JDDG
Journal of the German Society of Dermatology

Minireview

Submitted: 23.4.15
Accepted: 9.6.15
Conflict of interest
None.

DOI: 10.1111/ddg.12774

Hereditary epidermolysis bullosa

Martin Laimer, Christine Prodinger, Johann W. Bauer

Department of Dermatology, Paracelsus Medical University Salzburg, Austria

Summary

The term epidermolysis bullosa (EB) includes a group of rare genodermatoses characterized by mutational impairment of the structural and functional integrity of intraepidermal adhesion and dermoepidermal anchorage. Clinically, these disorders are marked by increased skin fragility as well as characteristic mechanically inducible blisters on the skin and mucous membranes. Extracutaneous manifestations and their complications in other epithelialized organs render EB a multi-system disease associated with significant morbidity and mortality. Cornerstones of a dynamically changing healthcare structure include precise and early diagnosis; coordinated, multidisciplinary, individually adjusted patient care at specialized centers; optimized symptomatic therapies; and access to research-based, potentially curative therapeutic strategies.

Introduction

Epidermolysis bullosa (EB) includes a group of rare, clinically and genetically heterogeneous genodermatoses characterized by moderate to excessive fragility of epithelial tissues as well as formation of blisters or erosions following minimal trauma (mechanobullous dermatoses). With a cumulative prevalence and incidence of 8.2 and 19.6 per 1,000,000 live births, respectively, EB ranks among the *rare* or *orphan diseases*[1, 2].

Etiopathogenesis and clinical manifestation

Until now, mutations have been described in at least 18 genes coding for components of keratin filaments in the cytoskeleton, adhesion contacts, desmosomes, and hemidesmosomes, including anchoring fibrils in the skin and mucous membranes. The molecular aberrations impair the structural and functional integrity of intraepidermal adhesion or dermoepidermal anchoring, and lead to cell and tissue dehiscence [3]. The index genes involved are also partly expressed in other epithelialized (gastrointestinal, respiratory, urogenital tract) or mesenchymal (skeletal muscle) organs. Apart from secondary extracutaneous involvement, this also explains the occurrence of primary extracutaneous manifestations and relevant complications in EB, which may thus develop into a multi-system disease with considerable morbidity and mortality. The cardinal clinical symptom is the moderate to excessive epithelial fragility, resulting in blister formation and corresponding secondary lesions such as erosions, ulcerations, crusts, and (usually atrophic) scars (Figure 1). The latter, especially in dermolytic subtypes, may lead to complications such as strictures, stenoses, synechiae, and pseudosyndactyly. Milia, pigmentary disturbances, microbial superinfection, nail dystrophy, and (scarring or atrophic) alopecia are further features of various EB types. In severe forms, systemic signs include malnutrition and a catabolic metabolic state with growth retardation or failure to thrive, chronic inflammation, infections/sepsis, anemia, and other symptoms corresponding to specific organ involvement (e.g. coprostasis, hydronephrosis, cardiomyopathy). Type (homo- vs. heterozygosity), number (monogenic, digenic inheritance), and location of the mutation(s) within the gene or gene segment, as well

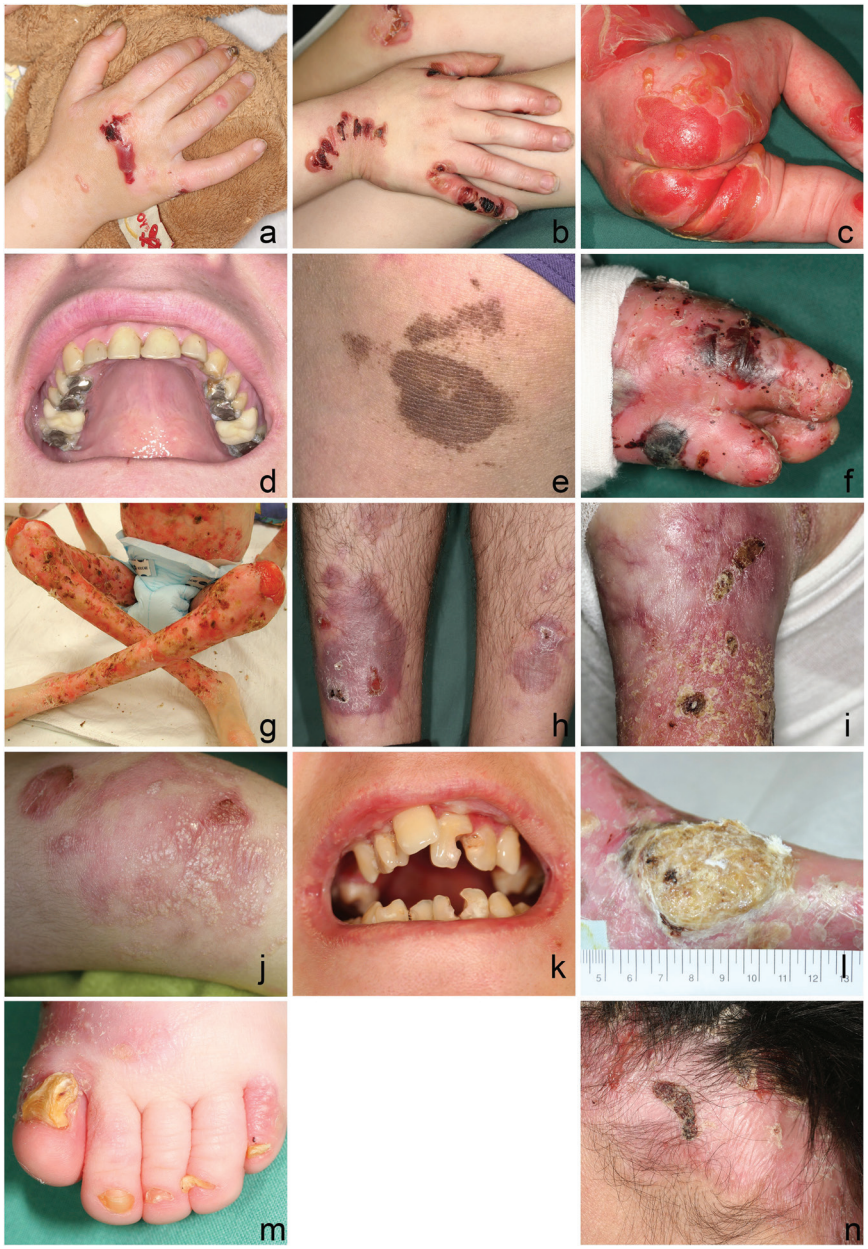

Figure 1 Phenotypic spectrum of epidermolysis bullosa.Localized EBS: blistering and erosions, predominantly on mechanically exposed skin such as the hands (a). Generalized severe EBS (formerly type Dowling-Meara): herpetiform, partly hemorrhagic blisters, erosions, and crusts (b). Generalized severe JEB (formerly type Herlitz): generalized blisters, erosions, and large areas of denudation (c). Generalized intermediate JEB: dental enamel hypoplasia, caries (d). EB nevus: large, asymmetric, bizarrely shaped, and irregularly pigmented lesion with extensions and satellite lesions in an area previously affected by a blister (e). Generalized severe recessive DEB: pseudosyndactyly (epidermal cocooning) with skin atrophy, nail loss, and contractures (f). Generalized severe recessive DEB: dystrophy, growth retardation (g). Generalized dominant DEB: erosions with crusts; atrophic, slightly hyperpigmented scars (h). Generalized severe recessive DEB: poorly healing ulcerations; superinfected crusts, and erosions (i). Generalized severe recessive dystrophic EB: atrophic scarring with milia (keratin-filled cysts) (j). Generalized severe recessive DEB: microstomia, tooth deformities, severe dental caries, and periodontitis (k). Generalized severe recessive DEB: highly aggressive squamous cell carcinoma arising from a large chronic wound (l). Generalized intermediate recessive DEB: onychodystrophy (m). Generalized intermediate recessive DEB: scarring alopecia (n).

as the spectrum of subsequent quantitative (absence, reduction) or qualitative disturbances (gradual loss of function) of protein expression result in considerable genetic heterogeneity with complex genotype-phenotype correlations. Here, apart from the primary structural-functional defect, secondary epigenetic (e.g. altered gene expression of other components of the 'micromilieu', induction of inflammatory cascades) and environmental factors also have an impact on the individual, and therefore highly variable, phenotype [4, 5]. The spectrum of the latter is immensely broad. On the one hand, there may be limited moderate blistering on primarily mechanically exposed predilection sites such as hands and feet, which causes only mild impairment and at times only becomes clinically manifest in late childhood or adolescence. On the other hand, patients may show extensive, generalized, fatal (multiorgan) involvement with (seemingly spontaneous) blistering already present at birth.

Classification

Based on the plane of cleavage, EB is divided into four major types. According to pheno- and genotype as well as inheritance

patterns, these are further classified into various subgroups, some of which contain extremely rare subentities (Table 1).

Epidermolysis bullosa simplex

Usually inherited in an autosomal-dominant fashion, epidermolysis bullosa simplex (EBS) represents the most common EB type (75–85 % of all cases).

Basal EBS

Basal EBS variants are frequently caused by dominant negative missense mutations in the genes coding for keratin 5 or 14 (*KRT5, KRT14*). Depending on location and severity of the mutation, there is partial or complete inhibition of the formation or cross-linkage of keratin filaments in basal keratinocytes, which – upon mechanical stress – leads to destabilization of the cytoskeleton and cytolysis. The more extensive the mutation-specific functional loss of the structural protein, the earlier there is more severe and generalized skin involvement (also beyond mechanically exposed predilection sites).

The most common subtypes are:

- *Localized EBS*: hands, feet; oral mucosa is mildly affected; at times clinical manifestation only in adolescence or adulthood (Figure 1a).
- *Generalized intermediate EBS*: hands, feet, extremities; lesions heal with atrophy and dyspigmentation; manifestation already at birth or in early childhood.
- *Generalized severe EBS*: disseminated, herpetiform lesions on the extremities, neck, trunk (Figure 1b); skin atrophy, oral mucosa is affected; palmoplantar keratosis; nail dystrophy and loss of nails; (telogen) effluvium; postinflammatory hyper-/hypopigmentation; milia. Although already present at birth, the clinical picture frequently improves with increasing age (regulatory compensation by other structural components?). Extracutaneous manifestations (laryngeal stenosis) result in increased mortality.
- Mutations in the *PLEC1* gene coding for the hemidesmosomal protein plectin, expressed in various tissues and also in gastrointestinal epithelium and the sarcolemma as well as the *z-discs* of skeletal muscle cells, cause the autosomal-recessive *EBS with muscle dystrophy* (progressive myasthenia in adolescence and adulthood) or *EBS with pyloric atresia* (through secondary fibrosis and obstruction, polyhydramnios, protein loss enteropathy). Furthermore, plectin mutations have been described in autosomal-dominant EBS type Ogna (predominantly acral blisters, onychogryphosis) [6], in another EBS variant marked by early mortality [7], and in an autosomal-recessive EBS form (with acral, later generalized blistering) without extracutaneous (mucous membrane, cardiac, muscle) involvement [8].

Suprabasal EBS

These very rare, autosomal-recessive EBS types are caused by defects of desmosomal components, adhesion contacts, or proteins regulating terminal epidermal differentiation (Table 1). Due to thin and therefore fragile blister roofs, intact blisters are hardly ever observed, but rather erosions or impaired keratinization with increased desquamation and clinical similarities to ichthyoses and palmoplantar keratoses. Associated with relevant morbidity and at times early mortality, extracutaneous manifestations are common in various subtypes.

Junctional epidermolysis bullosa

In junctional epidermolysis bullosa (JEB), the mode of inheritance is mostly autosomal recessive. Localized and generalized subtypes are usually distinguished.

- *Localized JEB*: hands, feet, elbows, and knees.
- *Generalized severe JEB*: extensive mucocutaneous blisters already present at birth (Figure 1c). Healing with atrophic scars; characterized by excessive formation of granulation tissue (perioral, perinasal, facial, axillary, periungual); onychodystrophy, anonychia; dental enamel defects (mutated structural proteins interfere with dental histomorphogenesis); complicated conjunctival, oral, gastrointestinal, respiratory, and urogenital mucous membrane involvement (Table 2); mortality nearly 100 % within the first years of life (sepsis, pneumonia, laryngotracheal obstruction).
- *Generalized intermediate JEB*: serous-hemorrhagic blisters in areas exposed to friction, trauma, or heat; ulcerations, atrophic scars; poikiloderma; alopecia, nail dystrophy; dental enamel defects, excessive dental caries (Figure 1d); relatively mild extracutaneous manifestations; however, severe laryngotracheal stenoses, esophageal strictures, and urogenital complications are also possible; increased risk for the development of squamous cell carcinoma.

EB nevi (large, asymmetric, often irregularly pigmented, sharply demarcated and bizarrely shaped melanocytic lesions, as well as satellite lesions (Figure 1e)), which typically develop in areas previously affected by blistering, are another characteristic cutaneous sign, which, however, also occurs in all other EB subtypes. These lesions presumably develop on the basis of repetitive epidermal destruction and a 'micromilieu' marked by permanent regeneration with stimulation of (melanocytic) proliferation. Despite their clinically and dermatoscopically suspicious appearance, they usually take

Table 1 Main types and subtypes of epidermolysis bullosa [20].

EB (sub-) type	Inheritance	Mutated gene	Affected protein
Epidermolysis bullosa simplex, EBS (intradermal [epidermolytic] blisters)			
Suprabasal EBS (cytolysis of suprabasal keratinocytes)			
Acral peeling skin syndrome	AR	*TGM5*	Transglutaminase-5
Superficial EBS	AD	?	?
Acantholytic EBS (includes variants formerly termed lethal acantholytic EBS and lethal congenital EBS	AR	*DSP, JUP*	Desmoplakin, plakoglobin
Skin fragility syndromes (very rare variants)			
Desmoplakin deficiency (skin fragility/woolly hair syndrome)	AR	DSP	Desmoplakin
Plakoglobin deficiency	AR	JUP	Plakoglobin
Plakophilin deficiency (skin fragility/ectodermal dysplasia syndrome)	AR	PKP1	Plakophilin 1
Basal EBS (cytolysis of basal keratinocytes)			
Localized EBS (formerly type Weber-Cockayne)	AD	*KRT5, KRT14*	Keratin 5, keratin 14
Generalized severe EBS (formerly type Dowling-Meara, herpetiform EBS)	AD	*KRT5, KRT14*	Keratin 5, keratin 14
Generalized intermediate EBS (formerly EBS, generalized-other; non-Dowling-Meara; EBS, type Koebner)	AD	*KRT5, KRT14, COL17A1*	Keratin 5, keratin 14, type XVII collagen
EBS with mottled pigmentation	AD	*KRT5*	Keratin 5
EBS with migratory circinate erythema	AD	*KRT5*	Keratin 5
Autosomal-recessive EBS K14	AR	*KRT14*	Keratin 14
Trauma-induced skin blistering	AR	*EXPH5*	Exophilin-5
EBS with muscle dystrophy	AR	*PLEC1*	Plectin
EBS with pyloric atresia	AR	*PLEC1, ITGA6, ITGB4*	Plectin, integrin α6, integrin β4
EBS type Ogna	AD	*PLEC1*	Plectin
Autosomal-recessive EBS, BP230 deficiency	AR	*DST*	Bullous pemphigoid antigen 1 (BP230)
Autosomal-recessive EBS, exophilin-5 deficiency	AR	*EXPH5*	Exophilin 5
Junctional epidermolysis bullosa, JEB (junctional [lucidolytic] blisters within the basement membrane zone			
Generalized JEB			
Generalized severe JEB (previously type Herlitz)	AR	*LAMA3, LAMB3, LAMC2*	Laminin α3, β3, γ2 laminin 332 chain
Generalized intermediate JEB (formerly type non-Herlitz; JEB, generalized other; GABEB)	AR	*LAMA3, LAMB3, LAMC2*	Laminin α3, β3, γ2 laminin 332 chain
JEB with pyloric atresia	AR	*ITGA6, ITGB4*	Integrin α6, integrin β4
JEB, late onset (formerly progressive)	AR	*COL17A1*	Type XVII collagen
Localized JEB,	AR	*COL17A1*	Type XVII collagen

Table 1 Continuation.

EB (sub-) type	Inheritance	Mutated gene	Affected protein
JEB with respiratory and renal involvement (previously EB congenital nephrotic syndrome-interstitial lung disease)	AR	*ITGA3*	Integrin A3
Localized JEB			
Localized JEB (previously localized JEB, non-Herlitz)	AD	*COL17A1*	Type XVII collagen
JEB inversa	AR	*LAMA3*, *LAMB3*, *LAMC2*	Laminin α3, β3, γ2-chains of laminin 332
JEB, laryngo-onycho-cutaneous syndromes	AR	*LAMA3A*	Laminin α3a chain of laminin 332
Dystrophic epidermolysis bullosa, DEB (dermolytic blistering below the lamina densa)			
Dominant DEB			
Generalized dominant DEB (formerly type Pasini, Cockayne-Touraine)	AD	*COL7A1*	Type VII collagen
Acral dominant DEB	AD, AR	*COL7A1*	Type VII collagen
Pretibial dominant DEB	AD, AR	*COL7A1*	Type VII collagen
Dominant DEB pruriginosa	AD, AR	*COL7A1*	Type VII collagen
Dominant DEB, nails only	AD	*COL7A1*	Type VII collagen
Dominant DEB, bullous dermolysis of the newborn	AD, AR	*COL7A1*	Type VII collagen
Recessive DEB			
Generalized severe DEB (formerly type Hallopeau-Siemens)	AR	*COL7A1*	Type VII collagen
Generalized intermediate DEB (formerly type non-Hallopeau-Siemens; RDEB, generalized other)	AR	*COL7A1*	Type VII collagen
Recessive DEB inversa	AR	*COL7A1*	Type VII collagen
Localized recessive DEB (formerly acral recessive DEB)	AR	*COL7A1*	Type VII collagen
Pretibial recessive DEB	AD, AR	*COL7A1*	Type VII collagen
Recessive DEB pruriginosa	AR	*COL7A1*	Type VII collagen
Recessive DEB (centripetal variant)	AR	*COL7A1*	Type VII collagen
Recessive DEB, bullous dermolysis of the newborn	AR	*COL7A1*	Type VII collagen
Kindler syndrome (intraepidermal, junctional or sub-lamina-densa blisters	AR	FERMT1 (KIND1)	Fermitin family homolog 1 protein (kindlin-1)

a benign course and sometimes resolve spontaneously [9]. Only recently, however, has the malignant transformation of a nevus in EBS been described for the first time [10] – clinical, dermatoscopic, and, if necessary, bioptic follow-up is therefore always indicated.

Through complete disintegration of hemidesmosomes, homozygous nonsense or frameshift mutations of the laminin 332 gene give rise to generalized severe JEB (formerly type Herlitz). Combined heterozygous missense mutations or in-frame deletions of laminin 332 but also α6β4 integrin genes are associated with residual protein expression and clinically milder variants. The latter are also caused by molecular defects of type XVII collagen, only expressed in hemidesmosomes, which limits clinical symptoms in affected individuals to skin, hair, and mucous membranes [3, 11, 12].

Revertant mosaicism is found in approximately 30 % of patients with generalized intermediate JEB. This phenomenon is based on spontaneous postzygotic somatic molecular events (intragenic crossover, second mutation, mitotic gene

Table 2 Extracutaneous manifestations and complications of epidermolysis bullosa [21].

Extracutaneous manifestations		Occurrence	Treatment strategy (examples)
Eyes	Corneal/conjunctival erosions, corneal scars; photophobia; symblepharon, pannus, ectropion formation; blepharitis; obstruction of the nasolacrimal duct; blindness	Generalized EBS, JEB; generalized, severe recessive DEB	Moisturizing eye drops, surgery (pannus removal, symblepharolysis, ectropion reconstruction, corneal transplant, lens implantation)
Oral cavity and teeth	Peri- and intraoral blisters, strictures, ankyloglossia, microstomia; infections (Candida); dental enamel hypoplasia, tooth dysplasia, excessive caries, premature tooth loss, tooth misalignment	JEB, DEB, Kindler syndrome	Consistent dental hygiene, comprehensive dental treatment (including extraction and replacement of teeth)
Gastrointestinal tract	Strictures, pseudodiverticles, gastroesophageal reflux, Barrett esophagus; obstructions; perforation, dysphagia, hiatal hernia, impaired peristalsis, atony, malabsorption, chronic constipation, megacolon, painful defecation	JEB, DEB	Repeated dilation of the esophagus, dietary counseling, stool regulation, gastrostomy
Respiratory tract	Mucous membrane edema and granulation; blisters, formation of erosions and scars; hoarseness, dysphonia, inspiratory stridor, laryngeal stenosis, dyspnea, pneumonia, acute airway obstruction	JEB	Tracheotomy, administration of corticosteroids or antibiotics
Urogenital tract	Dysuria, hematuria, hypospadias, epispadias, stenoses, obstruction; dysfunctional vesicoureteral reflux, urinary bladder hypertrophy, hydronephrosis, renal hypertension, renal insufficiency (glomerulonephritis following cutaneous streptococci infection, IgA nephritis, secondary amyloidosis); urosepsis	JEB, DEB	Regular follow-up, catheterization, cystoscopy, urethral dilation, meatotomy, ureterosigmoidostomy
Metabolism and general symptoms	Nutrient and protein loss in denuded areas, catabolic metabolic state with increased caloric requirement; impaired ingestion due to oral and gastrointestinal involvement; symptoms caused by nutrient deficiency; failure to thrive and grow; impaired wound healing; secondary hypogonadism, immunodeficiency, recurrent infections, chronic anemia (transcutaneous blood, protein, iron loss; decreased absorption; inflammation-related suppression of erythropoiesis); cardiomegaly (deficiency of trace elements, transfusion-related iron overload, viral myocarditis); osteopenia, osteoporosis (renal insufficiency, calcium deficiency, immobility)	All severe forms	Regular, daily (multiple) intake of small amounts of pureed or liquid food rich in calories, supportive substitution treatment, drip feeding, gastrostomy

conversion, reverse mutation), which locally correct the causal germ line mutation [13, 14]. Clinically, these forms often take a milder course, and typically show distinct skin areas without any or with significantly reduced blistering.

In generalized severe JEB, there is also more frequently *uniparental disomy*, i.e. both copies of a chromosome pair are inherited from just one parent. Thus, two copies of a recessive mutation may be transmitted by a heterozygous parent. Among others, somatic recombination or complementation of gametes are being discussed as molecular mechanisms for this phenomenon, which has to be taken into account for accurate genetic counseling [15].

Dystrophic epidermolysis bullosa (DEB)

Skin fragility, blisters, scars, milia, and nail changes are cardinal symptoms of most autosomal-dominant or recessive forms of dystrophic epidermolysis bullosa (DEB) (Figure 1f-n).

More than 600 usually family-specific (private) mutations in the *COL7A1* gene, coding for type VII collagen, have been described, which lead to variable structural and functional impairment of anchoring fibrils [16]. Here, too, biallelic nonsense mutations with complete protein loss are associated with generalized severe disease forms, characterized by extreme skin fragility, excessive scarring, joint contractures, pseudosyndactyly (Figure 1f), mutilations, severe (also extracutaneous) mucous membrane involvement and complications such as malnutrition, dystrophy, and growth retardation (Figure 1g). Accordingly, heterozygous aberrations with residual gene or protein expression cause milder clinical manifestations.

Three main variants are distinguished.

- *Generalized dominant DEB* (Figure 1h): Predominantly skin involvement (grouped hypopigmented papules, referred to as "albopapuloid" lesions, are typical).
- *Generalized severe recessive DEB* (gsRDEB) (Figure 1i, j): Chronic granulating wounds on knees, elbows, hands, feet, neck, shoulders, and across the spine; oral, esophageal, anal, ocular mucous membrane involvement; dystrophic teeth, microstomia and decreased tongue mobility induced by scarring lead to excessive caries and malnutrition (Figure 1k). Presumably based on chronically recurrent, inflammatory tissue traumatization and permanent reactive regeneration/hyperproliferation, *squamous cell carcinomas* occur disproportionately frequently (90 % cumulative risk at the age of 55); they develop early (already starting in the second decade of life); they are highly aggressive (early metastatic spread); and they are barely susceptible to treatment (Figure 1l). They represent the most common cause of death in these patients. Here, the tumor risk correlates with the severity, extent, and chronicity of skin involvement [17].
- *Generalized intermediate recessive DEB*: in comparison, less pronounced symptoms; mutilating deformations are generally missing; oral and dental manifestations, nail and hair changes (figure 1m, n), increased risk for squamous cell carcinoma.

Kindler syndrome

Inherited in an autosomal-recessive manner, Kindler syndrome (KS) is initially characterized by acral blisters, which predominantly occur in childhood. Later, photosensitivity and progressive poikiloderma with extensive skin atrophy and emphasis on UV-exposed areas come to the fore.

Gingivitis and periodontitis are common; esophageal and urogenital stenoses as well as gastrointestinal symptoms are possible. In addition, patients have an increased risk for the development of nonmelanocytic skin tumors [18].

Loss-of-function mutations in *FERMT1*, which codes for kindlin-1, a component of adhesion contacts in basal keratinoytes, periodontal tissue, and colon, causally impair anchorage of the actin cytoskeleton with the extracellular matrix as well as epithelial mesenchymal signal transduction [18].

Diagnostic workup of hereditary epidermolysis

The diagnosis is established using a diagnostic algorithm in order to rule out other genetic, autoimmune, infectious, traumatic, hematologic, metabolic, or drug-induced causes for cutaneous blistering. Focusing on candidate genes for molecular diagnostics is thus also possible [19]. The algorithm includes:

- Family history and clinical manifestations (note: in the early stages of life, cardinal clinical symptoms often occur only inconsistently or transiently),
- Testing for microbial contamination (e.g. swabs, serology, PCR),
- Histology: perilesional; important with respect to the evaluation of differential diagnoses,
- Immunofluorescence: perilesional; allows for identification of the plane of cleavage as well as determination of semiquantitative protein expression in an induced (e.g. rubbing with a pencil eraser until erythema occurs), fresh (< 12 hours, in order to avoid proteolytic degradation of index antigens and interfering reepithelialization) blister on skin not exposed to sunlight (e.g. medial aspect of the upper arm) (note: no topical anesthetic such as EMLA under occlusion (induction of artificial epidermal blisters is possible),

- Transmission electron microscopy (plane of cleavage, morphological aberrations),
- Mutation analysis (genome/exome/cluster or panel/exone sequencing).

Taking the results thus obtained into consideration, the recently revised classification of EB defines the various EB (sub-) types in an individually more or less detailed or extensive manner (*onion-skin approach*) [20]. The various levels of diagnosis include:

- *Main EB type*, according to the plane of cleavage (determined by immunofluorescence mapping and electron microscopy),
- C*linical phenotype*, with information on the relative severity of skin and mucous membrane involvement (mild, intermediate, severe) as well as the pattern of distribution (localized, generalized). If necessary, diagnostically useful or characteristic clinical symptoms are also mentioned (e.g. hypergranulation, *mottled pigmentation*; pseudosyndactyly),
- *Mode of inheritance*,
- *Specific morphological findings*, detected by electron microscopy or immunofluorescence mapping (e.g. "lucidolytic", decreased dystrophic anchoring fibrils etc.),
- The affected *protein* (according to immunofluorescence),
- The affected *gene*, the type of mutation, or the specific mutation.

Therapeutic principles

Current treatment is largely symptomatic. The mainstay of patient management is trauma prophylaxis (protective clothing and bandages, laxatives, physical therapy) as well as supportive treatments (wound dressings, antisepsis, antibiosis, analgesia, adequate supply of nutrients, transfusions, osteoporosis prophylaxis, surgical interventions, physical therapy) (Table 2) [21]. Patient care is optimized through multidisciplinary coordination in reference centers or clusters, as well as transnational reference networks [22].

In light of the morbidity of numerous EB subtypes, curative therapeutic approaches, albeit currently still largely experimental, are needed. Current molecular procedures include, gene, protein, and cell therapy; the cultivation and transplantation of revertant keratinocytes; and the use of induced pluripotent stem cells [23].

Gene therapy strategies include gene locus and cDNA transfer as well as ex vivo and in vivo gene transfer. Functional correction of gene expression by means of *spliceosome-mediated RNA trans-splicing* (SMaRT) has been shown for recessive DEB, EBS with muscle dystrophy, and autosomal-dominant EBS [24].

Cell therapy approaches include the injection of allogeneic fibroblasts into the dermis of RDEB patients, which resulted in the production of normal collagen and improved wound healing [25]. Alternatively, pluripotent stem cells from allogeneic bone marrow transplants may be reprogrammed to keratinocytes and migrate into the skin of patients with RDEB [26]. Following experiments in a mouse model that showed donor cells along the basement membrane zone and type VII collagen production, transplanted RDEB patients also exhibited improved wound healing with decreased blistering. The high mortality associated with immunomyeloablative chemotherapy, however, currently still limits the broader use of this method.

Protein therapies with local (intradermal) or systemic (intravenous) administration of recombinant type VII collagen in RDEB (animal tests) have also shown a temporary (a few weeks) clinical response with reexpression of type VII collagen along the basement membrane zone (BMZ) and restitution of anchoring fibrils and dermoepidermal adhesion [27].

Another therapeutic approach is to selectively antagonize the biochemical processes caused by the genetic defect. Keratinocytes of patients with generalized severe EBS, for example, release large amounts of IL-1β, which promotes the overexpression of mutated *KRT14*. Diacerein, an IL-1β inhibitor, inhibits the expression of *KRT14* in vitro and in preliminary clinical studies with topical application, resulting in an improvement of cutaneous symptoms [28].

Progress in clinical treatment, diagnostic procedures, as well as therapeutic approaches improve patient management in EB – a group of disorders particularly dependent on optimized therapeutic strategies.

Correspondence to

Assoc. Prof. Dr. Martin Laimer
Department of Dermatology
Paracelsus Medical University Salzburg
Muellner Hauptstrasse 48

5020 Salzburg
Austria

E-mail: m.laimer@salk.at

References

1 Fine JD. Inherited epidermolysis bullosa. Orphanet J Rare Dis 2010; 5: 12.
2 Fine JD. Epidemiology of inherited epidermolysis bullosa. In: Fine JD, Hintner H (Eds): Life with Epidermolysis Bullosa (EB): Etiology, diagnosis, multidisciplinary care and therapy, Wien, New York: Springer, 2008: 24–9.
3 Fine JD, Eady RA, Bauer EA et al. The classification of inherited epidermolysis bullosa (EB): Report of the Third International Consensus Meeting on Diagnosis and Classification of EB. J Am Acad Dermatol 2008; 58: 931.

 | JDDG | 1610-0379/2015/1311

4 Di Salvio M, Piccinni E, Di Zenzo G et al. Diverse TGF-beta signalling activation in fibroblasts from phenotypically discordant monozygotic twins with recessive dystrophic epidermolysis bullosa. J Invest Dermatol 2012; 132: S90.

5 Küttner V, Mack C, Rigbolt KT et al. Global remodelling of cellular microenvironment due to loss of collagen VII. Mol Syst Biol 2013; 9: 657.

6 Koss-Harnes D, Høyheim B, Anton-Lamprecht I et al. A site-specific plectin mutation causes dominant epidermolysis bullosa simplex Ogna: two identical de novo mutations. J Invest Dermatol 2002; 118(1): 87–93.

7 Charlesworth A, Gagnoux-Palacios L, Bonduelle M et al. Identification of a lethal form of epidermolysis bullosa simplex associated with a homozygous genetic mutation in plectin. J Invest Dermatol 2003; 121(6): 1 344–8.

8 Gostyńska KB, Nijenhuis M, Lemmink H et al. Mutation in exon 1a of PLEC, leading to disruption of plectin isoform 1a, causes autosomal-recessive skin-only epidermolysis bullosa simplex. Hum Mol Genet 2015; 24(11): 3 155–62.

9 Lanschuetzer CM, Laimer M, Nischler E, Hintner H. Epidermolysis bullosa nevi. Dermatol Clin 2010; 28: 179–83.

10 Hocker TL, Fox MC, Kozlow JH et al. Malignant melanoma arising in the setting of epidermolysis bullosa simplex: an important distinction from epidermolysis bullosa nevus. JAMA Dermatol 2013; 149(10): 1 195–8.

11 Varki R, Sadowski S, Pfendner E, Uitto J. Epidermolysis bullosa. I. Molecular genetics of the junctional and hemidesmosomal variants. J Med Genet 2006; 43: 641.

12 Kiritsi D, Kern JS, Schumann H et al. Molecular mechanisms of phenotypic variability in junctional epidermolysis bullosa. J Med Genet 2011; 48: 450.

13 Jonkman MF, Scheffer H, Stulp R et al. Revertant mosaicism in epidermolysis bullosa caused by mitotic gene conversion. Cell 1997; 88: 543.

14 Pasmooij AM, Pas HH, Deviaene FC et al. Multiple correcting COL17A1 mutations in patients with revertant mosaicism of epidermolysis bullosa. Am J Hum Genet 2005; 77: 727.

15 Castori M, Floriddia G, Pisaneschi E et al. Complete maternal isodisomy causing reduction to homozygosity for a novel LAMB3 mutation in Herlitz junctional epidermolysis bullosa. J Dermatol Sci 2008; 51: 58.

16 Bruckner-Tuderman L. Dystrophic epidermolysis bullosa: pathogenesis and clinical features. Dermatol Clin 2010; 28: 107–14.

17 Fine JD, Mellerio JE. Extracutaneous manifestations and complications of inherited epidermolysis bullosa: part II. Other organs. J Am Acad Dermatol 2009; 61: 387.

18 Has C, Castiglia D, del Rio M et al. Kindler syndrome: extension of FERMT1 mutational spectrum and natural history. Hum Mutat 2011; 32: 1 204.

19 Nischler E, Klausegger A, Hüttner C et al. Diagnostic pitfalls in newborns and babies with blisters and erosions. Dermatol Res Pract 2009; 2009: 320403.

20 Fine JD, Bruckner-Tuderman L, Eady RA et al. Inherited epidermolysis bullosa: updated recommendations on diagnosis and classification. J Am Acad Dermatol 2014; 70: 1 103–26

21 Fine JD, Hintner H (Eds). Life with Epidermolysis Bullosa (EB): Etiology, diagnosis, multidisciplinary care and therapy, Springer, Wien, New York, 2008.

22 Laimer M, Prodinger C, Ahlgrimm-Siess V et al. Österreichische und europäische Initiativen auf dem Gebiet der seltenen Krankheiten – Perspektiven für eine "Randgruppe" von vielen Millionen Patienten. J Dtsch Dermatol Ges 2015; 13: 261–4.

23 Murrell DF (Ed). Epidermolysis bullosa: Part II – Diagnosis and Management. Dermatol Clin 2010; 28(2).

24 Bauer JW, Murauer EM, Wally V, Koller U. RNA trans-splicing for genodermatoses. Methods Mol Biol 2013; 961: 441–55.

25 Yan WF, Murrell DF. Fibroblast-based cell therapy strategy for recessive dystrophic epidermolysis bullosa. Dermatol Clin 2010; 28: 367–70.

26 Kiuru M, Itoh M, Cairo MS, Christiano AM. Bone marrow stem cell therapy for recessive dystrophic epidermolysis bullosa. Dermatol Clin 2010; 28: 371–82.

27 Woodley DT, Wang X, Amir M et al. Intravenously injected recombinant human type VII collagen homes to skin wounds and restores skin integrity of dystrophic epidermolysis bullosa. J Invest Dermatol 2013; 133: 1910.

28 Wally V, Kitzmueller S, Lagler F et al. Topical diacerein for epidermolysis bullosa: a randomized controlled pilot study. Orphanet J Rare Dis 2013; 8: 69.