Recent Advances in Hereditary Epidermolysis Bullosa; a Review of Literature

Essay

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Abstract

Epidermolysis bullosa (EB) is a group of inherited bullous disorders characterized by blister formation in response to mechanical trauma, with varying degrees of severity. The dermal-epidermal junction of the skin is a vital area of attachment. Any defects in this junction would lead to fragility of the skin. EB is traditionally classified into three major categories: EB simplex, junctional EB, and dystrophic EB. In addition, a new category termed hemidesmosomal EB is described. There are different classification schemes for EB. The different forms of EB have been linked to mutations in no less than 10 genes encoding the major basement membrane zone proteins. EB can be diagnosed both postnatally and prenatally with the recent advances in molecular diagnosis. Current treatment of EB revolves around supportive care and prevention of complications. Potential future therapies for EB include protein and gene therapies.

Key words: epidermolysis bullosa - dermal-epidermal junction - mutations - molecular diagnosis - gene therapy - protein therapy.

Summary

Inherited epidermolysis bullosa (EB) is a heterogeneous group of genodermatoses, characterized by fragility and blistering of the skin and/or mucosa following mild mechanical trauma, often associated with extracutaneous manifestations. The clinical picture comprises severe subtypes with probable lethal outcome early in life as well as milder subtypes with minimal symptoms confined to nail or teeth abnormalities. EB is classified into 3 major categories: 1) EB simplex (EBS; intraepidermal skin separation), 2) junctional EB (JEB; skin separation in lamina lucida or central BMZ), and 3) dystrophic EB (DEB; sublamina densa BMZ separation). A new category termed hemidesmosomal epidermolysis bullosa (HDEB) is proposed, with blistering at the hemidesmosomal level in the most superior aspect of the BMZ.

The dermal-epidermal junction is a vital area of attachment between the dermis and the epidermis. It is composed of components with unique abilities to interact and bind to one another, forming a cell attachment matrix. The dermal-epidermal junction is composed of: basal cell membrane including hemidesmosomes formed of, the inner plaque, the outer plaque and the sub-basal dense plate, lamina lucida, lamina densa and sublamina densa. Molecular components of the dermal-epidermal junction represent a number of collagenous and non-collagenous macromolecules; collagen IV, collagen VII, plectin, BPAg-1, BPAg-2, α6β4 integrin, laminin-5, laminin-6, nidogen and perlecan. Defects in any of these components or their interactions can lead to skin fragility.

Epidermolysis bullosa has variable skin manifestations, extracutaneous findings and different underlying mutational defects. Hence, multiple classification schemes were revised. Traditionally, EB was classified on morphological basis, then classification based on mode of inheritance, later classification based on various subtypes and their common manifestations. Advances in molecular etiology resulted in a new molecular genetic classification.

EBS is characterized by intraepidermal blistering with mild internal involvement and lesions heal without scarring. It is mainly dominantly inherited, but recessively inherited cases have been reported. The common variants of EBS include: Weber-Cockayne, generalized Koebner and Dowling-Meara types. The less common variants include: EBS Ogna, EBS with mottled pigmentation, EBS with muscular dystrophy, lethal autosomal recessive EBS, EBS superficialis and Kallin's syndrome with mutations in the genes encoding K5 and K14. Mutations in the COL7A1 gene or the ITGB4 gene can be responsible of the Weber-Cockayne disorder. Plectin mutation causes EBS with muscular dystrophy and EBS Ogna.

JEB is a collection of diseases characterized by intralamina-lucida blistering. The major subtypes of this disorder include: Herlitz (gravis), non-Herlitz (mitis) and generalized atrophic benign EB

(GABEB) subtype. Absent or reduced laminin-5 in the skin and other organs is responsible for this disorder. Mutations in genes coding for laminin-5 subunits (α3, β3 and γ2), collagen type XVII (BP180), α6 integrin, and β4 integrin, are responsible for JEB.

DEB is a group of diseases characterized by sublamina densa blistering and is caused by defects of anchoring fibrils. Blisters heal followed by dystrophic scarring and milia formation. It can be both recessively and dominantly inherited. Autosomal recessive forms are more severe than the dominant forms and the most severe subtype is the Hallopeau-Siemens disorder. Non-Hallopeau-Siemens subtype is a less severe form of RDEB. Autosomal dominant forms include: Cockayne-Touraine, Pasini, Bart's syndrome, pretibial DEB, EB pruriginosa and transient bullous dermolysis of the newborn. All cases of DEB have been associated with mutations of the gene coding for type VII collagen (COL7A1). In addition to mutations in related genes, e.g. P53 and P16 tumor suppressor genes in RDEB-associated squamous cell carcinoma, and L-arginine metabolism associated genes in RDEB (Hallopeau-Siemens).

EBHD is a recently identified variant of EB; it is characterized by blistering at the basal cell/ lamina lucida interface. The two major subtypes of this variant are GABEB and EBHD with pyloric atresia, the other subtypes are EBHD with muscular dystrophy and the Ogna type of EB. Genetic mutations of this disorder involve: type XVII collagen (COL17A1), ITGA6, ITGB4, and plectin genes.

Diagnosis of EB begins with careful history and clinical examination followed by skin biopsies to determine the level of blistering. Electron microscopy is the main diagnostic method to detect specific structural defects. Immunofluorescent microscopy provides additional information and detects important clues to the underlying molecular defects. DNA mutation analysis is to be performed after immunofluorescent microscopy for EB patient and family members for mutation screening. EB-specific monoclonal antibodies confirm diagnosis

that results from either electron or immunofluorescent microscopy. It is very important to detect the precise nature of the underlying mutations in all the forms of EB to improve molecular diagnosis, genetic counseling and prenatal diagnosis. Simple, easy and noninvasive prenatal diagnostic methods during early stages of pregnancy are required. In conclusion, recent advances in molecular biology are not only changing the classification schemes of EB, but also are expected to influence the diagnostic techniques. Current therapy focuses on supportive care, prevention of complications, therapeutic trials for systemic treatment and careful follow up for the development of squamous cell carcinoma in patients with RDEB. Potential future therapies include protein and gene therapies. Although these therapies are currently unavailable, model systems using these approaches promise a realistic goal of significant advancement in the development of future therapies for EB.