STUDY

Generalized Atrophic Benign Epidermolysis Bullosa

Either 180-kd Bullous Pemphigoid Antigen or Laminin-5 Deficiency

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Background: Generalized atrophic benign epidermolysis bullosa (GABEB) is a form of nonlethal junctional epidermolysis bullosa, clinically characterized by generalized blistering after birth, atrophic healing, and incomplete universal atrophic alopecia with onset in childhood. Recently, we discovered a deficiency of the 180-kd bullous pemphigoid antigen (BP180) and a reduced amount of BP180 messenger RNA in three patients with GABEB. It is not yet clear, however, whether GABEB is invariably caused by BP180 deficiency.

Results: We examined 18 patients with nonlethal junctional epidermolysis bullosa from unrelated families; nine of these individuals presented with the clinical characteristics of GABEB. Specimens of clinically normal skin obtained from the patients were stained by immunofluorescence with monoclonal antibodies to BP180 and laminin-5. The BP180 epitopes were not expressed in eight patients, all of whom were sharing the typical clinical features of GABEB. In one of the nine patients with GABEB, the BP180 level was sufficient, but the laminin-5 level was reduced. Among the nine patients with junctional epidermolysis bullosa without atrophic alopecia, laminin-5 level was not expressed in one patient, while in the other patients both antigens were normally expressed.

Conclusions: Not all patients with GABEB are deficient in BP180, since some individuals with GABEB only exhibit reduction of the laminin-5 expression. The BP180 deficiency in the skin invariably seems to result in GABEB. Immunofluorescence analysis using monoclonal antibodies against BP180 (and laminin-5) may allow early subtyping, which is of prognostic significance, in children born with junctional epidermolysis bullosa.

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GENERALIZED atrophic benign epidermolysis bullosa (GABEB) is a clinical variant of junctional epidermolysis bullosa (JEB). The term *GABEB* was coined in 1982 by Hintner and Wolff[1] and is synonymous with epidermolysis bullosa atrophicans generalisata mitis.[2] The first kindred with GABEB was described in 1976 by Hashimoto et al[3] and was named Disentis type, according to the origin of the patients. The clinical features of GABEB include continuous blistering since birth, healing with cigarette paper–like atrophic skin with pigment shifts at sites of recurrent blistering with no scarring or milia. Characteristic is a follicular atrophy (not cicatricial) beginning in childhood and resulting in scalp baldness (particularly above the ears), partial absence of eyelashes and eyebrows, and the absence of body, pubic, and axillary hair (universal alopecia); the nails are hypoplastic or dystrophic, the dentition is affected, and the mucous membranes are mildly involved. Normal growth and lack of anemia are typical, as is moderate improvement with advancing age. In a consensus classification made in 1991,[4] GABEB was grouped together with other nonlethal generalized JEB forms into the category generalized nonlethal JEB, differing from Herlitz disease (generalized lethal JEB) by its absence of anemia and growth retardation.[4] However, the typical alopecia in GABEB distinguishes it from other forms of nonlethal JEB.

Recently, Jonkman et al[5] demonstrated that 180-kd bullous pemphigoid antigen (BP180) is a candidate protein for GABEB.[5,6] In three patients with GABEB, the intracellular and extracellular epitopes of the BP180 molecule were absent in clinically normal skin. Northern blot analysis of cultured keratinocytes ob-

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PATIENTS AND METHODS

PATIENTS

Eighteen patients with nonlethal JEB were included in the study: 13 patients with a generalized type and five patients with a localized or inverse type. The clinical features are summarized in **Table 1**. Patients 1 through 3[5], 4,[10] 6,[11(p 155)] 8,[12] and 13[13] have been described previously. The diagnosis of nonlethal JEB was established in each patient on the basis of clinical findings, family history, antigen mapping, and electron microscopy. Ultrastructurally, all patients had hypoplastic hemidesmosomes in clinically normal skin.

METHODS

Skin Specimens

Four-millimeter punch biopsy specimens were obtained from clinically normal skin (from the flexor aspect of the upper arm or the thigh) of the patients. Skin specimens obtained from healthy adults served as controls. The skin specimens were snap frozen for immunofluorescence.

Antibodies

Monoclonal IgG1 antibodies 1D1 and 1A8c are directed against the extracellular and intracellular domain of BP180, respectively, and the monoclonal IgG1 antibody R815 is directed against the 230-kd bullous pemphigoid antigen (BP230).[14,15] The specificity of antibodies was established by immunoblot on extracts of normal human keratinocytes and of the human carcinoma cell line A431.[5,14,15] Mouse monoclonal IgG1 antibody GB3[16] was directed against laminin-5 (nicein/kalinin/epiligrin).

Immunofluorescence Studies

Cryostat sections (4 μm) of skin specimens were processed for immunofluorescence as previously described.[17] In combination with the primary mouse monoclonal antibodies, we used biotinylated goat anti-mouse IgG1 dilution 1:100 (SBA, Birmingham, Ala) and dichlorotriazinyl-amino-fluorescein–conjugated streptavidin, dilution 1:200 (Jackson Immuno Research Inc, West Grove, Pa). The nuclei were counterstained in blue with fluorescent *bis*-benzimide, dilution 1:15 000 (Serva GmbH, Heidelberg, Germany). Digitized video microscopic images of tissue sections were obtained with a newly developed imaging system with long exposure times designed for the detection of very low levels of fluorescence.[18]

Table 1. Deficiency of BP180, BP230, or Laminin-5 in Skin of Patients With Nonlethal Junctional Epidermolysis Bullosa*

Characteristics	GABEB (n=9)	Non-GABEB (n=9)	All (N=18)
M:F ratio	3:6	5:4	8:10
Mean age, y (range)	44.0 (7-72)	32.3 (3-67)	38.1 (3-72)
Deficiency, No. of patients			
BP180 (moAbs 1D1 and 1A8c)	8/9	0/9	8/18
BP230 (moAb R815)	0/9	0/9	0/18
Laminin-5 (moAb GB3)	1/9	1/9	2/18

**Immunofluorescence results summarize negative or severely reduced staining in clinically normal skin. GABEB indicates generalized atrophic benign epidermolysis bullosa; BP180, 180-kd bullous pemphigoid (BP) antigen; BP230, 230-kd BP antigen; and moAb, monoclonal antibody.*

tained from a patient with GABEB revealed a reduced level of BP180 messenger RNA, suggesting that the BP180 deficiency was the primary defect.[5] In contrast, McGrath et al[7] found two mutations in the gene *LAMC2* coding for the γ2 subunit of laminin-5 (nicein/kalinin/epiligrin) in three related patients with GABEB. These studies suggest that the deficiency of at least two candidate proteins, BP180 and laminin-5, may be responsible for the clinical GABEB phenotype.

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The BP180 is a putative cell-matrix adhesion molecule that is restricted to the hemidesmosomes of stratified squamous epithelia. The sequence of the BP180 complementary DNA clones also shows that it is an unusual type II transmembrane molecule with the amino terminal head located intracellularly.[8] Moreover, the extracellular tail of BP180 contains an interrupted collagenous domain, and, because of that, it was classified as type XVII collagen.[9] However, the intracellular and extracellular ligands of BP180, as well as the molecular and supramolecular structures, remain unknown at present.

In this study, we investigated the relationship between the clinical phenotype of GABEB and the molecular expression of BP180 and laminin-5. We examined 18 patients from unrelated families with nonlethal JEB, of whom nine had GABEB with characteristic alopecia. Specimens obtained from the clinically normal skin of the patients were examined by means of immunofluorescence using monoclonal antibodies to different domains of BP180 and laminin-5. We found that most patients with GABEB have BP180 deficiency, although in a minority of the patients with clinically indistinguishable cases, the expression of laminin-5 may be reduced while BP180 is normally expressed.

RESULTS

Nine of the 18 patients (patients 1 through 9) had the clinical characteristics of GABEB, with alopecia of the scalp, eyebrows, and eyelashes (**Figure 1**); healing with skin atrophy and hyperpigmentation and depigmentation (**Figure 2**, top); and the absence of secondary and lanugo hairs (Figure 2, bottom).

Clinical features and immunofluorescence results are summarized in Table 1. The BP180 antigen was not expressed in eight of the nine patients with GABEB. In all eight patients, both the intracellular and the extracellu-

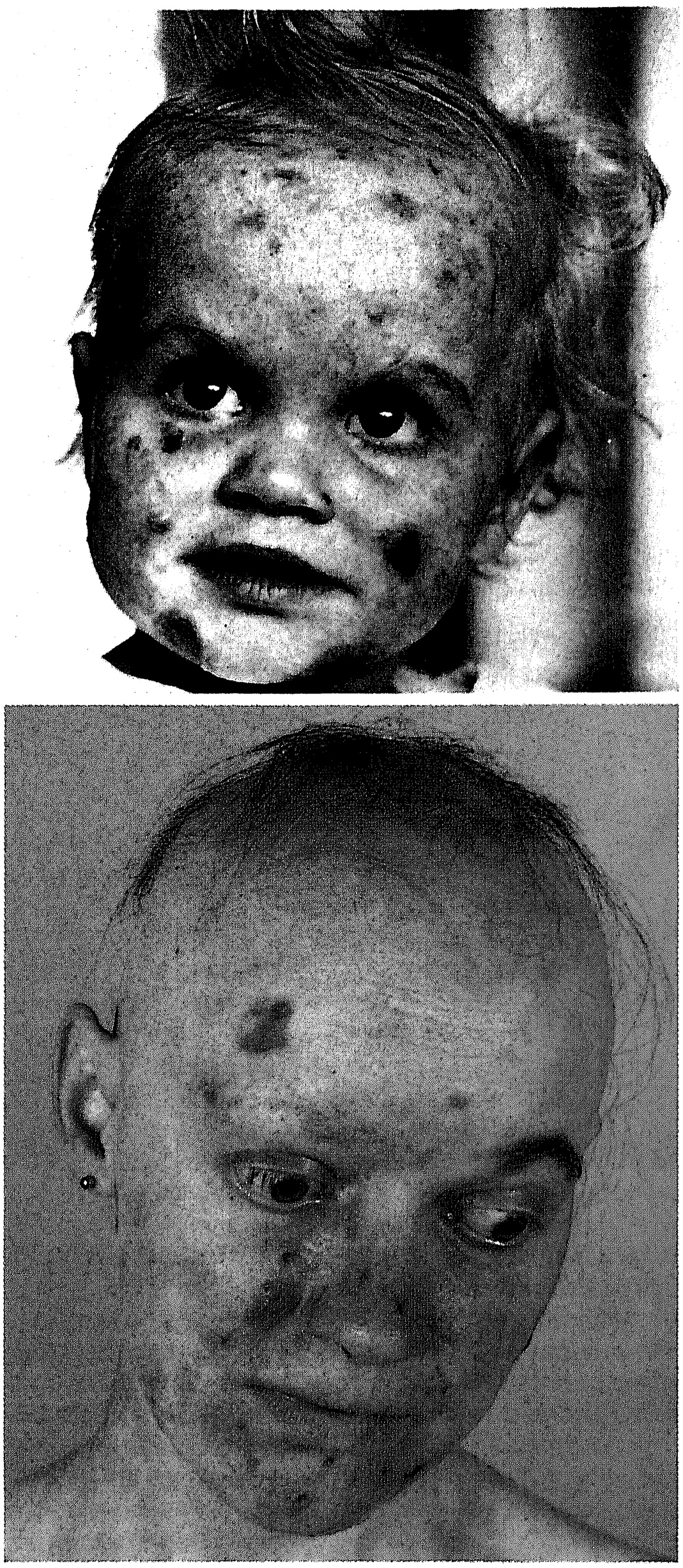

Figure 1. *Patient 3 with BP180-negative generalized atrophic benign epidermolysis bullosa at the ages of 3 years (top) and 26 years (bottom). Note alopecia of the scalp and eyebrows (the left eyebrow has been accentuated by pencil) that has developed after infancy.*

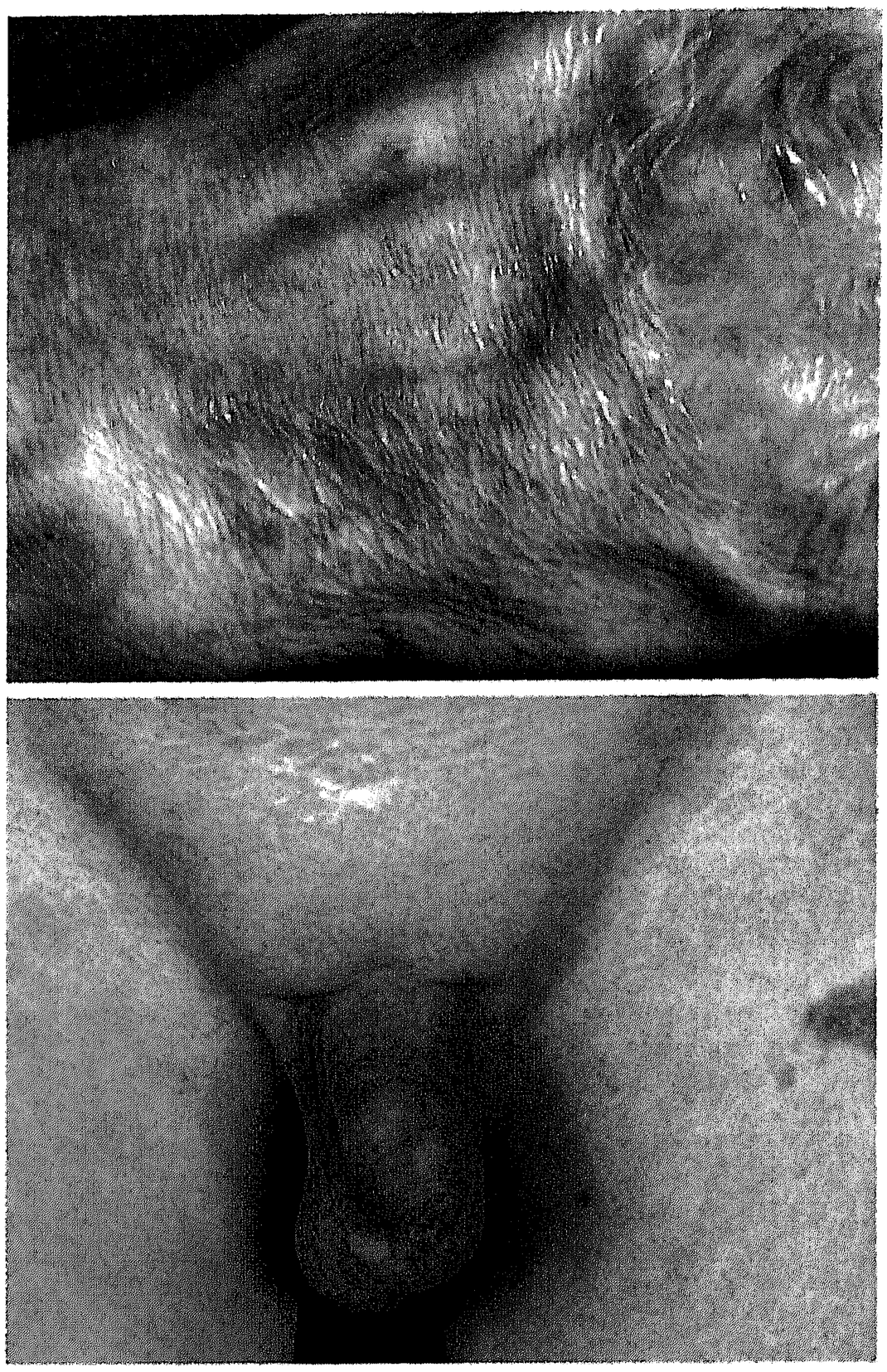

Figure 2. *Patient 1 with BP180-negative generalized atrophic benign epidermolysis bullosa at the age of 41 years. The skin heals with cigarette-paper–like atrophy with hyperpigmentation and hypopigmentation and without milia (top). Secondary hair in the pubic region and lanugo hair on the body are completely absent (bottom).*

lar BP180 epitopes were lacking (**Figure 3**, B) or were reduced (monoclonal antibody 1A8c in patient 6). However, the BP180 antigen was normally present in another patient with GABEB (patient 9) in whom expression of laminin-5 was reduced, as detected with the GB3 antibody (Figure 3, F). This patient had atrophic alopecia and skin atrophy and was clinically indistinguishable from the BP180-negative patients with GABEB, although the alopecia and skin atrophy were more limited (compare Figure 1, bottom, and **Figure 4**).

A unique interrupted pattern of BP180 expression was found in two patients with GABEB (patients 3 and 8). In specimens of intact skin, intracellular and extracellular BP180 epitopes were absent along stretches of up to 150 μm of the dermoepidermal junction. Both BP230 and laminin-5 were continuously present in the normal fashion along the dermoepidermal junction in these specimens (data not shown). Small interruptions in the BP180 fluorescent line can also be found in the skin of normal controls (Figure 3, A), caused by BP180-negative melanocytes in the basal layer, but the interruptions were clearly longer in the patients. In patient 3, this interrupted pattern was found only in areas of the skin that were never affected by blisters and in which we could not induce blistering by rubbing. These never-involved areas had a symmetrical leaflike distribution (phylloid pattern) over the extensor surface of the elbow, forearm, wrist, and hands (thenar and extensor surface of the index and middle fingers) (**Figure 5**). However, in this patient, BP180 was totally lacking in specimens from the complementary, almost normal-

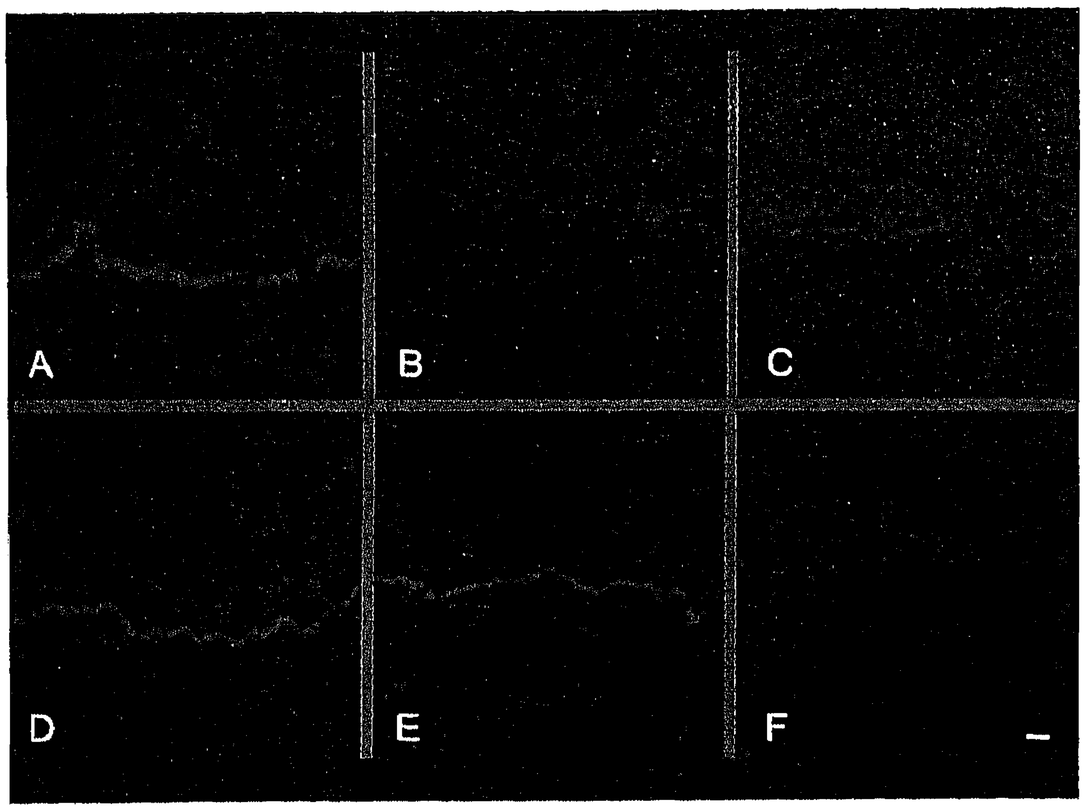

Figure 3. *Immunofluorescence of control skin specimens (A and D) and of clinically normal skin specimens of two patients with generalized atrophic benign epidermolysis bullosa: patient 1 (B and E) and patient 9 (C and F) using antibodies 1D1 (A through C) to BP180 and GB3 (D through F) to laminin-5. The BP180 antigen is not expressed in patient 1 (B), while patient 9 has severely reduced laminin-5 expression (F). The nuclei are counterstained in blue. The small interruptions in the BP180 fluorescent line in normal skin (A) are caused by BP180-negative melanocytes in the basal layer. Bar indicates 10 μm.*

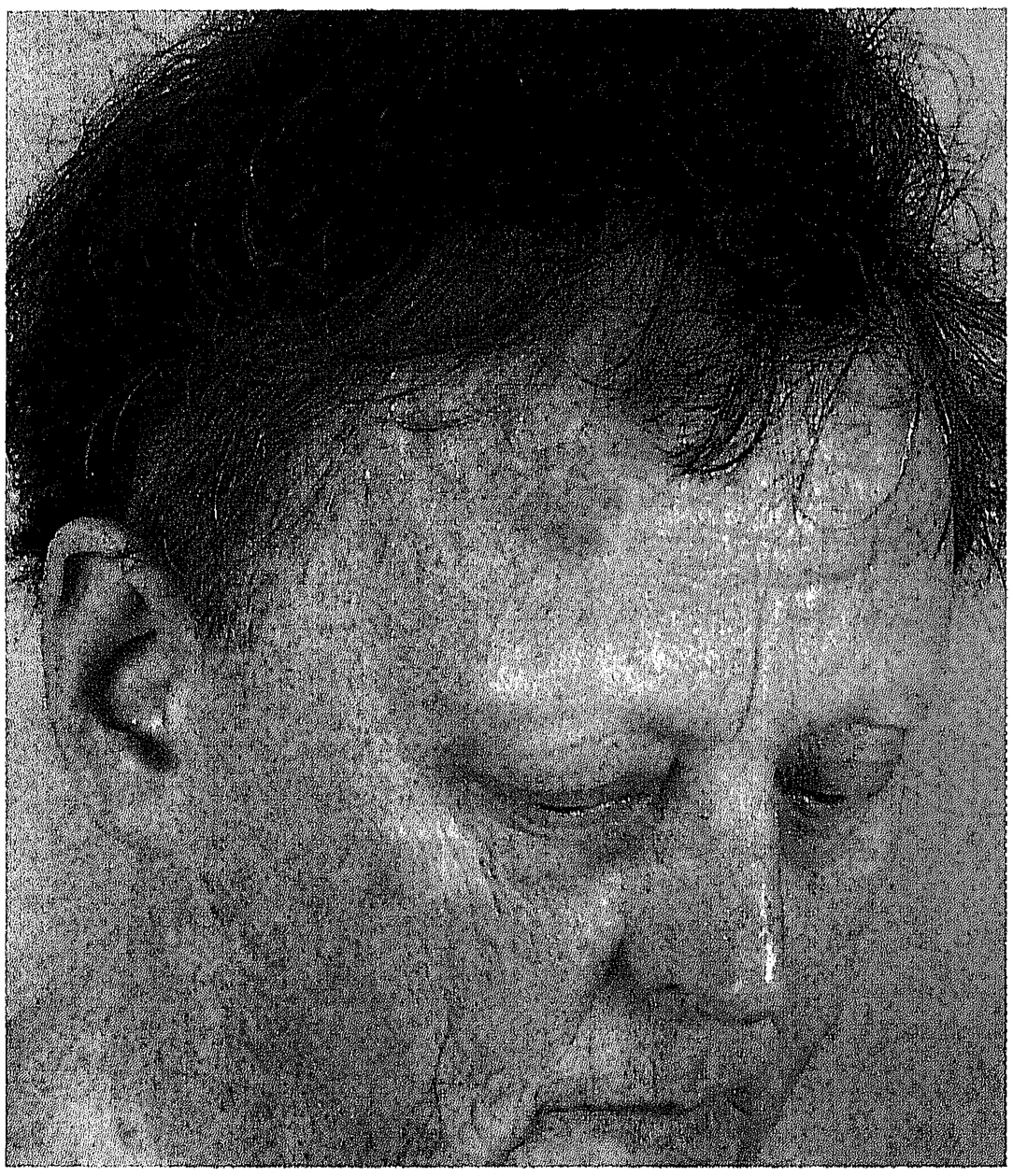

Figure 4. *Patient 9 with laminin-5–reduced generalized atrophic benign epidermolysis bullosa. Note the alopecia from the frontal and supra-auricular hair line and the loss of hair from the eyebrows and eyelashes.*

looking skin that blisters after rubbing. According to patient 8, her entire integument had been involved.

Reactions with monoclonal antibody GB3 in the skin specimens from the eight BP180-negative patients with GABEB revealed that laminin-5 exclusively lined the blister floor. Remarkably, in the patient with GABEB and with reduced laminin-5 expression (patient 9), GB3 stained both the blister roof and the blister floor. The split level seems to be lower in the lamina lucida in this patient than

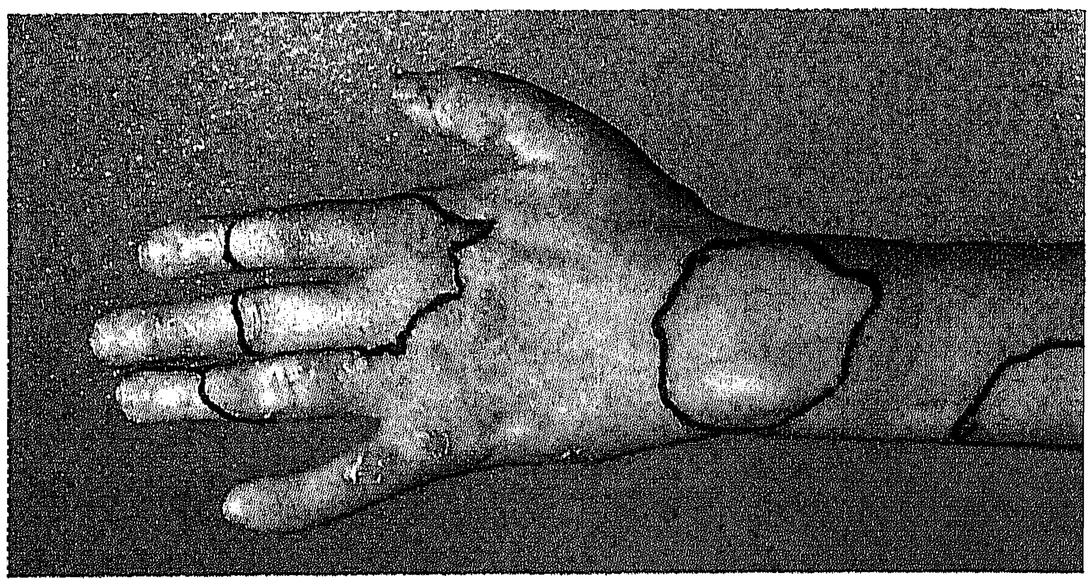

Figure 5. *Patient 3 with generalized atrophic benign epidermolysis bullosa. Areas of skin that never blister (outlined with a black marker) show normal pigmentation and no atrophy in a leaflike (phylloid) pattern.*

Table 2. Clinical Phenotype of Generalized Atrophic Benign Epidermolysis Bullosa

Generalized blistering since birth
Blister induction after trivial trauma
Predilection for flexor aspect of palms and fingers
Serous and hemorrhagic blisters
Healing with
Skin atrophy
Hyperpigmentation and hypopigmentation
No milia
No scarring
Universal atrophic alopecia beginning in childhood
Scalp (particularly above the ears)
Eyebrows (partial)
Eyelashes (partial)
Body (lanugo hair)
Secondary sexual hair (pubis and axilla)
Abnormal dentition with enamel hypoplasia
Nail dystrophy
Mild mucosal membrane involvement
Mild calluses on feet
No anemia or growth retardation

it does in the lamina lucida of patients with GABEB with BP180 deficiency.

Among the nine patients without atrophic alopecia, one patient (patient 10) was laminin-5 negative, while in the other three patients with generalized nonlethal JEB and in all five patients with the localized or inverse types of JEB, both BP180 and laminin-5 were normally expressed. One of the patients with generalized nonlethal JEB (patient 11) was only 3 years old; at that age, the clinical phenotype with alopecia may not yet be manifest.

COMMENT

In this study, we show that in the skin of the majority of patients with GABEB, BP180 is not expressed. However, in a minority of patients (patient 9), laminin-5 is reduced and BP180 is normally expressed.[7] The clinical phenotype of GABEB with reduced laminin-5 expression is indistinguishable from that of the phenotype with BP180 deficiency. Thus, GABEB appears to be heterogeneous on the molecular level. No abnormality in the expression of BP180 or laminin-5 was found in a recent

study on eight patients with GABEB that was conducted by Pohla-Gubo et al.[19] The discrepancy between their results and ours might be because of the type of GABEB or because the authors did not use a specific antibody against BP180 with a high signal-noise ratio to allow a definite conclusion.

In eight of the patients with nonlethal JEB without GABEB, both BP180 and laminin-5 levels were expressed as shown by immunofluorescence. Theoretically, there might be a defect in the genes encoding for BP180 or laminin-5 in these cases that does not affect the availability of these epitopes. No abnormal expression of BP230 was seen in any of the patients included in this study.

An alternative candidate molecule for involvement in JEB is uncein, which is an antigen located on the anchoring filaments in the lamina lucida, recognized by the monoclonal antibody 19-DEJ-1.[20] Uncein was absent in 100% of the patients with JEB and in 25% of the patients with recessive dystrophic epidermolysis bullosa. The significance of the absence of 19-DEJ-1 remains unclear until the antigen is characterized on the molecular level.

This study shows that the GABEB phenotype is related to the altered expression of either BP180 antigen or laminin-5, as determined by immunofluorescence. The clinical relevance of these findings is that patients with GABEB with either a BP180 or a laminin-5 defect are clinically indistinguishable. The GABEB phenotype can be distinguished from that in other patients with generalized nonlethal JEB using the clinical characteristics that are summarized in **Table 2**. However, the GABEB phenotype appears to be incomplete at birth but becomes completely penetrant at a later age, since the characteristic atrophic alopecia develops in later childhood. On clinical grounds, GABEB may thus be initially classified in patients as generalized nonlethal JEB until the complete phenotype is manifest. However, immunofluorescence investigation of the skin using monoclonal antibodies against BP180 and laminin-5 may allow early subtyping in children born with JEB. Abnormalities in the expression of BP180 are, to date, associated only with the GABEB phenotype, as shown in this study and in the previous work.[5] Abnormalities in the expression of the laminin-5 molecule may lead to the clinical phenotypes of generalized lethal JEB (Herlitz),[21,22] GABEB,[7] as in this study, or generalized nonlethal JEB.[23] In this study, one of the patients (patient 10) was classified as having the generalized nonlethal JEB because of the absence of alopecia. In that patient, laminin-5 was not expressed, which was probably the result of a defect in one of the laminin-5 genes. However, this patient was only 7 years old and the full clinical GABEB phenotype might not have been developed yet.

In a series of Austrian patients with GABEB, giant nevocytic nevi were found on their backs.[1,24] We did not find these lesions in our patients nor were they found in other studies on patients with GABEB.[12,25-30] Thus, the large nevocytic nevi may be associated with GABEB, but they are not a clinical criterion for the disorder.

Patient 3 presented a clinical mosaic with areas of never-involved skin that had a leaflike pattern (Figure 5) similar to the phylloid pattern (non-Blaschko lines), as described by Happle[31] in mosaicism in humans with pigment disorders. The unique (reduced) expression of BP180 in the phylloid areas along 50% of the epidermal basement membrane zone appears to be sufficient to prevent skin blistering. However, the same type of interruptions in patient 8 did not prevent generalized blistering. The BP180 interruptions in patient 3 might reflect somatic mosaicism, where part of the cells escaped the generalized autosomal recessive disorder. This could be the result of somatic reversion caused by a reverse mutation or by recombination of one of the two different mutations originally present on the two separate BP180 alleles in a compound heterozygote, thus rendering one allele normal. If somatic reversion did happen in a putative primordial stem cell, then the BP180-positive patches with a diameter of 50 to 150 μm might reflect the area in which the keratinocytes, supplied by divisions of one stem cell, are localized. Alternatively, the interruptions might be secondary to a primary defect of an unknown factor that focally down-regulates BP180 expression or up-regulates collagenase activity. In that case, the puzzling genetic explanation for the remarkable interrupted pattern remains the same.

The split level of laminin-5–reduced GABEB skin appears to be lower in the lamina lucida than in the BP180-deficient GABEB skin, which is in agreement with the ultralocalization of these molecules. The BP180 antigen is a transmembrane glycoprotein predicted from the deduced amino-acid sequence of the cloned BP180 complementary DNA[8] and demonstrated by immunoelectron microscopy, using antibodies to intracellular and extracellular epitopes,[15,32] while laminin-5 (GB3) is an extracellular matrix protein localized in the lower part of the lamina lucida.[21] However, the definitive determination of split levels in these junctional disorders has to await characterization of molecular interactions and binding sites of the involved proteins.

We conclude that the clinical phenotype of GABEB is heterogeneous on the molecular level, since the genes for BP180 or laminin-5 may be involved.

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