Immunobullous Diseases in Thai Children : Report of 24 Cases

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Abstract

Background : Acquired immunobullous diseases in children are very rare and difficult to distinguish clinically.

Objective : To study the clinical manifestations, immunopathologic features, treatment and outcome of immunobullous diseases in Thai children.

Material and Method : The authors reviewed 24 cases of immunobullous diseases in children under 18 years at Queen Sirikit National Institute of Child Health from 1983 to 2000. Diagnosis of all cases was made by clinical presentations of chronic blistering diseases and confirmed by histopathology and immunofluorescent studies.

Results : There were 18 cases of chronic bullous diseases of childhood (CBDC), 4 cases of bullous pemphigoid (BP) and 2 cases of pemphigus vulgaris (PV). The mean age of onset of CBDC and BP were 4 years and 2 years respectively. There was an equal male to female ratio in both CBDC and BP. Both cases of pemphigus (neonate and 4 years old) were female. Most CBDC patients (18 cases) responded well to dapsone therapy although 2 cases had to be treated with prednisolone simultaneously. All cases with BP were treated successfully with prednisolone and dapsone. Neonatal pemphigus was treated symptomatically without steroid therapy. The second case of oral pemphigus was controlled with low dose prednisolone.

Conclusion : Immunobullous diseases are very rare in children. All patients improved with corticosteroid and/or dapsone therapy.

Key word : Immunobullous, Children

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Acquired immunobullous diseases in children are very rare and difficult to distinguish clinically[1-3]. The diseases that have been reported in childhood include chronic bullous dermatoses of childhood (CBDC), dermatitis herpetiformis (DH), bullous pemphigoid (BP), pemphigus vulgaris (PV) cicatricial pemphigoid (CP) and epidermolysis bullosa acquista (EBA)[1-3]. CBDC, DH and BP may have similar clinical and histologic features. Direct and indirect immunofluorescense studies are essential to establish the diagnosis[4].

Several articles have described the various clinical manifestations, treatments and outcome of immunobullous diseases[5-9]. However, there are few reports of a large series of immunobullous diseases in children[3,9].

The present report includes the clinical manifestations, immunopathologic features, treatment and outcome of immunobullous diseases in a series of 24 children at Queen Sirikit National of Child Health, Bangkok, Thailand.

MATERIAL AND METHOD

A retrospective study was conducted from the medical records of patients diagnosed with immunobullous diseases (CBDC, BP, DH, PV, CP, EBA) in children under 18 years at Queen Sirikit National Institute of Child Health from 1983 to 2000. Diagnosis of all cases was made by clinical presentations of chronic non-hereditary blistering diseases and confirmed by histopathologic and immunofluorescense studies.

Skin biopsies from the perilesional area of blisters were taken in all cases. The histopathology and standard immunofluorescense techniques were used to detect IgA, IgG, IgM, C3 and fibrin. Indiect immunofluorescent examination for IgG antibody was performed with the use of normal human skin and rabbit esophagus as substrate.

Age at onset prior to diagnosis, clinical presentations, histopathology, immunopathology, treatment and outcome were reviewed.

RESULTS

Twenty-four cases were diagnosed as immunobullous diseases at Queen Sirikit National Institute of Child Health over an 18-year period. Of these patients,18 cases had CBDC, 4 cases had bullous pemphigoid, 2 cases had pemphigus and none had dermatitis herpetiformis nor cicatricial pemphigoid nor epidermolysis bullosa equista.

Chronic bullous dermatosis of childhood (Table 1)

The CBDC patients composed 8 boys and 8 girls. The age of onset of CBDC varied from 1 year to 11 years and the mean age of onset was 4.8 ± 2.2 years. Most of the CBDC patients were healthy except 2 cases, one case of retinoblastoma (case 1) and another case of neurogenic bladder (case 3).

The duration of the disease before diagnosis varied from 1 week to 1 year with a mean duration of 7.3 weeks. All patients complained of pruritus. The onset was abrupt with clear tense vesicles and bullae on erythematous or normal skin (Fig. 1). The eruption was generalized in all cases and 3 cases had facial involvement. There was no perioral or mucosal involvement in all cases. The characteristic "rosette formations" were seen in 3 cases (17%) (Fig. 2). Staphylococcal aureus was found as secondary bacterial infection in 5 cases (31%).

Histologically, 11 patients (69%) showed subepidermal bullae containing neutrophils, some eosinophils and some lymphocytes. Two patients had neutrophilic papillitis and 3 cases (17%) showed subepidermal bullae and neutrophilic papillitis. The histopathologic findings were unremarkable in another 2 cases. (case 4, case 13)

Direct immunofluorescence findings in all cases showed linear IgA deposits along the basement membrane. Both IgG and Ig A were demonstrated on the basement membrane in three cases (case 8, case 13 and case 18) but the immunofluorescent studies were negative for circulating IgG.

Indirect immunoflorescent studies were not performed in all cases. IgG antibodies were performed in cases that had both IgG and IgA and the results were negative.

All patients were treated initially with dapsone at the dose of 1-2 mg/kg/day. Most of the cases responded with dapsone therapy within 1-2 months. The duration of treatment varied from 1 month to 2 years. Most of the patients responded to treatment rapidly. Two patients (case 3 and case 16) developed hepatitis from dapsone therapy which resolved when dapsone was stopped. Ten cases were followed-up from 1 year to 5 years and there were no new lesions. Another six cases were lost to follow-up. Prednisolone therapy was added in two cases (case 17 and case

Table 1. Summary of 18 patients with chronic bullous dermatosis of childhood.

Patient no	Sex	Age at onset (years)	Duration before diagnosis	Histopathology	DIF	Indirect	Pus culture	Treatment	Duration	Follow-up
1	F	6	5 months	DH-like	IgA, IgM, C3, F	ND	S.aureus	DDS + Sulfa	1 month	1 year
2	F	10	1 week	DH-like, SB	IgA	ND	NG	DDS	5 months	1 year
3	F	3	2 months	SB	IgA, IgM	ND	NG	DDS	3 months	1 year
4	M	3	12 months	NS	IgA	ND	Gr.A Streptococci	DDS	3 months	5 months
5	M	5	10 months	DH-like	IgA	ND	NG	DDS	1 month	Lost follow-up
6	F	9	1 week	SB	IgA	ND	S.aureus	DDS	2 months	Lost follow-up
7	M	2.7	2 weeks	SB	IgA, C3	ND	NG	DDS	2 months	3 years
8	F	7	1 week	SB	IgG, IgA, IgM, C3	ND	Klebsiella	DDS	4 months	3 years
9	F	3	1 week	SB	IgA	ND	NG	DDS	2 months	Lost follow-up
10	M	1	1 month	SB	IgA,Ig M	ND	NG	DDS	1 month	Lost follow-up
11	M	5.6	2 weeks	SB	IgA	ND	NG	DDS	1 month	5 years
12	M	10	2 weeks	SB	IgA	ND	NG	DDS	3 months	Lost follow-up
13	M	3.4	1 month	NS	IgA,IgG,C3	ND	NG	DDS	2 months	Lost follow-up
14	F	1	1 week	SB	IgA	ND	NG	DDS	2 months	2 years
15	F	1	2 weeks	SB	IgA	ND	S.aureus	DDS + cloxacillin	2 months	Lost follow-up
16	M	1.8	1 month	SB	IgA	ND	NG	DDS	2 months	Hepatitis
17	F	6	2 months	SB, DH-like	IgA	ND	S.aureus	DDS + PDN	2 years	2 years
18	M	7.7	3 weeks	SB, DH-like	IgA,IgG,C3	ND	NG	DDS + PDN	3 months	Lost follow-up

M = male ,F = female, DIF = direct immunofluorescense, DH = dermatitis herpetiformis-like,
SB = subepidrmal bulla, NS = not significant, ND = Not done, NG = no growth, DDS = dapsone, PDN = Prednisolone

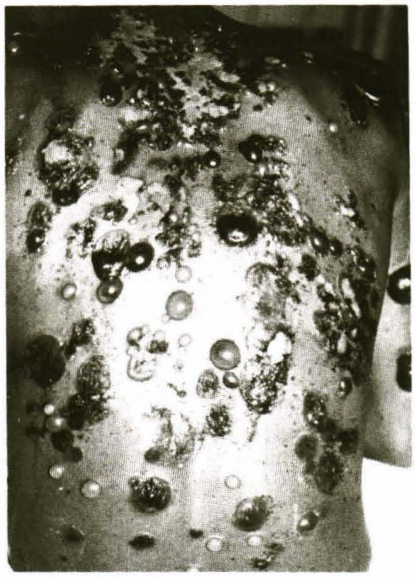

Fig. 1. CBDC: Widespread large tense bulla and crusted lesions on the back.

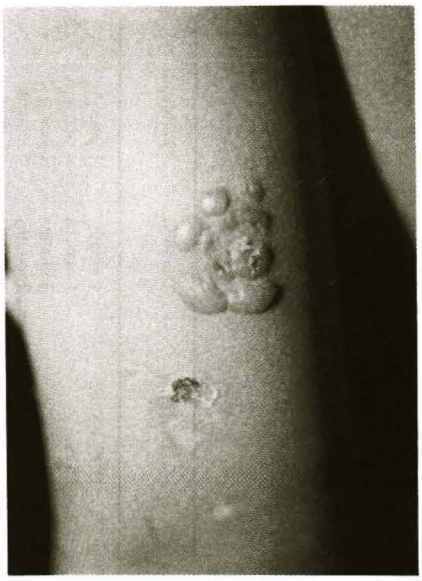

Fig. 2. Rosette pattern in a CBDC patient.

18) because the patients did not respond to dapsone therapy.

Bullous pemphigoid (Table 2)

Clinical manifestations of four BP patients were widespread tense vesicobullous eruptions similar to the CBDC patients except all the patients had oral mucosal involvement and 2 cases with palms and soles involvement (Fig. 3). The mean age of onset of the BP patients was 2 years which was younger than the CBDC patients, 3 cases of which were under 1 year, only one case had onset at 8 years.

Histopathology of all four BP patients revealed subepidermal bullae with inflammatory cells in all cases. DIF showed linear IgG in all cases. Indirect immunofluorescense showed circulating IgG in 2 cases. Two BP patients were treated with prednisolone with good outcome. Dapsone and prednisolone were given in another 2 cases. Duration of treatment varied from 1 month to 1 year. Spontaneous remission was found in 3 cases and 1 case was lost to follow-up.

Pemphigus vulgaris (Table 3)

There were two cases of pemphigus vulgaris. The first case was a female neonate, born to a 32 year-old-mother who had pemphigus vulgaris during pregnancy (Fig. 4). Her mother had circulating IgG in the titer of 1 : 80 and was treated with prednisolone at the dose of 40 mg per day. The baby was born with generalised flaccid bulla on the upper chest, trunk, back and extremities (Fig. 5). Skin biopsy for histopathology was unremarkable. Direct immunofluorescense was positive for intercellular IgG. Circulating PV antibody of the baby was positive 1 : 10. The baby was treated with cloxacillin and gentamicin for 10 days. The bulla improved in 2 weeks and disappeared in 1 month without corticosteroid therapy.

The second case of PV was a 4-year-old girl who had recurrent multiple painful oral ulcers since she was 2 years old. Physical examination revealed multiple erosions on buccal mucosa. Other physical examinations were unremarkable. Skin biopsy from the ulcer revealed suprabasal separation with acantholytic cells compatible with pemphigus vulgaris. Direct immunofluorescense revealed IgG and C3 at the intercellular space but indirect immunofluorescense was negative. She was treated with a low dose of prednisolone 0.5 mg/kg/day for 2 years until now and the oral lesions have improved.

DISCUSSION

Immunobullous diseases of children are uncommon, detected in only 24 patients over a 17 year

Table 2. Summary of 4 patients with bullous pemphigoid.

Patient no	Sex	Age at onset	Duration before diagnosis	Mucosa	Histopathology	DIF	Indirect	Pus culture	Treatment	Duration	Follow-up
1	F	2 months	1 week	+	SB	IgG	Neg	NG	PDN	2 months	1 year
2	M	3 months	1 month	+	SB	IgG, C_3	IgG 1:10	S.aureus	PDN	1 month	1 year
3	F	6 months	2 weeks	+	SB	IgG, C_3, F	IgG 1: 640	NG	DDS + PDN	1 year	4 years
4	M	8 years	4 months	+	SB	IgG, C_3, F	ND	S.aureus	DDS + PDN	4 months	loss follow-up

Table 3. Summary of 2 patients with pemphigus vulgaris.

Patient no	Sex	Age at onset	Duration before diagnosis	Mucosa	Histopathology	DIF	Indirect	Pus culture	Treatment	Duration	Follow-up
1	F	newborn	since birth	-	NS	IgG intercellular	1:10	S.aureus	Cloxacillin	2 weeks	Remission in 1 month
2	F	2.5 years	3 months	+	PV	IgG intercellular	Neg	NG	PDN	3 years	Until now

Fig. 3. Bulla on the sole of the BP patient.

period. The most frequently observed diseases were CBDC in 18 patients, BP in 4 patients and two pemphigus patients. The present study was different from other studies in Caucasians with no cases of DH[3,5,9]. Clinical diagnosis of immunobullous disease in children is difficult. Except from PV, both CBDC, DH and BP had multiple widespread tense bullae on the trunk and extremities. However, oral mucous membrane and lesions on the palms and soles were more common in BP than in CBDC[10-12]. In the present study the authors found no mucous membrane nor palms and soles involvement in all the CBDC patients.

For the definite diagnosis of immunobullous diseases, histology, direct immunofluorescence and a serum for indirect immunofluorescence should be obtained in all cases[1-4]. Pemphigus can be distinguished from other bullous diseases on histology of intraepidermal bulla and confirmed by IgG intercellular and circulating IgG antibodies. The remaining bullous diseases are all characterized by histologically of subepidermal bullae. Therefore, direct immunofluorescense is essential for the diagnosis of CBDC and BP[1-3].

CBDC is characterized by linear IgA at the basement membrane and BP by linear deposit of IgG and complement along the basement membrane. In BP, circulating IgG antibodies can be detected in 70 per cent of cases[12].

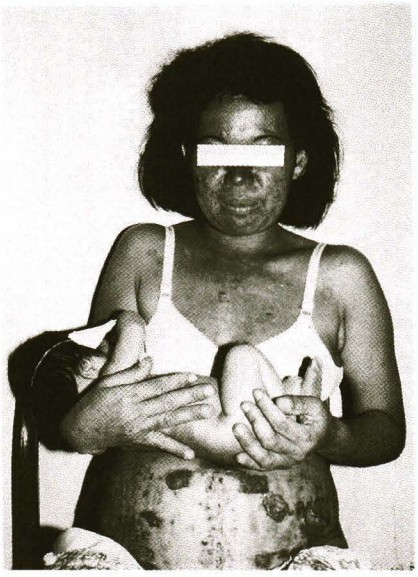

Fig. 4. Maternal pemphigus and the neonatal pemphigus.

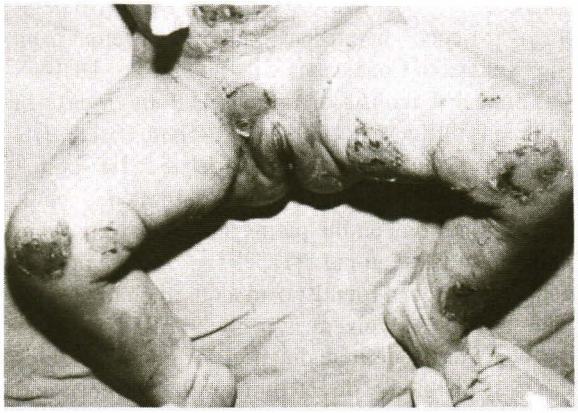

Fig. 5. Neonatal pemphigus vulgaris.

In the present study all cases showed typical immunofuorescense findings of immunobullous diseases.

Drugs for the treatment of CBDC patients are dapsone, sulfapyridine and corticosteroids[13-15]. Dapsone is the first line and is safe and effective in the management of CBDC. The mechanism of dapsone is to inhibit PMN chemotaxis. Most of the CBDC patients responded well to dapsone therapy. Dicloxacillin and colchicine have been reported for the treatment of CBDC patients refractory to dapsone or sulfapyridine[14]. The course of CBDC patients is benign and self limiting[16]. In the present study, 14/16 cases (89%) responded to dapsone therapy. Prednisolone was added in only 2 cases of CBDC because they were unresponsive to dapsone. Spontaneous remission occurred from 1 to 3 years after treatment.

BP is more difficult to treat than CBDC. Prednisolone is the first line of treatment[17-24]. The authors also found spontaneous remission in two infants with BP patients.

Pemphigus vulgaris is rare in children and neonatal pemphigus is very rare, only a few cases have been reported[25-29]. Neonatal pemphigus is caused by passive placental transfer of maternal IgG antibodies to the fetus. Affected infants are often noted at birth to have blisters and erosions. Neonatal pemphigus usually resolves within 3 weeks as the maternal antibodies are cleared from the baby[29]. Treatment is only topical skin care. The presented case of neonatal PV, born from a pemphigus mother was treated symptomatically without steroid therapy.

Oral pemphigus is not common in children. Symptoms are burning and pain. Mucosal lesions often preceede cutaneous lesions[30]. Treatment of oral pemphigus is topical corticosteroid gel. If the patients does not respond to topical treatment, systemic steroid should be given. The presented case of oral pemphigus was controlled by low dose prednisolone. The course and prognosis of pemphigus vulgaris is variable and can be fatal[31]. Early diagnosis and vigorous therapy are essential toward better prognosis.

SUMMARY

In summary, 24 cases of immunobullous diseases in Thai children were reported. Clinical presentations were chronic blistering diseases. The diagnosis was confirmed in all cases by histopathological and immunofuorescense study. Dapsone and/or corticosteroids were the mainstay therapy of immunobullous disease in children.

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โรคตุ่มน้ำอิมมูนในเด็กไทย : รายงานผู้ป่วย 24 ราย

ศรีศุภลักษณ์ สิงคาลวณิช, พบ, วนิดา ลิ้มพงษานุรักษ์, พบ**

ความเป็นมา : โรคตุ่มน้ำอิมมูนเป็นโรคผิวหนังที่พบไม่บ่อยในเด็ก อาการทางคลินิกของแต่ละโรคแยกจากกันได้ยาก ต้องอาศัยผลทางพยาธิอิมมูน

วัตถุประสงค์ : เพื่อศึกษาลักษณะทางคลินิก ผลการตรวจทางพยาธิวิทยา การตรวจอิมมูนวิทยา การรักษาและการดำเนินโรคของโรคตุ่มน้ำอิมมูนในเด็ก

วิธีการศึกษา : ศึกษาข้อมูลย้อนหลังจากเวชระเบียนผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็นโรคตุ่มน้ำอิมมูนที่มารับการรักษาที่สถาบันสุขภาพเด็กแห่งชาติมหาราชินีตั้งแต่ปี พ.ศ. 2526-2543 โดยทุกรายได้รับการตรวจทางพยาธิวิทยา การตรวจอิมมูน-วิทยา

ผลการศึกษา : มีผู้ป่วยทั้งหมด 24 รายแบ่งเป็น chronic bullous dermatosis of childhood (CBDC) 18 ราย, bullous pemphigoid (BP) 4 รายและ pemphigus vulgaris (PV) 2 ราย อาการแสดงของ CBDC ได้แก่ตุ่มน้ำเรื้อรังซึ่งแยกไม่ได้จาก BP อายุเฉลี่ยของ CBDCและ BPเท่ากับ 5 ปีและ 2 ปี ตามลำดับ อัตราส่วนเพศชายเท่ากับเพศหญิง การรักษาผู้ป่วย CBDC ส่วนใหญ่ 18 รายตอบสนองดีต่อ dapsone อีก 2 รายต้องให้ยา prednisolone ผู้ป่วย BP 4 รายรักษาด้วย prednisolone ร่วมกับ dapsone ผู้ป่วย PV รายแรกอายุ 4 ปีมีแผลเรื้อรังในปาก ผลการตรวจทางอิมมูนเข้าได้กับ pemphigus vulgaris ผู้ป่วยตอบสนองดีต่อ prednisolone รายที่ 2 เป็นทารกแรกเกิดซึ่งมารดาป็น pemphigus vulgaris ขณะตั้งครรภ์แรกเกิดมีตุ่มน้ำทั่วตัว รักษาตามอาการ ตุ่มน้ำหายไปเองโดยไม่ต้องให้ prednisolone

สรุป : โรคตุ่มน้ำอิมมูโนเป็นโรคผิวหนังที่พบไม่บ่อยในเด็ก ผู้ป่วยส่วนใหญ่ตอบสนองดีต่อการรักษาด้วย cortico-steroids และ/หรือ dapsone

คำสำคัญ : โรคตุ่มน้ำอิมมูน, เด็กไทย

ศรีศุภลักษณ์ สิงคาลวณิช, วนิดา ลิ้มพงษานุรักษ์
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