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REVIEW ARTICLE

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Bullous pemphigoid in adolescence

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Abstract

Bullous pemphigoid (BP) is the most common autoimmune blistering disease affecting the elderly but is quite rare in childhood. The majority of pediatric cases have been reported during early childhood. Adolescence is divided into three phases: early (10-13 years), middle (14-17), and late (18-21). This review aimed to identify BP cases in adolescence and demonstrate their clinical features and course. Our literature search was performed in Medline with the terms "bullous pemphigoid in childhood and adolescence," "childhood bullous pemphigoid," "juvenile bullous pemphigoid," and "autoimmune blistering and autoimmune bullous diseases in childhood." The data extraction for late adolescence was limited by the fact that this age group is included in adult BP registries. We identified nine cases in early adolescence. Mucosa were affected in 5 of 9 cases. Treatment consisted of systemic prednisone (8/9), in combination with dapsone (2/9), azathioprine (2/9), or erythromycin/nicotinamide (1/9). Relapses were reported in 3 of 9 cases. We identified five cases occuring in middle adolescence. Mucosa were not affected. Treatment consisted of systemic prednisone (5/5), in combination with dapsone (3/5), azathioprine (2/5), doxycycline/nicotinamide (1/5), or mycophenolate mofetil (1/5). Relapses were reported in two of five cases. No case of BP in the late adolescence was included in the results, as only one case met the search criteria, and overlapped with pemphigus vulgaris. With only 14 cases found in our review, BP in adolescence appears even rarer than in earlier childhood. Despite its low prevalence, BP should be included in the differential diagnosis of autoimmune blistering diseases in adolescents.

KEYWORDS
adolescence, bullous pemphigoid, childhood, juvenile

1 | INTRODUCTION

Bullous pemphigoid (BP) is the most common among the autoimmune blistering diseases affecting the elderly but is quite rare in childhood.[1,2] The most recently published review on this topic included approximately 100 cases in the literature, most present during early childhood.[2] This review aimed to identify BP cases in adolescence and demonstrate their clinical features and course.

2 | DEFINITIONS

Adolescence is a hormonally driven period of development during which physiologic, cognitive, and psychosocial functioning changes foster the transition from childhood to adulthood. It is divided into three phases: early (10-13 years of age), middle (14-17), and late adolescence (18-21).[3] All published data were reviewed according to these phases of adolescence.

TABLE 1 Cases of bullous pemphigoid in (A) early adolescence (B) middle adolescence

Case	First Author/Year	Age	Sex	Skin lesions	Mucosal lesions	Histological	DIF	IIF/ELISA[a]	Treatment	Course
(A)										
1	Bean, 1970[5]	11 y	M	Generalized bullous eruption	Erosions in mucosa	Subepidermal blister with abundant eosinophils	–	IgG linear BMZ 1:1280	Prednisone, azathioprine	>3 y, multiple relapses
2	Jablonska, 1971[6]	13 y	NA	Generalized bullous eruption			IgG linear BMZ	IgG, linear BMZ 1:320	Prednisone	
3	Esterly, 1973[7]	12 y	F	Generalized bullous eruption	Oral mucosa involvement	Subepidermal blister with moderate number of eosinophils	IgG,β1 C linear BMZ	IgG linear BMZ 1:1280	Prednisone, azathioprine	Poor disease control Died in 7 mo
4	Skeete,1976[8]	12 y	F	Generalized bullous eruption			IgG,C3 linear BMZ (IgM, weak)	IgG, linear BMZ 1:320	Prednisone	
5	Oranje, 1991[9]	12 y	F	Bullae in the vulvar area	Erosions of the genitalia	Subepidermal blister with small number of eosinophils	IgG,C3 linear BMZ (IgM, IgA weak)	neg	Dapsone, erythromycin with niacinamide	2 y, no relapse
6	Gajic-Veljic, 2010[10]	12 y	F	Generalized bullous eruption	Oral mucosa involvement	Subepidermal blisters, hydropic degeneration of basal keratinocytes, mixed infiltrate with eosinophils and neutrophils	Linear IgG BMZ	IgG linear BMZ 1:40	Prednisone	Response in 1 mo, no relapse for 12 y
7	Gajic-Veljic, 2010[10]	13 y	F	Generalized bullous eruption	Oral mucosa involvement	Subepidermal blisters, hydropic degeneration of basal keratinocytes, mixed infiltrate with eosinophils and neutrophils	IgG,C3 linear BMZ (IgM, IgA weak)	IgG linear BMZ 1:160	Steroids and dapsone	Response in 2 wks; remission 8 y
8	Das, 2014[11]	11 y	M	Extremely pruritic papulonodular lesions over bilateral shins, dorsum of feet, and nape of the neck		Subepidermal cleft with neutrophilic infiltration within the upper dermis	linear deposition of IgG and IgM along BMZ		Prednisone	
9	Muller, 2015[12]	13 y	F	Perioral and palmoplantar lesions		Subepidermal blister with abundant eosinophils	IgG,C3 linear BMZ epidermal side on salt split skin	Anti BP180 neg, anti BP230 neg	Prednisone	Relapse 2 y later

(Continues)

TABLE 1 (Continued)

Case	First Author/Year	Age	Sex	Skin lesions	Mucosal lesions	Histological	DIF	IIF/ELISA[a]	Treatment	Course
(B)										
1	Ratnavel, 1994[13]	15 y	M	Widespread, pruritic. bullous eruption on the trunk and limbs	No	Subepidermal blister with a mild infiltrate in the dermis	IgG, C3 linear BMZ	neg	Prednisone, dapsone, azathioprine	Relapse 18 mo after the initial control of the disease
2	Fox, 2010[14]	16 y	F	Generalized bullous eruption	No	Subepidermal blister with abundant number of eosinophils	IgG, C3 linear BMZ	IgG linear BMZ	Prednisone, Mucophenolate Mofetil	No relapse
3	Gajic-Veljic, 2010[10]	17 y	F	Periocular blistering, annular bullous lesions on trunk and limbs	No	Subepidermal blister, papillary microabscesses with neutrophils and eosinophils, mixed perivascular infiltrate	IgG and C3c Linear BMZ IgA weak	IgG linear BMZ 1:80	Steroids, 6 mo	Response in 2 wks; lost to follow-up after 6 mo
4	Aakhus, 2012[15]	15 y	M	Bullous lesions on the extensor arms, legs, and trunk	No	Subepidermal vesicle with festooning papillary dermis and underlying mild perivascular lymphohistiocytic infiltrate	Focal Linear BMZ IgG, C3 /Salt split skin epidermal side	Circulating IgG against soluble BP180 ectodomain	Prednisone, dapsone, azathioprine	Relapses
5	Kong, 2015[2]	17 y	M	Face, trunk, and upper/lower extremities	No	Subepidermal blister with eosinophils	C3 and IgG along BMZ	IgG linear BMZ, 1:40, roof pattern	Prednisone, dapsone, Doxycycline/niacinamide	Remission

[a]IFF/ELISA = indirect immunofluorescence/enzyme-linked immunosorbent assay

Childhood BP is diagnosed according to the criteria of Nemeth:[4] (a) patients 18 years of age or younger with the clinical appearance of tense bullae on erythematous or nonerythematous skin with or without mucosal involvement and routine histopathologic study showing subepidermal bulla formation with a variable number of eosinophils; and, more importantly, (b) direct immunofluorescence showing linear deposition of IgG and/or C3 as at the basement membrane zone (BMZ) and/or a positive indirect immunofluorescence showing IgG linear deposition at the BMZ.

3 | METHODS

Our literature search was performed in Medline with the search terms "bullous pemphigoid in childhood and adolescence," "childhood bullous pemphigoid," "juvenile bullous pemphigoid," and "autoimmune blistering and autoimmune bullous diseases in childhood."

Selection criteria among the published cases were age range 11-21 years and establishment of a diagnosis of BP according to the Nemeth criteria. We extracted data regarding the age, sex, skin and mucosal involvement, histology, immunofluorescence findings, enzyme-linked immunosorbent assay (ELISA) or Western blot, systemic treatment regimens, and disease course. (Table 1A,B) The data extraction for late adolescence (18-21) was limited by the fact that this age group is included in adult BP registries, and consequently only case reports including the terms "juvenile" or "adolescent" were reviewed.

4 | RESULTS

In early adolescence, we identified nine BP cases (six women, two men; in one, sex was not reported).[5-12] Mucosa were affected in 5 of 9 cases. Treatment consisted of systemic prednisone (8/9), in combination with dapsone (2/9), azathioprine (2/9), or erythromycin/nicotinamide (1/9). Relapses were reported in 3 of 9 cases (Table 1A).

In middle adolescence, we identified five BP cases (3 men, 2 women).[2,10,13,14,15] Mucosa were not affected. Treatment consisted of systemic prednisone (5/5), in combination with dapsone (3/5), azathioprine (2/5), doxycycline/nicotinamide (1/5), or mycophenolate mofetil (1/5). Relapses were reported in 2 of 5 cases (Table 1B).

The late adolescence age group was not included in the results because only one case was found to meet our search criteria, and it was an overlap case with pemphigus vulgaris.[16]

5 | DISCUSSION

The childhood form of bullous pemphigoid was first described as an entity distinct from pemphigus vulgaris by Lever in 1953.[17] Before 1970, almost all cases of acquired blistering diseases in children were reported as chronic bullous disease of childhood or juvenile dermatitis herpetiformis. Immunofluorescence techniques revolutionized the diagnosis of autoimmune bullous diseases (AIBD), and subepidermal AIBD (of the "pemphigoid" spectrum of diseases) was more reliably classified. For instance, before that time cases of epidermolysis bullosa acquisita were called BP and BP was called dermatitis herpetiformis. Many diagnoses changed by immunofluorescence studies.[6]

The first case of bullous pemphigoid in childhood, in an 11-year-old, was diagnosed by immunofluorescence findings by Bean et al in 1970.[5] Since then, 8 cases of BP *in early adolescence* have been described (Table 1). The clinical features of BP in this age range include a pruritic generalized bullous eruption, similar to the adult BP, with frequent involvement of the oral mucosa. One of the 9 cases reported was diagnosed as localized BP of the perineum.[9]

In 1994, Ratnavel et al described the first case of BP in middle adolescence, in a 15-year-old boy.[13] It was also the first case of pemphigoid nodularis described before adulthood. The clinical features in the 5 cases reported of BP in middle adolescence were similar to that seen with the adult BP, with disseminated tense blisters and erosions and no mucosal involvement.

Even though the treatment of choice was systemic steroids in 13 of 14 cases, all authors agree that the management plan should be the least aggressive possible and suggest the addition of immunomodulating agents such as dapsone, azathioprine, mycophenolate mofetil, or doxycycline/niacinamide.

The course of BP in adolescence seems favorable, with long remission after disease control. The analysis of nationwide inpatient sample data of children with AIBD in the United States, from 2002 to 2012 revealed that children at the age group 12-17 had significantly fewer hospitalizations in comparison with children with pemphigus or other AIBD.[18]

In conclusion, bullous pemphigoid in adolescence, with only 14 published cases, is even rarer than in childhood. The diagnosis of BP in childhood and adolescence should include salt-split skin in all cases, and the detection of circulating antiBP180 and anti-BP230 autoantibodies by ELISA tests, not routinely done for this diagnosis. Despite the low incidence, bullous pemphigoid should be included in the differential diagnosis of autoimmune blistering diseases in adolescents.

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