (Kho et al., 2010). The patients with EB belonging to a non-profit national organization, Dystrophic Epidermolysis Bullosa Research Association (DebRA) Australia were also eligible.

Informed consents were obtained from EB patients registered in AEBR to participate in the study. The study was conducted by reviewing all consenting patients' medical records and by contacting pathology laboratories where applicable across Australia; general practitioners were contacted for pathology results when necessary.

Patients without blood test results, incomplete data sets in files, and insufficient pathology results were excluded from the study. Of the 368 patients registered in AEBR by the end of 2012; 199 patients had no blood test results available for various reasons. These include patients with milder forms of EB such as EBS, who never had any blood tests taken unless indicated for other health concerns; some patients with JEB-GS subtype had died without blood having been taken; and some patients' contact details along with general practitioners' had changed so they were not contactable.

Study-outcome definitions

In the study, patients were also separated into pediatric (<18 years old) and adult (≥18 years old) subgroups. In the pediatric group, anemia was defined as hemoglobin of less than 11 g/dL. In adults, anemia is defined as hemoglobin below 13 g/dL in men or 12 g/dL in women (Moreno Chulilla et al., 2009). The pathological evidence of a decrease mean in hemoglobin levels from a reference range was defined based on age and sex (Janus & Moerschel, 2010; Moreno Chulilla et al., 2009; Tefferi, 2003). Anemic patients were further classified into macrocytic (MCV >98 fL), normocytic (MCV = 82–98) and microcytic (MCV <82 fL) categories based on the MCV (Mean Corpuscular Volume) (Janus & Moerschel, 2010; Tefferi, 2004).

Data collection and analysis

Data were collected according to standardized criteria. The information gathered from all subjects included; the age, gender, diagnosis of EB subtypes with confirmed histopathological evidence, and cross sectional values of hemoglobin in their lifetime as severe forms of EB patients die at early age. Data collections and statistical analysis of hemoglobin levels were also conducted using SPSS software version 16.0.1 (SPSS Inc, Chicago, Illinois) and Microsoft Excel program.

Results

Demographics

Of the 169 patients included in the analysis, the sex distribution was similar, with 76 males (44.9%) and 93 females (55.0%). Patient age ranged from 3 days to 99 years, with mean age of 29.2 years (Table 1). Hemoglobin ranged from 2.7 g/dL to 20.2 g/dL, with mean hemoglobin of 12.65 g/dL. Most of the patients in the study population had EBS (n = 80), DDEB (n = 43), RDEB (n = 25), JEB-I (n = 16), JEB-GS (n = 4) and KS (n = 1).

Hemoglobin levels in EB patients

The mean hemoglobin level for pediatric patients (n = 62) was 12.14 ± 3.02 g/dL, for adult male patients (n = 41) was 13.57 ± 2.29 g/dL, for adult female patients (n = 66) was 12.56 ± 2.01 g/dL. The mean hemoglobin level was 13.49 ± 1.62 g/dl in EBS, 12.87 ± 2.49 g/dL in DDEB, 10.19 ± 3.08g/dL in RDEB, 12.62 ± 2.53g/dL in JEB-I group and 8.55 ± 1.29g/dL in JEB-GS group. Fig. 1 describes the mean hemoglobin level in different subtypes of EB.

One-way ANOVA (F, 11.5; F critical value, 2.3), comparing hemoglobin levels among different subtypes of EB, suggests that the differences in mean hemoglobin values in different subtypes of EB are statistically significant.

Prevalence of anemia among adult men and women with EB, and in pediatric EB patients

Among the 169 patients, 47 (27.8%) had anemia. Among 41 male adult patients, 13 (31.7%) had anemia; among 66 female adult patients, 18 (27.3 %) had anemia; among 62 pediatric patients, 16 (25.8%) had anemia. The prevalence of anemia did not differ significantly according to sex in adult groups (p = .369, chi-test), however the prevalence of anemia among adults were higher than those among pediatric patients (p = .029, chi-test).

Prevalence of anemia in subtypes of EB

The overall prevalence of anemia in DDEB patients (n = 43) was 25.6% (n = 11/43). Among 43 DDEB patients, 17 were pediatric, 8

Table 1
Basic characteristics of EB patients in the study.

CHARACTERISTIC	*Patient No. (%)*
AGE, years	
<18	41 (24.3%)
≥18	107 (63.3%)
Mean age (range)	29.2 (3 days, 99 years)
GENDER	
Male	76 (44.9%)
Female	93 (55.0%)
EB SUBTYPES	
EBS	80 (47.3%)
DDEB	43 (25.4%)
RDEB	25 (14.8%)
JEB-nH	16 (9.5%)
JEB-H	4 (2.4%)
KS	1 (0.6%)
PRESENCE of ANEMIA	
Yes	47 (27.8%)
No	122 (72.2%)

EB, epidermolysis bullosa; EBS, epidermolysis bullosa simplex; DDEB, dominant dystrophic epidermolysis bullosa; RDEB, recessive dystrophic epidermolysis bullosa; JEB-nH, junctional epidermolysis bullosa – non-Herlitz, newly known as generalized intermediate; JEB–Herlitz, junctional epidermolysis bullosa – Herlitz, newly known as JEB generalized severe; KS, Kindler syndrome.