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Epidermolysis Bullosa Simplex

Jason F. Okulicz, MD; Nadia I. Kihiczak, MD; Camila K. Janniger, MD

Blistering is a common occurrence generally caused by moderate or repetitive trauma to the skin. Blistering due to minor trauma is less common and may be associated with a group of heterogeneous genetic diseases called epidermolysis bullosa (EB). The level of vesiculation within the skin defines 3 major subtypes of EB: EB simplex (EBS), dystrophic EB, and junctional EB. We will review the simple type—EBS.

Epidermolysis bullosa simplex (EBS) affects approximately 23,000 people in the United States.¹ Blistering in patients with EBS is seen most commonly at birth or in early infancy. Activities such as playing sports or walking to school may be significantly impaired in children with this disease. The severity and presentation of EBS depend on the type of underlying defect.

EBS is a hereditary skin disorder characterized by lysis of basal keratinocytes, leading to the formation of intraepidermal blisters.² Terminal differentiation otherwise is normal, mainly because the suprabasal layers are not disrupted.³ The mode of transmission is usually autosomal dominant, although autosomal-recessive inheritance has been noted in rare instances. EBS is caused by mutations in the genes encoding keratins 5 and 14 and plectin.²

The 3 major subtypes of EBS include: herpetiformis or Dowling-Meara EBS (EBS-DM), localized or Weber-Cockayne EBS (EBS-WC), and Köbner EBS (EBS-K).⁴ Vesicles and bullae, commonly present in each variant, typically heal without scarring. These vesicles and bullae usually form secondary to minor trauma, friction, sweating, or increased body temperature. Clinical findings in patients with EBS vary depending on the subtype.

Dowling-Meara EBS

EBS-DM is the most severe form of EBS. Extreme blistering of the skin and mucous membranes often occurs in the neonatal period. The disease may be

fatal if the child cannot survive this early stage, usually because of sepsis.⁵ The blistering pattern in EBS-DM is herpetiform with marginal spreading. Central healing of the lesions is associated with light-brown pigmentations. Involvement of the oral cavity is common. Other features may include nail dystrophy, milia formation, and progressive palmoplantar hyperkeratosis.² In contrast to other forms of EBS, electron microscopy shows the circumscribed clumping of keratin intermediate filaments in basal epidermal keratinocytes.²

In general, the nature of the mutation, its position in the protein, and its effect on the formation of keratin filaments determines the clinical severity of EBS-DM. The most common mutations involving the EBS-DM phenotype are found at the end portions of the α -helical rod domains of keratins 5 and 14. These ends are highly conserved initiation and termination motifs, which are critical for filament formation. Rare mutations also have been observed in plectin, an intermediate filament-associated protein located in hemidesmosomes of basal keratinocytes.^{2,6} Plectin deficiency in EBS patients has been associated with late onset muscular dystrophy. Muscle involvement has been reported to occur as early as 2 years of age and as late as the fourth decade of life.⁶

Weber-Cockayne EBS

EBS-WC is the mildest and most common form of EBS. Blistering usually begins between infancy and early childhood, although initial appearance of lesions during adolescence has been observed in rare cases. Blistering primarily is restricted to the hands and feet (Figure), and oral involvement is uncommon.⁷ The condition is often at its worst during the summer months. EBS-WC mutations, compared to other variants, occur outside the α -helical rod domains. The mutations are located within the L12 linker region of keratins 5 and 14 and within the H1 histone domain of keratin 5.²

Köbner EBS

Köbner⁷ originally described this form of EBS in 1886. EBS-K is associated with milder blistering

From Dermatology and Pediatrics, New Jersey Medical School, Newark.

Reprints: Camila K. Janniger, MD, Dermatology, New Jersey Medical School, 185 S Orange Ave, Newark, NJ 07103-2714.



A child with Weber-Cockayne form of epidermolysis bullosa simplex with blisters and bullae on the plantar aspect of the foot.

compared to EBS-DM. Unlike the acral distribution seen in EBS-WC, blisters in EBS-K are widespread. The mutations are clustered internally within the rod domains, most often in the 1B or 2B segments of keratin 14.² This differs from the peripheral mutations seen in EBS-DM.

Diagnosis

The evaluation of any patient suspected to have EBS should begin with a thorough history and physical examination. A typical history includes spontaneous blister formation in areas of frequent trauma (most notably the hands and feet) from birth or early infancy. A provisional diagnosis can be supported by examination of perilesional skin histopathology revealing intraepithelial tissue separation. All EBS variants show blister formation within the subnuclear area of the basal cell cytoplasm, midway between the hemidesmosomes and the nucleus.⁹ Further analysis of tissue samples should be performed using transmission electron microscopy, which can verify EBS by showing the epidermolytic ultrastructural level of skin cleavage. Electron microscopy also can suggest EBS-DM by demonstrating the characteristic feature of clumped tonofilaments in basal keratinocytes. Additional studies may be performed on nonfixed cryopreserved skin using monoclonal antibodies to keratins 5 and 14 and plectin.¹⁰

Mapping of the family pedigree is important for accurate genetic counseling of family members and may be useful as an aid in determining the pattern of inheritance. Although autosomal-dominant

transmission is observed in most patients with EBS, autosomal-recessive transmission also should be considered. When autosomal-recessive transmission is suspected, inquiries regarding clinical findings in family members and the possibility of consanguinity should be made. Determining the mode of transmission can be difficult because of incomplete penetrance and spontaneous mutations.¹⁰

For the past 2 decades, prenatal diagnosis of EBS has been possible through the use of ultrastructural and immunohistochemical staining of fetal skin biopsy specimens. This invasive technique cannot be performed until about 16 to 18 weeks gestation and has a small risk of fetal mortality. However, the gold standard is the more recent development of molecular biological testing. Unlike previous methods, molecular biological testing can determine a diagnosis at about 10 to 12 weeks gestation using amniotic or chorionic villi fluid samples.¹⁰

Treatment

Traditionally, treatment of EBS has been both supportive and preventive. Common strategies include wound management, nutritional support, and infection control. Saline compresses, topical steroids, and topical antibiotics frequently are used to promote healing and prevent secondary infection of blisters. Patients should be encouraged to maintain a cool environment, wear loose-fitting shoes, and avoid trauma if possible. Patients with EBS also can seek genetic counseling.

A recent study¹¹ has suggested that the use of oral tetracycline may be beneficial for patients with EBS.

Although initially given for acne, oral tetracycline was noted to dramatically reduce blister counts and mechanical skin fragility. The response was dose dependent, with a maximal benefit observed at 1500 mg/d. Although a long-standing benefit was observed, the disease activity recurred as the dosage was reduced.^{1,11}

Tetracycline is inexpensive and has few adverse effects. However, future studies are needed to further assess its value as a treatment for EBS.

As a result of advances in the localization of mutations in various EBS variants, gene or protein replacement may become available in the future. Because keratinocytes can be cultured from a skin biopsy, it may be possible to remove the mutated gene from these cultured cells and graft the repaired cells back into the patient. Because the defective keratinocytes are prone to cytolysis, the normal keratinocytes have a competitive advantage and offer the possibility of populating the skin outside the graft. If this holds true, severe cases of EBS may be amenable to gene therapy.^{3,12}

The National Epidermolysis Bullosa Registry (NEBR) collects information about individuals with various forms of EB and correlates the clinical information with genetic analysis to provide people with the best current information on their condition. The Dystrophic Epidermolysis Bullosa Research Association of America, Inc. (DeBRA) is an organization dedicated to helping patients with EB and their families. Further information can be obtained from the DeBRA Web site at www.debra.org.

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