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Original Research

Prevalence of anemia in patients with epidermolysis bullosa registered in Australia

Shelley Ji Eun Hwang, BSc(Med), MBBS(Hons) [a,c], Benjamin S. Daniel, BA, BCom, MBBS, MMed (Clin Epi) [a,b,c], Bonnie Fergie, MBBS [a], Jessica Davey [a,c], Dédée F. Murrell, MA, BMBCh, MD, FACD, FRCP(Edin) [a,c,*]

[a] Department of Dermatology, St. George Hospital, Sydney, Australia
[b] University of Sydney, Sydney, Australia
[c] University of New South Wales, Sydney, Australia

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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.

* Corresponding author.
E-mail address: d.murrell@unsw.edu.au (D.F. Murrell).

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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.

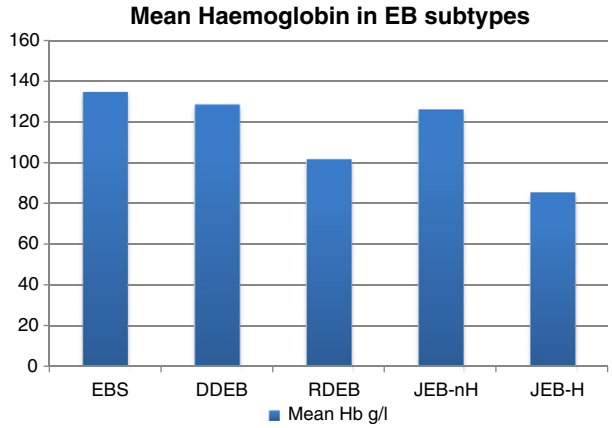

Fig. 1. Mean haemoglobin level in different subtypes of EB.

were male adults, and 18 were female adults. The prevalence of anemia in pediatric, male adults and female adults were 23.5% ($n = 4/17$), 50.0% ($n = 4/8$) and 16.7% ($n = 3/18$) respectively.

The overall prevalence of anemia in EBS patients ($n = 80$) was 11.3% ($n = 9/80$). Among 80 EBS patients, 25 were pediatric, 21 were male adults, and 34 were female adults. The prevalence of anemia in pediatric, male adults and female adults were 4.0% ($n = 1/25$), 14.3% ($n = 3/21$) and 14.7% ($n = 5/34$) respectively.

The overall prevalence of anemia in JEB-I patients ($n = 16$) was 37.5% ($n = 6/16$). Among 16 JEB-I patients, 9 were pediatric, 4 were male adults, and 3 were female adults. The prevalence of anemia in pediatric patients, male adults, and female adults were 22.2% ($n = 2/9$), 50.0% ($n = 2/4$) and 66.7% ($n = 2/3$) respectively.

The overall prevalence of anemia in RDEB patients ($n = 25$) was 68.0% ($n = 17/25$). Among 25 RDEB patients, 7 were pediatric, 7 were male adults, and 11 were female adults. The prevalence of anemia in pediatric patients, male adults, and female adults were 71.4% ($n = 5/7$), 57.1% ($n = 4/7$) and 72.7% ($n = 8/11$) respectively. Of these, 22/25 were known to be receiving intermittent iron or blood transfusions which would elevate the average hemoglobin level. Two of these patients had thalassemia trait uncovered on transition to the adult EB center; iron infusions were therefore ceased and changed to blood transfusions.

The overall prevalence of anemia in JEB-GS patients ($n = 4$) was 100.0% ($n = 4/4$). There were only pediatric patients in this subtype, as the mortality is very high at a young age.

There was only one patient with KS in the study population and he was not anemic.

Discussion

To our knowledge, this is the first descriptive study that presents the epidemiologic data on anemia in all major subtypes of EB patients. Although several studies have described anemia as one of common complications encountered in severe forms of EB (Van den Akker et al., 2009), no epidemiologic data on anemia in all subtypes of EB patients from an adequate sized cohort has been published for statistical evidence. Such data have been collated from AEBR and analysed leaving statistical grounds for future researches on the topic of anemia.

In our study, the overall prevalence of anemia among EB patients (27.8%) was higher than the general population. According to the Australian Bureau of Statistics, in the Australian general population between 2011 and 2012, 4.5% of the adult population was at risk of anemia (Australian Bureau Statistics, 2013). Hence our findings indicate the necessity of routine hematological parameter monitoring in EB patients in general.

Anemia is commonly observed in more severe forms of EB, notably RDEB and JEB (Kho et al., 2010). This is similarly demonstrated in our study as the top three most prevalent anemic EB subtypes were JEB-GS (100.0%), RDEB (68.0%), and JEB-I (37.5%). Thus, this constitutes further evidence of the need for more closely monitoring hematological parameters of EB patients routinely in the severe forms than non-severe subtypes of EB to ensure that mortality and morbidity are minimized and quality of life are optimized.

Variable degrees of anemia occur in different subtypes of EB. Comprehensive literature search review by Fine and Mellerio (2009) suggests that a hemoglobin level of 8g/dL was maintained in severe forms of EB despite iron supplements. This literature suggestion fits with our findings that some of the most severely affected EB patients demonstrated mean hemoglobin levels of 8.55 ± 1.29g/dL and 10.19 ± 3.08g/dL in JEB-GS and RDEB respectively.

In more severe forms of EB, such as RDEB and JEB-GS; the prevalence of anemia was higher or similar in pediatric group compared to the adult groups. This finding was contrasting in mildly affected types of EB, such as EBS and JEB-I; in which adult group's prevalence of anemia was higher than pediatric group. This suggests that chronic blood loss from the skin and mucosae in milder forms of EB may result in anemia later and hence, anemia should be checked for in adults with EBS as well as JEB-I.

In most EB patients, anemia is known to be multifactorial in origin, one of the causes being anemia of chronic disease (Fine & Hintner, 2009). Other factors contributing to anemia include chronic blood, iron, and protein loss from open wounds on the skin, and through erosions present within the intestinal tract (mouth, esophagus, and anal canal), and poor intake and absorption of iron and other nutrients leading to iron deficiency (Van den Akker et al., 2009). Another known cause of anemia in EB patient is from chronic inflammation from persistently open wounds and skin ulcerations leading to repeated skin infections, resulting in a blunted bone marrow response to the elevated levels of erythropoietin (Clark, 2009; Fine & Hintner, 2009; Tefferi, 2004).

Hence, the anemia is an additional co-morbidity of this severe dermatologic disorder (Fine et al., 2008). Therefore, it is important to identify and treat anemia as optimally as possible in EB patients to reduce the morbidity of the patients.

Our study findings are consistent with several published smaller reviews and case-series, which all indicate anemia is prevalent in EB patients [8,10,13,20]. 54% of JEB-GS patients in a small longitudinal retrospective study ($n = 22$) performed in Netherlands were reported to have anemia as one complication, without going into details as to severity [20]. Similarly, prevalence of anemia in this group was significantly high, as 100% of JEB-GS patients in our study were anemic. It may be possible to conclude that the significance of our study's result may be limited due to missing data, mainly from the milder patients; however our study's sample is representative of population. For instance, the general consensus is that patients with JEB-GS do not survive to adulthood. JEB-GS cohorts in Australia ($n = 11$) (Kho et al., 2010) showed a 100% mortality in childhood, with patients not surviving past 13 months.

Hubbard et al. (Hubbard et al., 2011) found that 96% ($n = 52/54$) of pediatric RDEB patients were anemic in a cross-sectional study conducted in a multidisciplinary team study day in London. This study was limited to more severe patients already seeing a dietician and multidisciplinary team. This finding is similarly presented in our study finding as 71.4% of pediatric RDEB patients were found to be anemic; possibly the prevalence in our group was less as it included some milder cases of localized RDEB.

Based on the results of our study and in accordance with the literature on this topic, we conclude that anemia is prevalent among EB patients, and is highly prevalent in patients with severe forms of EB.

Some limitations to our study should be noted; potential sample selection bias may have affected the findings. The study population is not representative of the entire EB population in Australia. This

is due to lack of availability of pathology results for some patients, refusal to be registered in the AEBR and loss of follow up. Second, the prevalence of anemia may have been overestimated in some EB subtypes, such as EBS, as healthy patients may not have been required to take bloods in their lifetime. Whereas, in severe forms of EB such as RDEB, the prevalence of anemia may have been underestimated as RDEB patients are often being treated with blood and iron transfusions, which elevate their hemoglobin. Third, the design of the study was observational and cross-sectional. We were able to examine potential association but were unable to measure causation. Fourth, the data which allow the classification of the causes of anemia such as reticulocyte counts, erythropoietin levels, and iron studies were not measured as the study was retrospective and these values were not available in all patients. Moreover, due to the rare nature of the disease and high mortality in severe forms of EB such as JEB-GS, the limited number of patients may have affected the power of the study.

Overall, such profound anemia certainly contributes to chronic fatigue, reduced energy levels, dyspnea, reduced exercise tolerance, impaired wound healing, and anorexia, thereby decreasing patients' quality of life (Fine & Hintner, 2009; Fridge & Vichinsky, 1998). These patients often require frequent blood transfusions to correct their anemia to a level that reduces clinical symptoms (Fine et al., 2008). Currently, there are no international recommendations or consensus on treatment for these anemic EB patients. As this study included a relatively large number of EB patients given that EB is a rare orphan disease, looking at the degree of anemia; it will form an epidemiological foundation for future studies on this diverse topic of anemia in EB and treatment options.

We also recommend the development of a standardised protocol for the evaluation of anemia in both pediatric and adult EB patients, in particular for severe forms of EB in order to facilitate early intervention if required. We would recommend that each EB patient have screening for anaemia and a baseline of their renal function at diagnosis, since chronic blood loss from the blistering may already show reduced hemoglobin. If reduced, iron studies should be performed. Mild patients with EBS should have their hemoglobin checked every 2 years after puberty, as it appears from this data that a proportion of the milder patients develop anaemia as adults. Severe EB patients should be having their blood screened every 3 to 6 months, as recommended by Martinez (Martinez, 2010). Before iron infusions are given, some patients with Asian or Mediterranean ancestry should be screened for thalassemia trait, as this is relatively common in those populations, and they can develop iron overload from iron rather than whole blood infusions. A descriptive epidemiological study of anemia in EB population in other countries to correlate findings from our study may be helpful for future management of anemia in EB patients.

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