

Childhood Bullous Pemphigoid

Clinical and Immunological Findings in a Series of 4 Cases

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Background: Bullous pemphigoid (BP) is an autoimmune blistering disease that is rare in childhood. As in adult BP, antibodies against the 180-kDa antigen (BP180) seem to be involved in the pathogenesis of the disease, but, to date, only a small number of children with the disease have been examined immunologically.

Observations: We report the cases of 4 infants with BP aged 5 to 12 months. All of them had involvement of the hands and feet, and they all achieved a complete remission in less than 6 months when treated with oral prednisolone stearoyl glycolate. Three patients could be examined using antigen characterization techniques. Autoantibodies against the NC16A domain of BP180 were found by immunoblot assay in all 3 and by enzyme-

linked immunosorbent assay in 2 of them. Interestingly, although IgA autoantibodies were detected in only 1 of them by indirect immunofluorescence, all of them had IgA autoantibodies, and 2 of the 3 had IgG autoantibodies against NC16A as detected by immunoblot assay. One patient also had IgG autoantibodies against the carboxyterminal domain of BP180.

Conclusions: IgA-specific antibodies against BP180 were detected in all our patients. These findings further raise the question about the relationship between BP and linear IgA bullous dermatosis, the most common autoimmune blistering disorder in children.

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BULLOUS PEMPHIGOID (BP) IS an autoimmune subepidermal blistering disease that commonly affects elderly individuals. The disease is very rare in children, and most cases occur in school-aged children (generally, those older than 8 years).¹ Mucous membrane involvement seems to be more frequent in childhood BP, as well as involvement of

tested against the 2 main antigenic domains of BP180 (recombinant NC16A and carboxyterminal domains) both by immunoblot assay and ELISA.

REPORT OF CASES

CASE 1

A 5-month-old boy with a sudden eruption of blisters and bullae on his hands and feet was referred to our institution. He also had small oral erosions that had been noted by the pediatrician. The cutaneous lesions quickly generalized to involve the trunk, face, and lower limbs. On physical examination, the patient had an eruption of tense vesicles and blisters with surrounding erythema on these sites. We were not able to see mucosal lesions. Histologic examination of a perilesional skin biopsy sample revealed a subepidermal blister with abundant eosinophils. Direct immunofluorescence (IF) examination showed linear deposits of IgG, IgA (faint deposits), and C3 (intense deposits) along the basement membrane zone (BMZ). Treatment with 2 mg/kg per day of oral

*See also pages 249
and 272*

the hands and feet in infants younger than 1 year.² As in adult BP, antibodies against the 180-kDa BP antigen (BP180, also known as type XVII collagen) seem to be involved in the pathogenesis of the disease.³ However, to date, the target antigen of the autoantibodies has been studied by immunoblot assay or enzyme-linked immunosorbent assay (ELISA) in only a small number of children with BP. Herein, we describe a series of 4 infants with BP seen at a single institution (Hospital Sant Joan de Deu, Barcelona, Spain). The serum samples of 3 of them were

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Figure 1. Case 2. Pompholyxlike appearance at presentation with tense vesicles and blisters on the hands (A) and feet (B).

prednisolone stearoyl glycolate was started, and remarkable clinical improvement was noted within a few days; therefore, the dosage was quickly tapered and finally discontinued when complete remission was achieved after 3 months of therapy. The patient was still in remission 2 years after follow-up.

CASE 2

A 5-month-old boy was referred to our institution for evaluation of a vesicular eruption affecting his hands, feet, and trunk. On physical examination, his general condition was good, but he exhibited vesiculobullous lesions arising from inflamed skin on his hands and feet (**Figure 1**) and isolated lesions on the anterior side of his trunk. Mucous membranes were not affected. Results from laboratory studies were all within reference range, except for a finding of slight leukocytosis with eosinophilia (14%). Findings from histopathologic examination revealed spongiosis, subepidermal vesicles, and mixed inflammatory infiltrates in the papillary dermis consisting predominantly of eosinophils. Direct IF examination of perilesional skin showed linear deposits of IgG, IgA (faint deposits), and C3 (intense deposits) along the BMZ. Treatment with topical mometasone propionate was tested for 1 week, without improvement, so treatment with 1 mg/kg per day of oral prednisolone stearoyl glycolate was begun. This therapy was continued for 2 weeks, when complete remission was achieved. It was then gradually tapered and finally stopped after 3 months, with no recurrence of lesions after 6 months of follow-up.

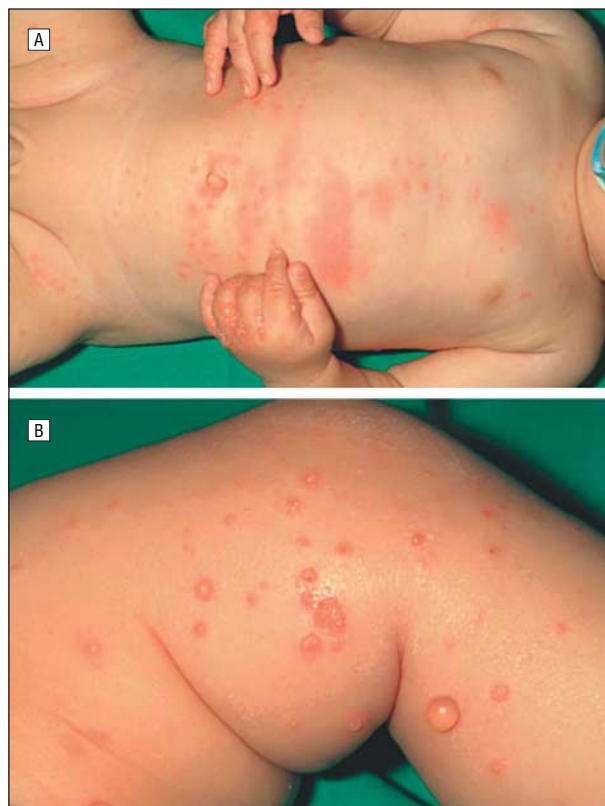


Figure 2. Case 4. A, Widespread eruption of bullae arising on erythematous base. B, Detail of lesions on the thigh.

CASE 3

A 12-month-old boy was sent to our institution for evaluation of a 3-month history of blisters, erosions, and crusted lesions on his hands, feet, abdomen, and scalp. An initial clinical diagnosis of chronic bullous dermatosis of childhood had been made at another institution, and treatment with 1 mg/kg per day of dapsone was started. Despite an apparent initial response to treatment, the lesions quickly spread on his trunk and lower limbs. On physical examination, the patient was found to have crusted lesions on his scalp as well as on his trunk and limbs, with tense blisters on his palms and soles. Subepidermal bullae were found on histologic examination, and direct IF of perilesional skin detected linear deposits of IgG and intense deposits of C3 along the BMZ. No blood samples were drawn for indirect IF or further studies in this case. A diagnosis of BP was then made, and treatment with dapsone was stopped when therapy with 1 mg/kg per day of oral prednisolone stearoyl glycolate was prescribed. Complete remission was achieved in 1 month while tapering the dosage of corticosteroids. Ten months after therapy ended, the patient was still in remission.

CASE 4

A 4-month-old boy was referred for a widespread eruption of blisters affecting his abdomen, limbs, scalp, palms, and soles that had started a few days previously. On physical examination, he had tense blisters with surrounding erythema on these sites (**Figure 2**), with-

out mucosal involvement. Histopathologic examination showed subepidermal bullae with a mixed infiltrate in papillary dermis, with abundant eosinophils. Topical therapy with betamethasone dipropionate was started. Results from routine laboratory testing were within reference range except for a slight leukocytosis with a normal differential. Direct IF showed linear deposits of IgG and intense deposits of C3 along the BMZ. Therapy with 1 mg/kg per day of oral prednisolone stearoyl glycolate was started, with immediate improvement. Complete remission was achieved during the next 2 weeks. The dosage of prednisolone was then gradually tapered and finally stopped after 4 months, and 1 year later the patient was still in remission.

METHODS

Sera were obtained from 3 of the 4 children when they first presented with active disease. Sera from patients with well-characterized BP (n=4) and from healthy donors (n=20) were used as controls. All sera were stored at -20°C.

INDIRECT IF STUDIES

Indirect IF studies were performed according to standard techniques using fluorescein isothiocyanate-labeled goat antihuman IgG, IgA, and IgM antibodies on 1M sodium chloride on split human skin.

PREPARATION OF HUMAN BP180 RECOMBINANT PROTEINS

Recombinant fusion proteins glutathione-S transferase (GST)-NC16A (NC16A domain of BP180), GST-4575 (carboxyterminal domain of BP180), and GST alone were expressed in *Escherichia coli* and affinity-purified using glutathione-sepharose beads (Sigma-Aldrich Corp, St Louis, Mo) by affinity 15 chromatography as previously described.^{4,5}

IMMUNOBLOT ANALYSIS AND ELISA

Recombinant proteins were subjected to 15% sodium dodecyl sulfate polyacrylamide gels and then electrophoretically transferred to nitrocellulose. Serum samples were tested with the nitrocellulose strips at the dilution of 1:200 for IgG and 1:100 for IgA in washing buffer. Bound autoantibodies were visualized using peroxidase-conjugated second antibodies (Dako Corp, Glostrup, Denmark) at the manufacturer's recommended dilutions. Serum samples from patients and controls were tested using ELISA produced with recombinant proteins GST-NC16A and GST-4575. Briefly, the fusion proteins were coated in 96-well microtiter plates and incubated with diluted serum first and then with peroxidase-conjugated antihuman IgA or IgG. The optimal working conditions (the amount of protein applied to each well and dilution of the primary antibody) were adjusted previously (data not shown). The optical density at 492 nm (OD₄₉₂) in each well was measured. The OD value corresponding to the reactivity of each serum with GST alone was subtracted from the OD value obtained with GST fusion proteins. To compare the results from different plates, the test sample ODs were adjusted according to positive and negative control samples. The final result was expressed as a percentage (ELISA index) according to this calculation:

$$\text{ELISA Index} = \frac{(\text{OD Sample} - \text{OD Negative Control})}{(\text{OD Positive Control} - \text{OD Negative Control})} \times 100.$$

The cutoff value was calculated as the mean + 3 SDs of the indices of the normal control group. These indices were 4,4 and 8,6 for IgG and IgA against NC16A, respectively, and 30,3 and 34,8 for IgG and IgA against the carboxyterminal domain, respectively. Serum samples showing higher indexes than this cutoff value were regarded as positive for BP.

RESULTS

The clinical and immunological findings of all the patients are summarized in the **Table**.

INDIRECT IF STUDIES

All the patients' sera that could be tested (cases 1, 2, and 4) had circulating autoantibodies of the IgG class directed against the epidermal side of 1M sodium chloride split human skin at titers ranging from 1:10 to 1:320. Only case 4 had detectable circulating IgA against the BMZ (titer 1:10), even though faint deposits of this immunoglobulin class had been detected by direct IF along the BMZ in the 2 other patients (cases 1 and 2).

IMMUNOBLOT STUDIES

All 3 patients tested had IgA antibodies against the NC16A domain of BP180, and 2 of the 3 (cases 1 and 4) also had IgG antibodies against this domain. Circulating IgG antibodies against the carboxyterminal domain of BP180 were detected in only 1 patient (case 1), whereas studies with IgA using the same domain were negative in all cases (**Figure 3**).

ELISA STUDIES

The ELISA using the NC16A domain detected reactive IgG and IgA autoantibodies in 2 patients (cases 1 and 4), whereas results for the other patient were negative for antibodies (case 2). The results from ELISA using the carboxyterminal domain were negative for antibodies in all 3 patients (both for IgG and IgA).

COMMENT

Childhood BP is a rare condition, but it is still the most common IgG-mediated subepidermal bullous disease in children. It is usually diagnosed on the basis of the following criteria: (1) the patient is younger than 18 years with bullous skin lesions, with or without mucous membrane involvement, (2) there is characteristic histopathologic features of BP (subepidermal bullae with variable amount of eosinophils), and (3) direct IF shows linear deposition of IgG and/or C3 at the BMZ, or a positive indirect IF demonstrates IgG antibodies reacting with the BMZ.²

Bullous pemphigoid was first described as a distinct entity from pemphigus vulgaris by Lever⁶ in 1953. Before the use of IF techniques, earlier cases of childhood BP were probably categorized as dermatitis her-

Table. Clinical and Immunological Findings for the Patients

Characteristic	Case 1	Case 2	Case 3	Case 4
Age, mo	5	5	12	4
Disease duration, mo	4	2	4	4
Skin involvement*	Generalized	Localized	Generalized	Generalized
Palmoplantar involvement	Yes	Yes	Yes	Yes
Mucosal involvement	Doubtful; not at presentation	No	No	No
Scarring	No	No	No	No
Therapy with prednisolone stearoyl glycolate, mg/kg per day	2	1	1	1
CR	Yes	Yes	Yes	Yes
Follow-up after CR, mo	27	8	10	12
DIF (BMZ linear deposits)	IgG+ IgA± C3++	IgG+ IgA± C3++	IgG+ C3++	IgG+ C3+
IIF	IgG: 1:20 IgA: negative	IgG: 1:10 IgA: negative	ND	IgG: 1:320 IgA: 1:10
IB (NC16A)	IgG, IgA	IgA	ND	IgG, IgA
IB (4575)	IgG	Negative	ND	Negative
ELISA index (NC16a)†	IgG: 33.1 IgA: 86.7	Negative	ND	IgG: 52.5 IgA: 49.7
ELISA index (4575)†	Negative	Negative	ND	Negative

Abbreviations: BMZ, basement membrane zone; CR, complete remission; DIF, direct immunofluorescence; ELISA, enzyme-linked immunosorbent assay; IB, immunoblot; IIF, indirect immunofluorescence; ND, not done; +, moderate deposits; ±, faint deposits; ++, intense deposits.

*Localized: less than 25% of body surface area affected. Generalized: 25% or more of body surface area affected.

†Cutoff values: 4.4 and 8.6 for IgG and IgA against NC16A, respectively, and 30.3 and 34.8 for IgG and IgA against the carboxyterminal domain, respectively.

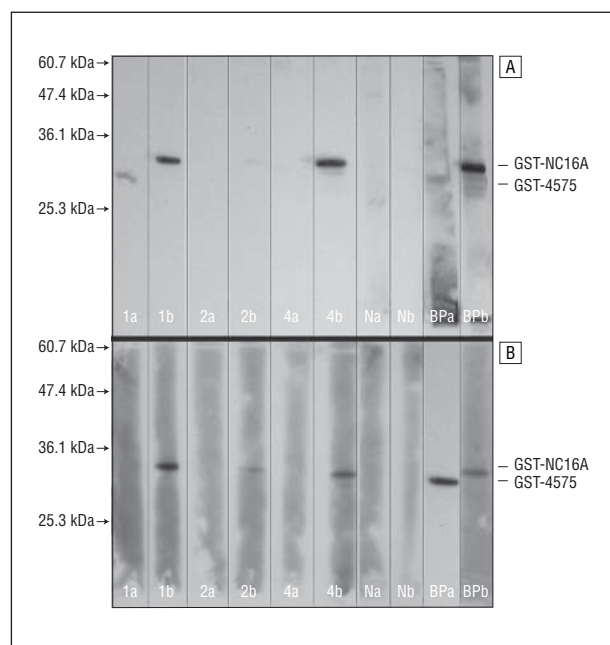


Figure 3. Immunoblot that is a digitally manipulated composition. Nitrocellulose membranes containing fusion proteins (GST-4575 [a] and GST-NC16A [b]) were incubated with serum samples of patients and controls and then with polyclonal antihuman IgG (A) or IgA (B). An adult bullous pemphigoid serum (BP) sample, and a normal human serum sample (N) were used as positive and negative controls, respectively. All 3 patients tested (cases 1, 2, and 4) had IgA antibodies against the recombinant form of NC16A, and 2 of the 3 (cases 1 and 4) also had IgG antibodies against this domain. Circulating IgG antibodies against the carboxyterminal domain (4575) of BP180 were faintly detected in only 1 patient (case 1); findings from studies with IgA using the same domain were negative in all cases.

petiformis of childhood.⁷ In children, BP is clinically similar to its adult counterpart except that mucous membrane involvement is more common in children

and involvement of the hands and feet is much more common in infants younger than 1 year. Oral corticosteroids are the treatment of choice at a dosage of 1 to 2 mg/kg per day,² but dapsone,⁸ sulfapyridine,⁹ cloxacillin sodium,² erythromycin ethylsuccinate,¹⁰ cyclosporine,¹¹ and immunoglobulins¹¹ have been suggested as alternative options. Little is known about the prognosis of the disease in children, but most reported cases had a disease duration of 1 year or less,² as in our cases.

Before the introduction of the sodium chloride-split skin technique,¹² differentiation between BP and epidermolysis bullosa acquisita and bullous systemic lupus erythematosus could be difficult. Immunoelectron microscopic studies had to be performed, if available, to verify that immunoreactants were distributed along the lamina lucida and on the undersurface of basal keratinocytes as in BP¹³ or if by contrast they were deposited within the lamina densa and/or sublamina densa as in bullous systemic lupus erythematosus.¹⁴ In a recent article,³ the presence of autoantibodies specific for BP180 in childhood BP was studied and shown to be similar to adult BP. Sporadic reports of cases have also been published, but only a few articles report series of patients with characterization of the targeted antigens by immunoblot assay or ELISA.^{3,9,15,16} Serum samples were available from 3 of our patients for further immunoblot assay and ELISA testing. The presence of autoantibodies against the NC16A region of BP180 were detected in all of them by immunoblot assay, and in 2 cases this was also confirmed by ELISA. These findings are in accordance with previous studies that show that immunoblot assay is slightly more sensitive than ELISA in detecting the presence of

autoantibodies against NC16A.¹⁷ A recent study showed that the presence of autoreactivity against both the NC16 and carboxyterminal domains was more frequently detected in patients with mucosal lesions.¹⁸ Autoantibodies against the carboxyterminal domain were also detected by immunoblot assay in 1 of our patients (case 1). This patient was supposed to have oral erosions according to his pediatrician, but we could not confirm that these were due to mucosal affection of BP.

Levels of IgG autoantibodies against NC16A have been clearly related to disease activity in adults with BP.¹⁹ All our patients had a similar clinical course with a rapid remission, so we could not find any relationship between autoantibody levels and prognosis, but interestingly, lesions did not generalize in patient 2, in whom we were not able to demonstrate IgG autoantibodies against NC16A. Another interesting finding in this group of patients was the detection by immunoblot assay of autoantibodies of the IgA class against the NC16A domain in all tested serum samples (and in 2 of 3 cases also using ELISA). IgA deposits could be demonstrated by direct IF in 2 of these patients, and circulating IgA autoantibodies against the BMZ were found in the other patient. These findings further raise the question about the relationship between BP and linear IgA bullous dermatosis, the most common autoimmune blistering disorder in children. It was shown in a previous study²⁰ that patients with BP and those with linear IgA bullous dermatosis have a dual IgG and IgA autoimmune response to BP180. Kromminga et al²⁰ found that patients with BP had IgG (81%) and IgA (65%) autoantibodies against NC16A, and that linear IgA bullous dermatosis serum samples also had IgG (32%) and IgA (16%) autoantibodies against this domain. However, we believe that our patients had BP rather than linear IgA bullous dermatosis because the clinical course, histologic and immunological studies (predominant deposits were linear IgG and C3 in all 3 cases on immunofluorescence), and response to corticosteroids (1 of them after failing therapy with dapsons) all support a diagnosis of BP. The predominance of an IgA-mediated autoimmune response in children with bullous diseases (in contrast to the IgG response that is predominant in adults) may be due to the fact that an IgA autoimmune response might be generally more prevalent in this age group because of an immunological immaturity or because of more frequent exposure to infectious agents and/or vaccines. Interestingly, both adult and childhood BP have been reported in association with vaccination.²¹⁻²³ And those findings could also be explained by the "epitope spreading phenomenon."²⁴ In this phenomenon, the primary disease, such as ordinary BP, exposes the BMZ to the immune system, which responds by producing an array of autoantibodies against proteins of the exposed BMZ without being pathogenetic themselves.

In summary, we have reported herein the cases of 4 infants with the characteristic clinical, histopathological, and immunological features of childhood BP. All of them had blisters predominantly on their hands and feet, without residual scarring. Although mucosal

lesions seem to be more frequent in children, none of our patients presented with them. All of them were younger than 1 year, and complete remission was quickly achieved with treatment with oral prednisolone in less than 6 months, with no recurrences during follow-up. Autoantibodies both of the IgA and IgG class to the NC16A domain of BP180 were demonstrated in these patients.

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ARCHIVES Web Quiz Winner

Congratulations to the winner of our November quiz, Johann E Gudjonsson, MD, PhD, Department of Dermatology, University of Michigan. The correct answer to our November challenge was *hypopigmented sarcoid*. For a complete discussion of this case, see the Off-Center Fold section in the December ARCHIVES (Verma S, Patterson JW, Derdeyn AS, Pasale R, Patel D, Ganju A. Hypopigmented macules in an Indian man. *Arch Dermatol.* 2006;142:1643-1648).

Be sure to visit the *Archives of Dermatology* Web site (<http://www.archdermatol.com>) to try your hand at the interactive quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month's print edition of the ARCHIVES. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also receive a free copy of *The Art of JAMA II*.