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REVIEW PAPER OPEN ACCESS

Overview of Heriditary Epidermolysis Bullosa

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Abstract

Epidermolysis is a monogenic disease, constitute several genodermatosis due to metamorphosis in numerous structural and functional cohesion in skin. Epidermolysis Bullosa (EB) is considered a multi-system disorder associated with significant outer-layer manifestation with severe complications in other epithilized organ possibly provided. After 19th century several proceeding in classification has been switched. This review will recapitulate the most recent classification with epidemiological and clinical features; recent effective gene therapy treatment with positive potential focused on EB recently identified forms in autosomal recessive manner one of Junctional Epidermolysis Bullosa (JEB) and other two in EBS (DST-e, EXPH5 and ITGA3).Level of skin cleavage is identified by IFM Immunoflourescence mapping and Electron microscopy EM. Requires far-reaching patient treatment management on advance level because EB addicts a long-term cure and medicines which is an expensive and conviction to stress on financial ground, much more research need to be developed and used in clinical practices. This review provides practical knowledge of disease including classification and phenotypes.

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Introduction

Epidermolysis bullosa (EB) got the first public attention by a documentary named "The Boy Whose Skin Fell Off" which was broad casted, with centered attention boy named Johnny Kennedy, who was diagnosed with EB (Channel 4, 2004). EB diagnosed children's are usually named as "Butterfly children's" (Isles, 2005) "Cotton wool babies" due to skin fragility by birth (Hinde, 2006) or "crystal skin children" in some exceptional cases (Gobert, 2002). Basically any sort of mutation or defect found in keratin or collagen gene results EB (Prockop and Alakokko, 2005). Etymology of skin consists of different layers of skin, epidermis which forms the outer layer while dermis forms the inner layer, etymologically EB is breakdown and blistering of skin.

Inherited epidermal bullosa (EB) is a serious genetic disorder distinguished by regular blister formation which shows structural weakness within the skin and specific tissues. EB can be resulted in more than 25 phenotypically or genotypic dissimilar symptoms which shows involuntary fragility of exterior tissues. (Fine and Hintner, 2009). Clinical features mostly notable in EB are reoccurrence of blisters on the skin which is more than enough for minor grip of EB. Rareness is shown in all major categories of EB. Clinically phenotype shows a vast range of roasting or blistering majorly on hands and feet, sometimes in rare cases oral blistering is also been observed with internal organs injuries.

Epidermolysis bullosa (EB) is a rare skin disorder with a long-term uncommon responsibility of the skin to blister after small involuntary trauma. Due to a genetic irregularity, the various skin layers do not attach adequately, so that the skin exteriorly can break down definitely after being hit, rubbed, and lacerate or during the activity of swallowing (Fine, 1999).

There is appreciable clinical, inherited and molecular diversity both within and between the three major EB types (Uitto and Richard, 2004). Due to complexity, the mode of inheritance of these disorders can be either autosomal dominant or autosomal recessive, with the recessive forms tending to be more clinically severe (Keefe, 2008).

classification

Blisters formation on the basis of ultra structural level formation on the epidermal layer, genotypic features are more than enough for the categorization of EB type recognition of classes and subclasses (Fine *et al.*, 2008). According to general classification of EB there are 4 major categories of genetically inherited EB: EB Simplex (EBS) involves epidermal separation in basal keratinocyte,Junctional EB (JEB) which lies between keratinocyte and basal lamina, Dystrophic EB (DEB) which shows defect in separation beneath the basal lamina., and Kindler Syndrome . Kindler syndrome another type has been added to the general classification of EB. (Sawamura *et al.*, 2003;Lai Cheong *et al.*, 2009).All of these major types of EB are different from each other not only genotypically but also on phenotypic level, more seriously on the ultra-structural distraction. (Fine *et al.,* 2008).

Epidermal bullosa simplex

The first known and most common type of epidermal bullosa is the EB simplex, which was previously called Weber-Cockayne disease. Almost 75-85% cases among the EB are simplex subtype in autosomal dominant form. Phenotypic findings includes palm and sole blistering, lesion clusters, nail dystrophy is uncommon among few cases, while these symptoms lead to high risk for carcinomic factors arising in a few rare cases at mid-adulthood (Fine and Hintner, 2009). Complete obstruction of the cross-linkage of keratin filaments in basal keratinocyte, due to mechanical stress and cytoskeleton destabilization. EBS is further classified into fewer subtypes. Most severe form of EBS is Dowling-Meara type, including skin blistering with oral mucosa. Blistering usually present from birth, improves with age. Targeted genes involved in EB simplex are PK P1(MIM604536), DSP(MIM125647), KRT5(MIM148040), KRT14(MIM148066), PLEC14(MIM601282), ITA6, ITAGB4(MIM147557) and DST genes(MIM113810) (Fassihi *et al.*, 2005),

including proteins Plakephilin-1, Desmoplakin, Keratin-5, Keratin-14, Plectin, Alpha6, B4 integrin and Dystonin proteins which codes for respective genes.

Junctional epidermal bullosa

On the basis of dermal level of lamina Lucida in skin division has an association with junctional form of EB. Further it is divided into different sub-types like the Herlitz subtype, the non-Herlitz subtype and subtype pyloric Artesia. JEB with type Herlitz are caused due to the non-functional expression of laminin-332(MIM150292), which is mostly commonly observed at fatal stage, where severe tissue erosions and tissue crumbling around eye, tracheolaryngeal, kidney system, gastrointestinal, genitourinary tract are found (Fine *et al.*, 2008). BPAG2 gene is found mutated in the non-Herlitz JEB, which is responsible for polypeptide BP180 encoding. Till date mostly reported inherited types of JEB are in an autosomal recessive form. In lamina Lucida special blisters are formed, this character is observed in JEB autosomal recessive form. The most serious and highly severe subtype is the JEB-Herlitz. At the time of birth it shows a small blister which further spread to other body parts with the passage of age up to 2 years. Symptoms arise within few months from the time of birth majorly blisters on oral passage, mouth opening areas, decrease extension of tongue, other organs involvement like esophagus, eye, genitourinary tract (Fine *et al.*, 2004).18% of risk is involved for squamous cell carcinomas in JEB-H patients at the age of 25 (Fine *et al.*, 2009). JEB-H patient may show post inflammatory hypo-pigmentation leading to severe anematic condition association with growth retardation. In some rare cases skin blistering, esophagus erosions and vaginal erosion are reported in some cases (Fine *et al.*, 2008). Overall LAMA3(MIM150292), LAMC2(MIM150292), LAMC3(MIM614115), COL17A1(MIM113811), ITGA6(MIM147556) and ITGB(MIM147557) are found to bring in mutation (Fassihi *et al.*, 2005).

Dystrophic epidermal bullosa

Gene COL7A1(MIM120120) is responsible for dystrophic epidermal bullosa which encode for type VII collagen. On chromosome no. 3p21, COL7A1 gene encodes type VII collagen. Where below the basement membrane in top dermis, gives dermal-epidermal adhesion is located in anchoring fibrils, which is its major component of type VII collagen (Shinkuma *et al.*, 2011). Tissue separation in the sub lamina densa in involved in DEB. Both autosomal dominant as well as recessive forms are involved in DEB. A milder phenotyping are present in dominant for of DEB as compared to recessive one. A gene which encodes for collagenous domain in type VII collagen have a mutation in any single allele in which glycine substitution related to DEB. Type VII collagen(MIM 150292) is directly affected by the amino acid glycine if substituted in any case (Aberdam *et al.*, 1994). According to recent sub-classification of dystrophic epidermal bullosa, it has been classified into two major groups one is Dominant Dystrophic Epidermal Bullosa (DDEB) and the other one is the recessive dystrophic epidermal bullosa (RDEB).

Recessive dystrophic EB (RDEB)

Generalized RDEB have confirmed several phenotypic characters observed on individuals like by-birth blistering, corneal erosions, knowledgeable findings of growth retardation, thrive failure, palm and sole deformalities, nutritional deficiency and extracutaneous complications has dominant importance found at early childhood and effects dominantly the individual daily life routine throughout life (Fine *et al.*, 2004). RDEB patients show symptoms as early as at the age of 2 years and as growing leads to at age 20 years (Fine *et al.*, 2005).

Kindler syndrome

Few years back a new subtype has been included to the EB named kindler syndrome. It is found in autosomal recessive form, which is due to any type of specific mutations in FERMTI (KIND1) (MIM607900) which normally encodes for fermitin family homologue 1(kindling-1) (Fine *et al.*, 2008). The type of mutation so found in kindler syndrome is the loss of mutation basically in FERMT1. This is observed in fixing of basal keratinocyte, pridontal

tissue, and colon, casually impair anchoring of the actin cytoskeleton with the extracellular matrix with signal transduction of epithelial mesenchymal (Has *et al.*, 2011). Focal adhesion destruction is cause for kindler syndrome. Symptoms are characterized by a severe blistering, inflammation of mucosa, poikliloderma, photosensitivity, keratoderma, bone abnormalities, gastrointestinal problems, and esophagitis and in some cases involvement of mental retardation (Lia- Cheong *et al.*, 2010).

Phenotypes

Wound healing

Multiple factors are involved in the wound healing action including foreigner, bacteria, nutritional factors abnormality and tissue anoxia. These factors can be controlled by optimization of wound healing, on the basis of laminin-5 deficiency Herlitz JEB patients shows slow healing (Fine and Mellerio., 2009).

Infections

Large area permits microbial activities. Bacterial growth increases due to moisture content and accumulation of lymph. Poor nutritional profile decelerates resistance to infections. In early childhood has a higher death risk due to excess susceptibility of developing sepsis (Fine and Mellerio, 2009). Area to be covered with a best quality self-adhesive dressing (Mellerio *et al.,* 2007).

Eyes

In JEB and RDEB shows large frequency of blisters or erosions recurring, if seriously not treated, causes progressive visual impairment, scarring Blindness, nasolacrimal duct obstruction, erosion of cornea, ectropion formation and blepharitis observed in severe recessive DEB, JEB and Generalized EBS (Fine *et al.*, 2006).

Dental manifestations

Mostly RDEB and JEB are severely affecting oral mucosa tissues leads to tooth loss, while RDEB develops microstomia and ankyloglossia (Feijoo *et al.,* 2011).

Ears, nose and throat

Some cases have shown evidence against stenosis of the vocal cords, which causes death. Mostly found at first year of life (Fine *et al.*, 2006).

Genitourinary tract

Urethra is affected by formation of recurring vesicles; obstructive processes end up with hydronephrosis at ureterovesical junction and urethers. Most common complications in RDEB include hydronephrosis, streptococcal glomerulonephritis, mesangial IgA disease and amyloidosis (Fine *et al.*, 2009). JEB and DEB patients are observed with hypertrophy urinary bladder, hydronephrosis, renal hypertension, vesicoureteral reflux dysfunction, hematuria and renal insufficiency and IgA nephritis.

Musculoskeletal system

In the first year of life contracture of palm and sole develops along with osteopenia and osteoporoses are most common in RDEB. Epidermolysis bullosa simplexes (EBS) commonly are affected with muscular dystrophy (Fine *et al.*, 2005).

Gastrointestinal tract

Major portions or areas of GI tract develop swallowing of intestine other than gallbladder, pancreas and liver. Mal-absorptive syndrome may be due to denudation of the small bowel mucosa (Fine *et al.*, 2009). Other phenotypes observed in JEB and DEB is chronic constipation, severe painful defecation, esophagus obstruction, hernia and impaired peristalsis.

Cardiomyopathies

Dilated Cardiomyopathies and renal failure associated within few patients, exceptional in patients with RDEB-HS. Causes due to micronutrient deficiency, iron-loss and viral myocarditis (Fine *et al.*, 2009).

Skin tumors

Chronic lesions are found at various sites with occurrence of squamous cell carcinoma (SSC). Basal cell carcinoma (BCC) is developed in EBS-DM.

Tumorigenesis with high risk because of repeated injuries. 80-90% patients reported confirmed SSC development. Recurrence of blisters or erosions results in skin ulceration (Ortiz-Urda *et al.,* 2005).

Metabolism and general symptoms

All severe forms of Epidermolysis bullosa (EB) have disturbance in metabolism with general symptoms, like in high calories required for catabolic metabolism, nutrient deficiency involves oral and gastrointestinal involvement, poor or slow wound healing, severe or chronic anemia, osteopenia due to low calcium level and immobility which can further led by osteoporosis, in denuded areas protein and nutritional loss (Fine and Hintner, 2008).

Table 1. Modified table including clinical and genetic heterogeneity of EB.

Major types of EB	Targeted Genes	Targeted proteins	Gene OMIM NO.	Symptoms	References
EB Simplex (EBS)	PKP1	Plakephilin-1	604536	Blisters inside mouth and throat.	(Arbiser *et al.*,2004;Fine *et al* 2008;Lanschutzer *et al* .,2009)
	DSP	Desmoplakin	125647	Blisters on hand and feet	
	KRT5	Keratin-5(k5)	148040	Scarred skin	
	KRT14	Keratin14(k14)	148066	Blisters starts at birth	
	PLEC14	Plectin	601282	Scalp blistering	
	ITA6, ITAGB4	Alpha6, B4integrin	147557		
	DST	Dystonin	113810		
Junctional EB (JEB)	LAMA3, LAMB3,	Laminin-332	150292 150310	Nail dystrophy	(Groves *et al* .,2010;Intong and Murrel 2012; Lanschutzer *et al* .,2009)
	LAMAC2	Laminin-332	150292	Hypo pigmentation or depigmentation	
	LAMAC3, LAMB3,	Type VII collagen	150292 150310		
	LAMC2 COL17A1	Alpha 6B4 integrin	150292	Severe anemia	
	ITGA6, ITGB		147557		
Dystrophic EB (DEB)	COL7A1	Type VII collagen	120120	Skin fragility, skin erosion Digestive tract blistering,	(Arbiser *et al* .,2004; Intong and Murrel 2012; Lanschutzer *et al* .,2009)
	COL7A1	Type VII collagen		Slow growth, Chronic malnutrition,	
	FERMT1(KIND1)	Kindlin-1	607900	Bumpy patches, Joint deformities, Hair loss	

Epidemiology and clinical description

The clinical description of EB with general description shows blister inducibility, skin fragility; nail dystrophy, scarring and pustules. Further with intense distracted cutaneous study include no hairs or decreased hair count, albopapuloid lesions which are associated with hypo-pigmented papules found on inferior stem (Fine *et al.*, 2008). It is not necessary that all of the above mentioned phenotype will be involved in a single patient, but some of them are involved at neonates or infants. In some cases tissue granulation may be developed even in few months after birth or may be carried out throughout life (Fine *et al.*, 2008). In most rare cases of EB patient in their childhood excited tissue granulation has been found in generalized JEB (Fine and Hintner, 2009).

Analyses on the basis of sensitivity and specificity it was observed that on the cutaneous level the tissue granulation is irrepressible, giving importance to characteristic attributive risk factors associated with depending on too heavily entirely on the existence or absence of EB-related skin findings (Fine *et al*., 1999). Differentiation among the basic types of EB, JEB and RDEB patient has more fragility in skin, mostly skin fragility is observed in hot weather or warm environment, which may lead to worst conditions. Epithelium surface potentially may get injured in EB (Fine and Mellerio, 2009). Complication related to mastocytoma is age-dependent. In severe EB patients the major organs like heart and kidneys may also get injured in muscular dystrophic level (Fine *et al*., 2008).

Latest clinical methods and techniques have been discovered and applied which added a new life to this field. EB identification is confirmed by a number of latest techniques like transmission EM (Electron microscopy), IFM (Immunoflourescence mapping) and analysis of mutation (Intong and Murrel, 2010).

IFM is influence by firm-blister by taking the specimens in appropriate media. Manufactured blisters can get resulted indictable diagnosis. Pathogenic diagnostic samples contain blood, skin, and fresh blisters. Level of skin cleavage is identified by IFM and EM. Non-reliable diagnosis for EB, in a routine is Light microscopy (Eady *et al*., 2010). Transmission EM has a plus point of recognition of micro splits and subtle changes in the outer-layer junction in light forms of EB with normal IFM (Fine *et al*., 2008;Eady *et al*., 2010). Unfortunately, any individual cure with Epidermolysis bullosa is still symbolic with modern wound care and treatment implementation on complications associated to this specific disease (Chiaverini *et al* .,2017).

Conclusion and future perspectives

Epidermal bullosa the idea was formed by German dermatologist Heinrich Koebner in 1886. A genetically transmitted disorder characterized by dermal blistering with monogenic basis, mode of inheritance may be autosomal dominant or autosomal recessive. Anemias, nutritional deficiency, Cardiomyopathies, cell carcinoma are most serious problems associated with EB patients, which lead to difficulty in life. Up till now no such an effective treatment or therapy has been introduced which could be helpful for EB patient. Effective drug therapy is also not yet introduced for healing wounds. On the reality ground, at applied research level, access to the genomic transformation is the important but before that a major cure methods for wound healing should be given a descriptive attention much more because an EB patient suffers a lot on daily life basis due to its skin blistering, fragility, lesions, skin structure instability, Blistering or epithelial disadhesion in EB patient is not improved.

In some exceptional cases gene therapy made an effective contribution but still EB is an orphan disorder. IF assembly need more specific understanding the mechanism at living cell, somehow protein replacement and gene modification is under large research experimental stage. Bone marrow stem cells can give a positive and effective development in this disorder treatment. A broad range of complications is associated with EB patients. Targeted therapy will be more effective at molecular level, advanced studies are needed. An improvement of the clinical situation can lead to a significant change in patient's management quality of life.

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