Epidermolysis bullosa hereditaria simplex. Case report.

N. I. Kihiczak, A. J. Papadopoulos, R. A. Schwartz and C. K. Janniger

SUMMARY

Blistering is a common childhood phenomenon. There is a group of heterogeneous, genetic mechanobullous diseases termed epidermolysis bullosa (EB) whose hallmark is blistering due to minor trauma or pressure. Some patients with EB may be limited in common extracurricular activities such as playing tennis or hiking, while others may be asymptomatic with occasional blistering. The level of vesiculation within the skin defines three major subtypes of EB: EB simplex, dystrophic EB and junctional EB. We describe a patient and review the simple type of epidermolysis bullosa (EBS), which has an incidence of approximately 10-30 cases per million. The incidence of EBS is most probably higher than the stated figure, due to underreporting of mild cases. The severity of EBS depends upon the type of underlying defect.

Introduction

Skin blistering is a relatively frequent manifestation in dermatological disorders of childhood. Blister formation may be observed in infectious diseases such as impetigo or primary varicella, in certain acquired immunological conditions such as linear IgA dermatosis or dermatitis herpetiformis Duhring and in hereditary diseases such as incontinentia pigmenti Bloch-Sulzberger and hereditary bullous epidermolysis (EBs).

EBs are subdivided into three groups according to their pathogenetic mechanisms. *Dystrophic epidermolysis bullosa (DEB)* includes seriously disabling conditions characterized by subepidermal blister formation. Blisters commonly heal with scarring and milia formation. The pathogenesis of DEB has been attributed to varying degrees of faulty Type VII collagen, which results in deficient anchoring fibrils of the basement membrane zone. There are four major forms of DEB that make up the majority of cases. Rare variants, which usually produce severe disease, also exist. The two autosomal dominant DEBs are the Cockayne-Touraine variant and the Pasini variant. The two autosomal recessive forms of DEB are localized recessive DEB (RDEB) and generalized RDEB. RDEB is transmitted recessively and inlcudes a variable spectrum of clinical severity. The Hallopeau-Siemens variant, or HS-RDEB, is notable due to its severely deforming course. The disease begins

KEY WORDS

blistering disorder, epidermolysis bullosa, simplex, hereditary, child

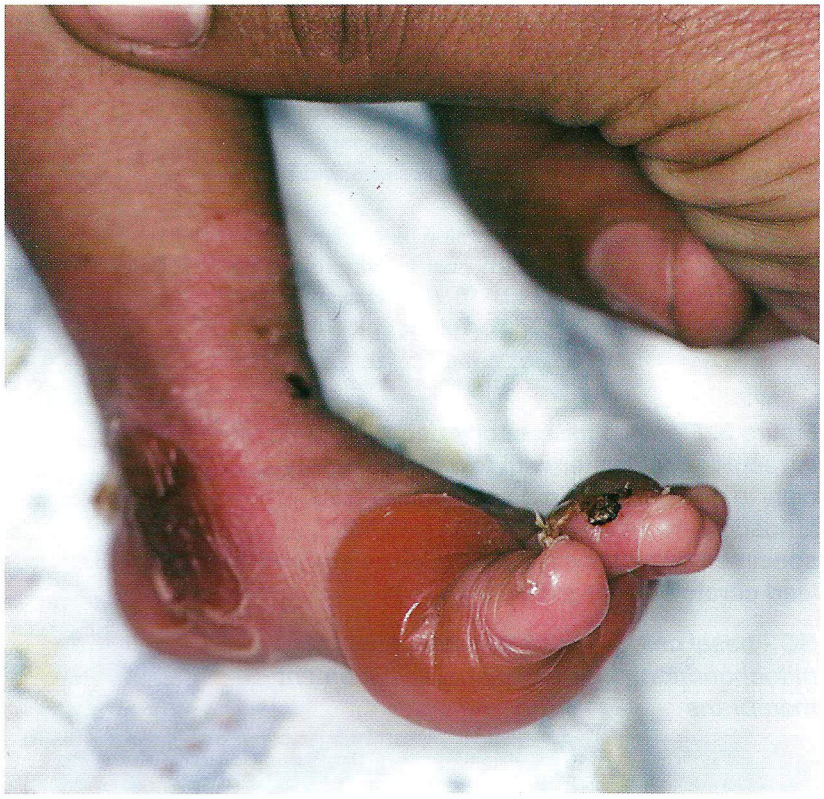
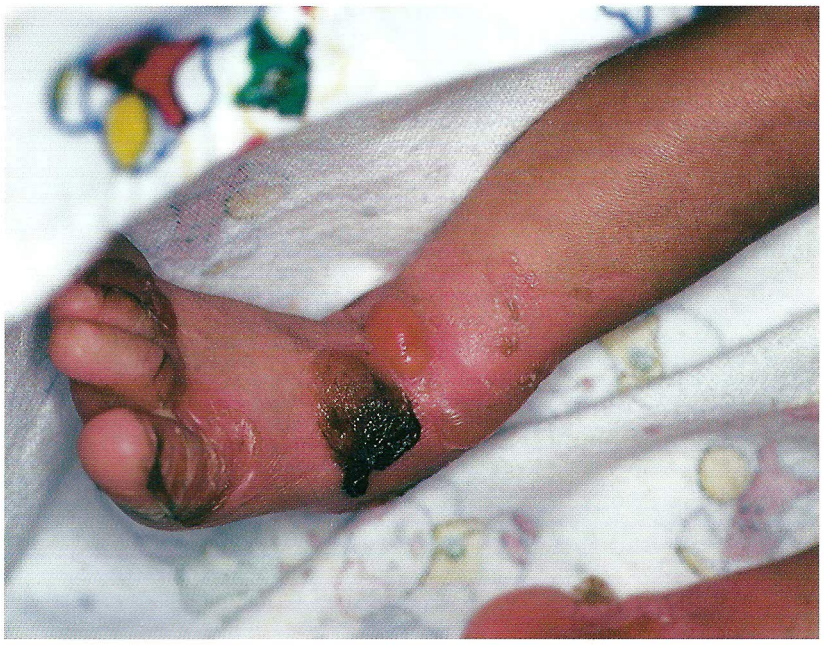


Figure 1. An 18-month-old child with epidermolysis bullosa simplex (EBS), autosomal recessive type, with bullae on the distal tarsal aspect of the foot and a healing, open blister on the medial malleolus of the left foot.

Figure 2. Child in Figure 1 with bullae and blisters at different stages of healing on the dorsal aspect of the right foot.



at birth with generalized blistering, and severe scarring is the rule. Nails and teeth are also affected. These patients must be monitored for the formation of squamous cell carcinomas in areas of chronic erosions, which is a common occurrence in the second or third decade of patients affected with the Hallopeau-Siemens variant.

Junctional EB (JEB), which appears at birth, is histologically characterized by blister formation within the lamina lucida of the basement membrane zone. JEB is recessively inherited with a wide clinical spectrum. One important variant, termed Herlitz disease, is the most lethal variant of all the hereditary EBs; mortality may be as high as 40% in the first year of life. A generalized blistering is evident at birth, and the development of periorificial involvement is quite characteristic. Nail, tooth and scalp involvement is common. Respiratory, gastrointestinal and urological epithelia are also affected in severe disease. JEB mitis and generalized atrophic benign EB (GABEB) are milder forms of JEB that also appear at birth. Survival past infancy is the rule.

Another subtype of EB is characterized by intraepidermal blister formation, most commonly appearing in early infancy. This group of disorders is termed *epidermolysis bullosa simplex, or EBS.* Many variants of EBS exist; the three most common variants are inherited in an autosomally dominant fashion. All subtypes are characterized by vesicle/bullae formation secondary to friction; minor trauma or sweating combined with an increased body temperature. As a rule, healing of vesicles and bullae occurs without scarring. The most common variant is EBS Weber-Cockayne (EBS-WC), or localized EBS. This is the mildest form of EBS and is limited to the palms and soles; the form may appear in early adolescence. The EBS-Koebner variant, or generalized EBS, appears at birth or in early infancy. The most common clinical presentation is acral involvement; healing occurs without scarring. EBS Dowling-Meara, or herpetiform EBS, appears at birth as a generalized blistering disorder. Oral involvement is common in this variant. We describe the case of a child whom we believe has a rare, recessive variant of EBS.

Case report

An 18-month-old white girl was evaluated for recurrent blister formation, mostly limited to acral areas. Figures 1 and 2. The parents stated that the blisters would develop into mild ulcerations, and then heal without scarring. The patient had no significant past medical history. There was no family history of blistering disorders, psoriasis or atopy. The child's parents were related as second cousins. The child had been given antibacterial ointments for denuded vesicles/bullae. A biopsy specimen was never done.

On physical examination, a 1x3 cm crusted erosion was evident on her right dorsal foot. The erosions had been large blisters, which were deroofed. Smaller erosions and a few small vesicles were noted on the fingers, bilaterally, and on her left elbow. Oral vesicles were not noted. Nails and teeth appeared normal. A relatively recent vesicle was biopsied from the patient's left elbow; the sample was sent for routine histological and electron microscopy (EM) examination. Mupirocin, an antimicrobial ointment, was provided for topical application on erosions. Avoidance of mechanical trauma or excessive heat was also stressed.

The child returned three months later, with healing of most of the previous lesions and residual post-inflammatory hyperpigmentation. Some crusted erosions were noted on the dorsum of the hands and the fingers, which the parents stated were relatively new blisters that had denuded. Milia formation was also noted in these areas. Similar crusted erosions were also observed in the popliteal fossa, bilaterally, and on the dorsum of both feet.

The patient returned on two more occasions. Healing of bullae/vesicles without scarring was noted on the dorsum of the hands/feet, fingers, left elbow and bilateral popliteal fossa. One new bulla was noted on the patient's left great toe.

A biopsy specimen of a vesicle from the left elbow revealed a separation in the basal layer of the epidermis causing a bullous process. Electron microscopy confirmed the diagnosis of epidermolysis bullosa simplex (EBS) revealed by intraepidermal, midbasal cell separation. Figure 3. Hemidesmosome and other BMZ structures were normal, essentially ruling out DEB and JEB. Ultrastructural examination did not reveal clumping of tonofilaments in basal keratinocytes, a characteristic finding of herpetiform EBS (EBS Dowling-Meara variant).

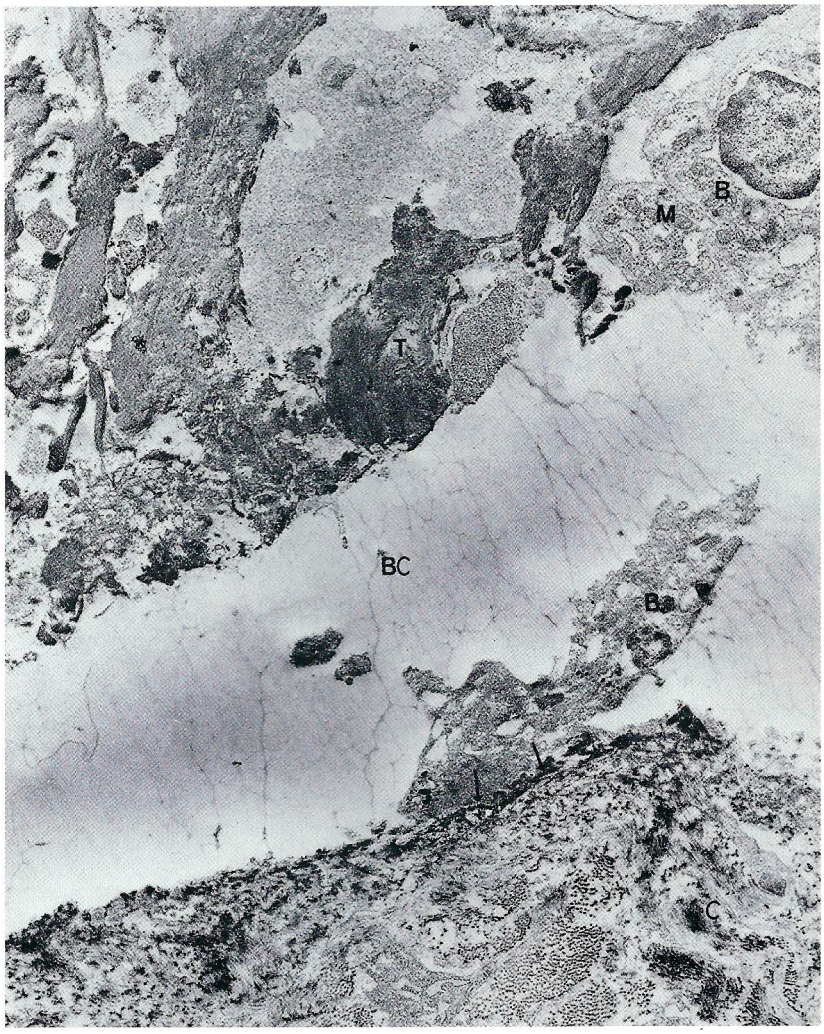
Discussion

EBS is a hereditary, noninflammatory cutaneous disorder that typically is transmitted as an autosomal dominant trait, commonly first seen at birth or in early infancy. Epidermolysis bullosa (EBS) has an incidence of approximately 10-30 cases per million (1-3). Several subtypes of EBS have been identified. The most common variants include *generalized,* or *Koebner, EBS (EBS-K), localized,* or *Weber-Cockayne, EBS (EBS-WC),* and *herpetiformis,* or *Dowling-Meara, EBS (EBS-DM)* (4,5). Each of these variants shares the common feature of autosomal dominant inheritance and mechanically fragile skin. Many more variants exist, with the majority being inherited as autosomal dominant traits. Rarer forms included autosomal recessive variants (6,7). The patient with EBS of any subtype typically has vesicles or bullae secondary to minor trauma, sweating, friction, or increased temperature (Fig. 1, Fig. 2). The expression of EBS ranges from patients being asymptomatic, to minor acral blistering, to widespread, life-threatening erosions of the skin and mucous membranes with dental and nail deformities. Typically, the vesicles and bullae of EBS heal without scarring.

Ultrastructural examination of skin biopsy specimens of a patient with suspected EBS enables differentiation of the different subtypes of EBS (8,9). This examination commonly reveals the separation of the epidermis from

Figure 3. Electron microscopy demonstrating an intraepidermal blister with few inflammatory cells in an 18-month-old patient with EBS, autosomal recessive type. (The original specimen was stained with uranylacetate and lead citrate and magnified 5 x 10^3.)

BC - basal cell, B - parts of a basal cell, M - mitochondrion, ↓↓ - remenants of basement membrane



the dermis due to the fragility of basal cells with suprabasal clefts. These clefts progress into intraepidermal blisters which are devoid of inflammatory cells (Fig. 3) (10). A distinctive ultrastructral finding in the Dowling-Meara variant of EBS is clumping of tonofilaments within basal keratinocytes (11). This fragility is due to genetic defects of keratin 5 (K5) and keratin 14 (K14), which are intermediate filaments expressed in the cytoskeleton of suprabasal keratinocytes (12,13). Keratins are the intermediate filament proteins that join to form dimers and polymerize to form filaments, which are a main component of the epidermal cytoskeleton (14). Instead of forming fine threads, the mutated keratins 5 and 14 clump together, thus causing clefts in the keratinocytes; this is the etiology of blister formation in EBS. Molecular biologists have detected various mutations in keratin 5 and 14 genes in EBS patients.

Our patient has no family history of blistering disorders, which points away from an autosomal dominant inheritance. The consanguinity evident in the patient's family tree most likely points to a recessively inherited EBS. Less likely is the development of a spontaneous mutation in EBS-implicated genes.

Diagnosis

Diagnosis of EBS relies on a thorough history and physical examination. These patients typically have a history of spontaneous blister formation on the hands and feet from birth. Older patients develop blisters at sites subject to minor trauma. A biopsy specimen of perilesional skin, taken after slight mechanical provocation, may support a provisional diagnosis of EBS if histological evidence of intraepithelial tissue separation is evident. Tissue samples should be sent for further evaluation, including electron microscopy (Fig 3). Characteristic suprabasilar, intraepidermal blistering is seen. Immunodiagnostic techniques, such as immunofluorescence microscopy, are also being used in many centers. In patients with severe forms of EBS, blood samples from family members should be attained for genetic analysis. Since it has been thought that the nature and location of the mutation may predict the severity of EBS, such analysis is a means of screening family members for any defect in the genes for K5 and K14 (15).

Treatment

Treatment for patients affected with EBS is typically supportive and preventive, consisting of avoidance of trauma, wound management, nutritional support and infection control. Antiseptic baths, saline compresses and topical antibiotics are commonly used in order to provide relief and prevent secondary infections in areas of blistering. Topical corticosteroids are also used; in principle, their mechanism of action slows down reepithelization. Tense blisters can also be evacuated for symptomatic relief. Patient education involves informing the patient of maintaining a cool environment, avoidance of trauma, and wearing loose, leather shoes. Genetic counseling is available for couples affected with EBS.

Due to the continued research and localization of mutations in patients with various EBS subtypes, future therapies may eventually include protein replacement and/or gene therapy. Protein replacement encompasses the production of a defective protein by recombinant methods and topical application in a lotion, or cream, form. Gene therapy would deliver cultured keratinocytes, or stem cells, directly into patients with a specific gene defect. Murine EBS models hold great promise for future investigation of gene therapy and protein replacement techniques and eventual application to human patients (16-18).

Acknowledgment

We thank César E. Fernandez and the New Jersey Medical School Center for Electron Microscopy.

REFERENCES

1. Horn HM, Priestley GC, Eady RA, Tidman MJ. The prevalence of epidermolysis bullosa in Scotland. *Br J Dermatol* 136: 560-564, 1997.

2. Inaba Y, Kitamura K, Ogawa H *et al.* A study on the estimation of prevalence of epidermolysis bullosa in Japan. *Nippon Hifuka Gakkai Zasshi* 99: 1021-1026, 1989.

3. McKenna KE, Walsh MY, Bingham EA. Epidermolysis bullosa in Northern Ireland. *Br J Dermatol* 127: 318-321, 1992.

4. Muller FB, Kuster W, Bruckner-Tuderman L *et al.* Novel K5 and K14 mutations in German patients with the Weber-Cockayne variant of epidermolysis bullosa simplex. *J Invest Dermatol* 111: 900-902, 1998.

5. Combemale P, Kanitakis J. Epidermolysis bullosa simplex with mottled pigmentation. Case report and review of the literature. *Dermatology* (Basel) 189: 173-178, 1994.

6. Jonkman MF, Heeres K, Pas HH *et al.* Effects of keratin 14 ablation on the clinical and cellular phenotype in a kindred with recessive epidermolysis bullosa simplex. *J Invest Dermatol* 107: 764-769, 1996.

7. Batta K, Rugg EL, Wilson NJ *et al.* A keratin 14 žknockout' mutation in recessive epidermolysis bullosa simplex resulting in less severe disease. *Br J Dermatol* 143: 621-627, 2000.

8. Puddu P, Angelo C, Faraggiana T *et al.* Epidermolysis bullosa of the Dowling-Meara type: clinical and ultrastructural findings in five patients. *Pediatr Dermatol* 13: 207-211, 1996.

9. D'Onghia FS, Rosina P, Barba A. Epidermolisi bullosa di Dowling-Meara. *Chron Dermatol* (Roma) 5: 547-552, 1995.

10. Metze D. Explaining clinical features and histopathologic finding by electron microscopy: epidermolysis bullosa simplex. *Dermatopathology: Practical and Conceptual* 3: 232-233, 1997.

11. Pearson RW. Histopathologic and ultrastructural findings in certain genodermatoses. *Clin Dermatol* 3: 143-174, 1985.

12. Hu ZL. Smith L, Martins S, *et al.* Partial dominance of a keratin 14 mutation in epidermolysis bullosa simplex - increased severity of disease in a homozygote. *J Invest Dermatol* 109: 360-364, 1997.

13. Horn HM, Tidman MJ. The clinical spectrum of epidermolysis bullosa simplex. *Br J Dermatol* 142: 468-472, 2000.

14. Galligan P, Listwan P, Siller GM *et al.* A novel mutation in the L12 domain of keratin 5 in the Kobner variant of epidermolysis bullosa simplex. *J Invest Dermatol* 111: 524-527, 1998.

15. Shemanko CS, Mellerio JE, Tidman MJ *et al.* Severe palmo-plantar hyperkeratosis in Dowling-Meara epidermolysis bullosa simplex caused by a mutation in the keratin 14 gene (KRT14). *J Invest Dermatol* 111: 893-895, 1998.

16. Fuchs E. Genetic skin disorders of keratin. *J Invest Dermatol* 99: 671-674, 1992.

17. Fuchs E, Coulombe P, Cheng J *et al.* Genetic bases of epidermolysis bullosa simplex and epidermolytic hyperkeratosis. *J Invest Dermatol* 103: 25S-30S, 1994.

18. Troy TC, Turksen K. In vitro characteristics of early epidermal progenitors isolated from keratin 14 (K14)-deficient mice: insights into the role of keratin 17 in mouse keratinocytes. *J Cell Physiol* 180: 409-421, 1999.

A U T H O R S ' A D D R E S S E S

Nadia I. Kihiczak MD, Dermatology and Pediatrics, New Jersey Medical School, South Orange Ave 185. Newark 07103-2714, New Jersey
Anthony J. Papadopoulos MD, same address
Robert A. Schwartz MD, M.P.H., Professor and Chairman, same address
Camila K. Janniger MD, same address
Reprint requests to Dr. C. Janniger