

Inherited epidermolysis bullosa: epidemiology and patient care in Slovenia with a review of the updated classification

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Abstract

Introduction: Inherited epidermolysis bullosa (EB) is a heterogeneous group of rare genetic skin disorders characterized by fragility of the skin and mucous membranes. The prevalence of all types of EB is estimated at approximately 11 per million, based on recent data from the American National Epidermolysis Bullosa Registry.

Methods: A national registry of EB has not yet been established in Slovenia. Because all cases of EB are diagnosed and treated at our department, we have collected data on all known cases of EB in Slovenia.

Results: Based on our data, the prevalence of all EB types in Slovenia is about 20 per million. As of December 2020, our data consist of 29 EB simplex, three junctional EB, 10 dominant dystrophic EB, and four recessive dystrophic EB patients.

Conclusions: The prevalence of all EB types in Slovenia is higher compared to the estimated prevalence in the United States. The multidisciplinary care of EB patients in Slovenia has been developed based on patients' needs, including a wide group of various specialists, and it has been adapted to the resources and treatment options available. This article also reviews the up-to-date classification and diagnostic protocol for EB, and international recommendations for interdisciplinary patient care.

Keywords: inherited epidermolysis bullosa, epidemiology, Slovenia, multidisciplinary treatment, wound care

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Introduction

Hereditary epidermolysis bullosa (EB) is a group of genetically heterogeneous disorders that are characterized by fragility of the skin and mucous membranes, with formation of blisters and wounds in response to minor mechanical trauma (1). Mutations involving at least 20 different genes have been identified so far, leading to conformationally altered or absent proteins of one of the components of the cytoskeleton, cell matrix, or cell-cell adhesion proteins (2, 3).

Based on the level of blister formation, four major types of EB are classified: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler syndrome (KS). Based on phenotypic, immunofluorescence, ultrastructural, and molecular findings, EBS, JEB, and DEB are further subdivided into several subtypes (4).

The extent and severity of skin and mucous membrane lesions and the involvement of other organs vary in different clinical subtypes (5) and in relation to age. Depending on the genetic defect, phenotypes range in a wide spectrum from mild cutaneous fragility caused by subtle molecular defects (such as single amino acid substitutions) to severe involvement of the skin and other organs caused by lack of key adhesion proteins (such as mutations in the genes for laminin 332 or type VII collagen) (1). In several EB subtypes, severe cutaneous and extracutaneous involvement can cause significant morbidity and even premature death (5).

Despite the progress in preclinical investigations with novel molecular treatment approaches and the promising results of some clinical studies, successful treatment is currently not available (6, 7). The management of patients is directed to appropriate skin care, regular follow-up, prevention of complications, early detection of malignant skin tumors, and an interdisciplinary treatment approach.

Epidemiology of epidermolysis bullosa in Slovenia

The prevalence of all types of EB in the United States (National Epidermolysis Bullosa Registry, data collected over 16 years) is estimated at 11.07 per million and the incidence at 19.57 per million live births (8). In this registry, the prevalence of EBS is estimated at 4.6, JEB at 0.4, and dominant DEB (DDEB) and recessive DEB (RDEB) at 1 per million, respectively.

In Slovenia, an official registry of EB has not yet been established. However, because all cases are diagnosed and treated at our department, we do have data on all the known cases of EB in Slovenia. Calculated from our data, the prevalence of all EB types in Slovenia is about 20 per million.

As of December 2020, our national data on EB consist of 29 EBS, three EBJ, 10 DDEB, and four RDEB patients. We are in the process of genetic diagnostic procedures for all our patients with EB. To date we have diagnosed two EBS patients with keratin 14 (KRT 14) gene, one with keratin 5 (KRT 5) gene, and one with kelch-like family member 24 (KLHL24) gene mutation. The patient with KRT5 gene mutation presented as EB with mottled pigmentation, a rare subtype of EBS presenting with nonscarring blistering and reticulated hyperpigmentation (9). The EBS patient with KLHL24 mutation also presented with aplasia cutis congenita on one leg. In all four patients with RDEB, collagen VII mutation was genetically confirmed.

Slovenia, as a small country, has allowed us to define the geographical distribution of families affected by EB. We found that specific subtypes of EBS and DEB tend to cluster together in different regions of the country (Fig. 1).

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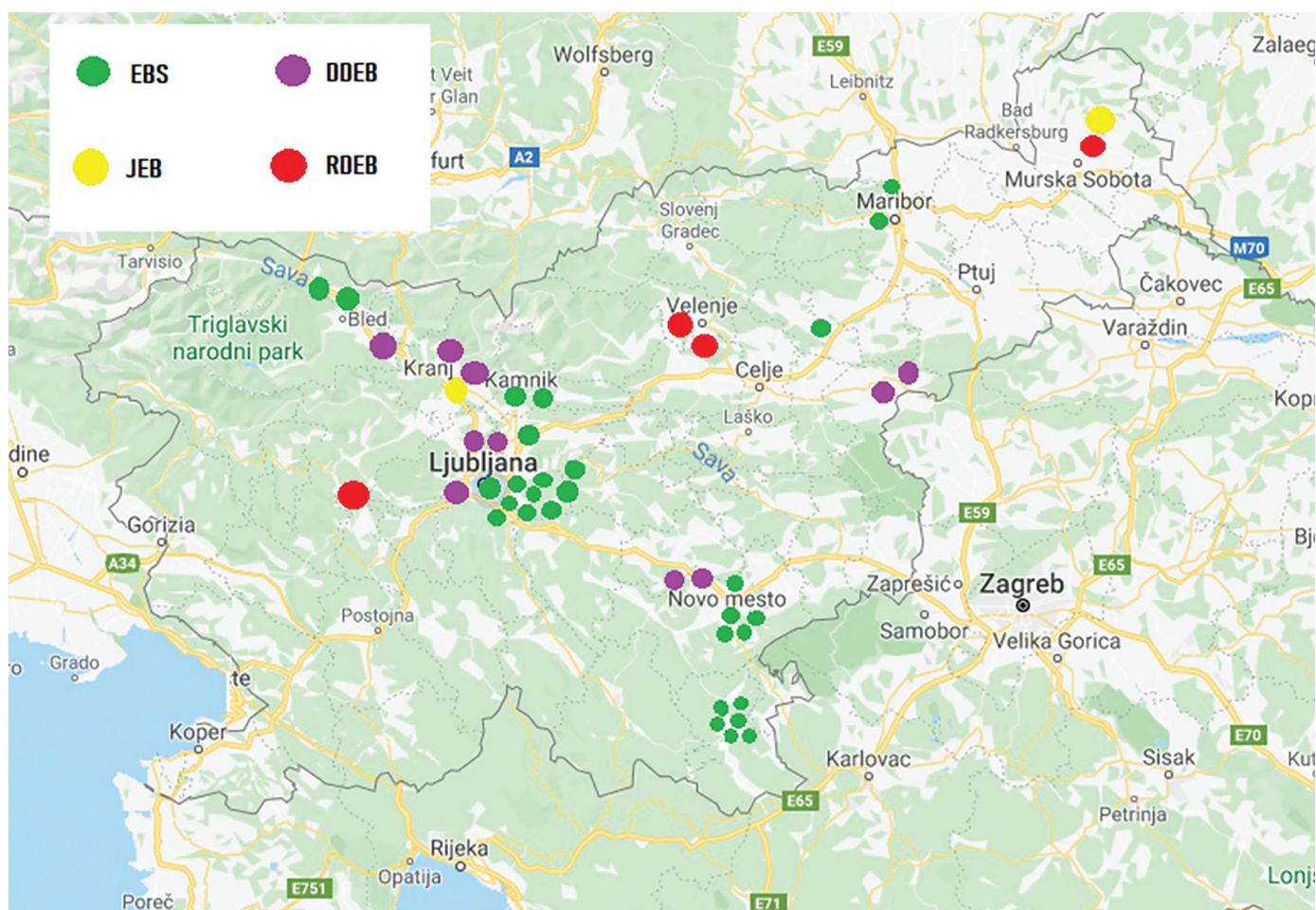


Figure 1 | Geographical clustering of epidermolysis bullosa (EB) families. Green circles represent EB simplex (EBS), yellow junctional EB (JEB), violet dominant dystrophic EB (DDEB), and red recessive dystrophic EB (RDEB).

Updated classification

Mutations in 20 distinct genes have been identified so far, causing the genetic and clinical heterogeneity of EB. Several new genes and clinical phenotypes of EB have been identified in the last decade (1). In April 2019, classification of EB and other skin fragility disorders was revised, based on new molecular and clinical findings (2). In Table 1, four major EB types are presented, with different levels of skin cleavage, modes of inheritance, and targeted proteins involved. EBS, JEB, and DEB are further subclassified according to the clinical severity, inheritance pattern, and molecular features at the genetic and protein levels (1, 4).

Diagnostic procedures

The stepwise approach in the classification of EB starts with determination of the level of skin cleavage, using immunofluorescence antigen mapping and/or transmission electron microscopy (10). Identification of the level of blister formation allows differentiation between EBS, JEB, and DEB.

EB is then further classified based on clinical characteristics, such as distribution (localized or generalized), severity (intermediate or severe), and presence of extracutaneous involvement. The patient's family history may suggest the inheritance pattern (10).

Examination with monoclonal antibodies directed against skin basement membrane zone proteins and epidermal antigens allows further subclassification (1).

After this first step, mutational analysis is recommended, which allows the most precise subclassification and insight into the mode of transmission (4). Schematically, the updated diagnostic procedure is recommended in the "onion skin" subclassification approach: major EB type → phenotype (severity and distribution) → mode of transmission → ultrastructural level of cleavage and associated findings → protein involved → gene involved and mutational type → specific mutation in the patient (4).

Table 1 | Classification of four major epidermolysis bullosa types (2).

Skin cleavage	EB type	Inheritance	Targeted protein(s)
Intraepidermal	EBS	Autosomal dominant	Keratin 5, keratin 14 Plectin Kelch-like member 24
		Autosomal recessive	Keratin 5, keratin 14 Bullous pemphigoid antigen 230 Exophilin-5 Plectin CD151 antigen
Junctional	JEB	Autosomal recessive	Laminin-332 Type XVII collagen Integrin $\alpha 6 \beta 4$ Integrin $\alpha 3$ subunit
Dermal	DEB	Autosomal dominant	Type VII collagen
		Autosomal recessive	Type VII collagen
Mixed	Kindler syndrome	Autosomal recessive	Fermitin family homolog 1 (syn. kindlin-1)

EB = epidermolysis bullosa, EBS = epidermolysis bullosa simplex, JEB = junctional epidermolysis bullosa, DEB = dystrophic epidermolysis bullosa.

Clinical presentation

The clinical cutaneous hallmark of EB is fragile skin with easy inducibility of blisters in response to minor mechanical trauma. Additional clinical findings may include milia, nail dystrophy, scarring alopecia, exuberant granulation tissue (periorificial, axillary vaults, nape, lumbosacral region, and periungual nail folds), localized or confluent palmoplantar keratoderma, and dyspigmentation (postinflammatory hypo- or hyperpigmentation and mottled or reticulate hyperpigmentation). Infrequent cutaneous findings include albopapuloid lesions (skin-colored or hypopigmented papules, usually on the lower trunk), and hypo- or hyperhidrosis (11).

Mucous membranes are often affected in DEB, with oral cavity, esophagus, nasal, and eye involvement (12, 13). The development of the child is delayed, and the onset of puberty is postponed.

The more severe and widespread the blistering on the skin, the more likely is the involvement of other organs (14). The time of onset of extracutaneous complications depends on the EB subtype and is also age-dependent (14).

In adult patients with DEB, various comorbidities and late complications develop. Due to scarring, severe deformations of the hands and feet, nail dystrophy, and pseudosyndactyly develop with flexural contractures of joints. Patients have a higher predisposition for squamous cell carcinoma and basal cell carcinoma (11). Mucous membranes are affected, with painful erosions in the oral cavity, microstomia, and esophagus constriction. Caries and periodontitis are common. Eye involvements include chronic blepharoconjunctivitis, ectropium, corneal scarring, symblepharon, and keratitis, leading to vision problems (12, 13). Muscular atrophy, osteopenia and osteoporosis, and chronic anemia can already be observed in childhood and are more severely manifested in adults. Patients are often severely affected and are invalids, unable to take care of themselves and to perform usual daily activities.

Patient care

The rarity of EB and the phenotypic variability challenge the appropriate care of these patients (5). Although specific guidelines for care of EB patients are lacking, some of the consensus recommendations can help practitioners consider the complex needs of patients in daily practice. In 2012, Pope et al. developed a consensus approach to wound care in four steps (15):

- A. Treat the cause
 - Evaluation of EB type, comorbidities, patient age, nutritional status, and hemoglobin levels can help assess the patient's ability to heal
 - Development of individual goals and a plan of care
- B. Patient-centered concerns
 - Pain and itching
 - Daily living activities
 - Education and support of patient and parents
- C. Local wound care
 - Location and characteristics of wounds
 - Wound cleaning with a low-toxicity solution
 - Wound debridement
 - Assessment of critical colonization or abnormal inflammation or infection
 - Selection of appropriate topical dressings
 - Evaluation of healing rate

- Biopsy for suspicious malignant skin tumors (squamous cell carcinoma)

D. Organizational support

- Support of specialized nurses, interprofessional clinics, and a structured approach to new cases

In 2014, El Hachem et al. published the European multicenter consensus recommendations for skin care in EB (5). These recommendations focus on the patients' age, wound care, management of itching and pain, early diagnosis of squamous cell carcinoma, and a multidisciplinary approach.

Interdisciplinary patient care in Slovenia

It is of utmost importance to ensure regular follow-up of EB patients from neonatal age onward and during the disease course in childhood and adulthood. An early diagnosis, appropriate skin and wound care, and prevention of complications can improve patients' quality of life. This is especially important for patients with DEB and JEB. The care of EB patients requires a coordinated multidisciplinary approach (5). In Slovenia the multidisciplinary treatment of EB patients has been established over the last few decades.

Our interdisciplinary team consists of a team of dermatologists, nurses, and consultant specialists from other medical specialties. The core treatment is provided by a dermatologist and is supplemented with the expertise of a variety of other members of the interdisciplinary team, the selected pediatrician, and home medical services.

Children and adult patients with DEB are the most severely affected and are especially in need of a multidisciplinary treatment approach. Immediately after birth, hospitalization in the neonatal ward is required, with intermittent visits from a pediatric dermatologist. If further intensive care is needed, the patient is admitted to one of the surgical pediatric wards and visited by a consultant dermatologist. Once the general health condition is stable, the infant is transferred to the children's ward at the Department of Dermatovenereology.

The usual diagnostic protocol requires a skin biopsy and diagnosis of EB via histopathology and electron microscopy. Nowadays genetic testing is also performed, allowing precise identification of the subtype and genetic counseling for parents.

Parents are taught about appropriate skin and wound care. Contacts with home medical services and their pediatrician is established. Subsequent follow-up hospitalizations at our department are required in patients with JEB and DEB. Children under age 10 should be hospitalized once or twice a year, and children older than 10 require more frequent hospitalizations (four times per year).

During these follow-ups, appropriate medical specialists are consulted, based on patients' needs. A dermato-oncologist also needs to be part of the team for early detection of malignant skin tumors in chronic wounds (16). We have established good cooperation with pediatricians, specialists in infectious diseases, hematologists, gastroenterologists, plastic surgeons, and thoracic surgeons. Cooperation with otorhinolaryngologists, specialists in dental medicine, ophthalmologists, endocrinologists, nephrologists, neurologists, orthopedists, anesthesiologists, specialists in physical medicine and rehabilitation, psychologists, and nutritionists is also needed for many patients. Adult patients with DEB are followed up regularly at least two times yearly.

Conclusions

EB is a heterogenous group of rare genetic skin fragility diseases. Treatment is still mainly directed at skin care with associated symptoms and prevention of cutaneous and extracutaneous complications, and it requires a multidisciplinary approach.

In Slovenia, the prevalence of all EB types is estimated at 20 per million and is therefore higher compared to the estimated prevalence in the United States. A multidisciplinary approach has been developed based on patients' needs, including a wide group of

different specialists, and it has been adapted to the resources and treatment options available.

Understanding of the molecular pathogenesis of EB has significantly improved in the last decade (17). New diagnostic techniques allow more accurate identification of EB subtypes and recognition of some new phenotypes. New genetic variants and new clinical phenotypes can be expected to emerge in the future. Genetic tests will become crucial in the future, when molecular treatments are expected to become available.

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