Linear IgA Bullous Dermatosis of Childhood: A Long Term Study

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Abstract

Background: Linear IgA bullous dermatosis (LAD) of childhood is a rare acquired subepidermal blistering disease of young children. Most of the studies were reported from the USA and European countries.

Method: Twelve cases of Thai patients diagnosed as LAD of childhood were analyzed concerning clinical, histopathological, immunopathological findings including treatment responses and courses compared with those of Caucasians.

Result: The mean age of onset was 5.1 years. The areas of common involvement were the perioral region, lower abdomen, perineum, buttock, inner thighs and extremities. Histopathology in half of the cases showed features of dermatitis herpetiformis or bullous pemphigoid. All patients had positive linear IgA band at the basement membrane zone (BMZ) by direct immunofluorescence. Only one patient had positive circulating anti BMZ antibody at the titer of 1:10. Most patients responded well to dapsone. The mean duration before remission was 1.9 years.

Conclusion: Our study in Thai patients with LAD of childhood produced data similar to previous studies carried out in the Caucasian nations.

Key word : Linear IgA, Bullous Dermatosis, Childhood

Linear IgA bullous dermatosis (LAD) of childhood or the old term "Chronic bullous dermatosis of childhood" (CBDC) is a rare acquired subepidermal blistering disease of young children. The disease is characterized by immunofluorescence finding of linear IgA band at the epidermal basement membrane by DIF[1,2]. Clinically large tense and often clustered bullae develop chiefly on the lower abdomen, perineum, lower extremities and perioral region. Patients with this disease have a

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markedly increased frequency of HLA B8 haplotype[3]. Other HLA associated were HLA Cw7 and -DR3[4]. There are reports of the immunogenetic difference between Oriental and Caucasian races resulting in differences in clinical presentation and frequency of autoantibodies detected in some autoimmune diseases[5,6].

The purpose of this study was to analyze clinical, histological, immunopathological findings including treatment responses and courses of LAD in Thai patients compared with those of Caucasians.

PATIENTS AND METHOD

Twelve cases diagnosed as LAD of childhood at the Institute of Dermatology between the years 1984-1990 were included in the study. Patients were considered to have the disease if the onset occurred before the age of 16 and clinically defined as having a chronic tense vesiculo-bullous eruption predominantly affecting perioral and pelvic regions[3].

Skin biopsies from the perilesional area were obtained for routine histopathologic and direct immunofluorescent (DIF) studies. A standard DIF technique was performed as previously described (Beutner et al, 1973). Briefly, tissues were embedded in OCT compound (Tissue-Tek, Mile Inc) and snapped frozen at - 70°C . Four micron frozen sections were cut on a cryostat and incubated for 30 minutes with fluorescein isothiocyanate-conjugated rabbit anti-human IgG, IgA, IgM, C3 and fibrinogen (DAKO). All conjugates were diluted to 1:20 with phosphate buffer saline (PBS). Negative control sections from healthy individuals and positive control sections of known LAD were run together with the tested specimens. Immunofluorescent patterns were interpreted according to standard criteria[7].

Sera were examined by the standard indirect immunofluorescence technique (Beutner et al, 1973) using human skin as substrates. The serum dilutions were made in PBS beginning with 1:10.

All patients were then reviewed concerning their clinical presentation, treatment responses and clinical courses.

RESULTS:

Clinical findings:

Of 12 patients studied, 9 were boys and 3 were girls. The age of onset of the patients ranged from 1.1 year to 10 years, mean 5.1 years (Table 1). The onset was usually rather abrupt. Most of the patients had large clear tense bullae on normal skin with some bullae occurring on the erythematous base. Hemorrhagic bullae and urticarial wheals were occasionally seen (Table 2). Most of the patients had blisters on the perioral area, lower trunk, perineum, buttocks, inner thighs and also on the extremities (Table 3). Scalp involvement was seen in some cases with extensive involvement. No oral mucosal lesions were noted. Most, but not all, of the patients had pruritic symptoms of varying degrees. None had symptoms of malabsorption.

Histology findings:

All specimens showed subepidermal seperation. Four out of twelve specimens (33.3%) showed the features of dermatitis (DH) with prominent neutrophils and/or dermal papillary neutrophilic microabscesses. We did not observe the prominent infiltrative pattern of neutrophils in the basal vacuoles and tip of rete pegs. In two cases (16.7%) the histology revealed a resemblance to bullous pemphigoid (BP) with subepidermal vesicles containing numerous eosinophils. The other biopsies (50%) showed subepidermal bullae with no specific features or BP or DH.

Immunofluorescence findings:

All immunofluorescence studies were done while the diseases were active. A linear BMZ band of IgA was found in all cases. Two out of twelve cases also had a linear BMZ band of IgM and one case had a fibrin band at the BMZ in addition to a linear BMZ IgA band. A circulating IgA anti-BMZ antibody was present in the serum of one patient at the titer of 10.

Treatments and courses:

Dapsone (1-2 mg/kg/day) could control the disease in most cases. The drug initiated a rapid response usually within a few days. However, clearing of the lesions took 2 weeks or more. In seven patients, dapsone could control the eruption within 2 weeks after starting treatment. Partial control was achieved with dapsone (2 mg/kg/day) in four cases, requiring the addition of low dose of prednisolone (<0.5 mg/kg/day). Prednisolone alone was replaced in one case who developed fixed drug eruption due to Dapsone. This patient had widespread lesions and required a two months period until prednisolone could control the disease.

Table 1. The details of the patients studied.

Case	Sex	Age onset (years)	Duration (years)	Histo-pathology	DIF (linear BMZ)	IIF (Linear BMZ)		treat-ment	improve-ment (wks)	Remis-sion (yrs)
						IgA	IgG			
1	M	3	1	DH-L	IgA	-	-	DDS	2	NL, 6
2	F	5	0.75	DH-L	IgA	-	-	DDS	1	NL, 5
3	M	2.5	3.3	BP-L	IgA	1:10	-	DDS +pred	8	NL, 5
4	M	7	3.4	NS	IgA	-	-	DDS +pred	12	NL, 5
5	F	8	3.2	BP-L	IgA	-	-	pred +DDS*	8	NL til adult
6	M	3.5	1.3	NS	IgA, F	-	-	DDS	2	NL, 6
7	M	10	0.5	DH-L	IgA IgM	-	-	DDS	2	NL til adult
8	M	12	0.6	NS	IgA	-	-	DDS	2	NL til adult
9	M	5	3	NS	IgA	-	-	DDS	2	NL, 5
10	M	1.5	3	NS	IgA	-	-	DDS +pred	12	NL, 5
11	M	2.2	2	NS	IgA	-	-	DDS +pred	16	NL, 6
12	F	1	0.5	DH-L	IgA, IgM	-	-	DDS	2	NL, 6

N.B.; DH-L = dermatitis herpetiformis-like, BP-L = bullous pemphigoid-like, NS = susepidermal bullae with nonspecific infiltration in the dermis, DDS = dapsone, pred = prednisolone, NL = no lesion, * = The patient developed fixed drug eruption when they received dapsone, till adult = until 16 years old

Table 2. Signs and symptoms of the patients.

Signs and symptoms	No. of patients	%
Wheal	2/12	17
Vesicle, bullae		
Erythematous base	3/12	25
Normal skin base	12/12	100
Clear content	12/12	100
Hemorrhagic content	1/12	8
Cluster of jewels	12/12	100
Oral lesion	0/12	0
Pruritus	11/12	92

Table 3. Distribution of the lesions.

Location	No. of patients	%
Scalp	3/12	25
Perioral	11/12	92
Trunk	8/12	67
Perineum	9/12	75
Buttock	9/12	75
Inner thighs	11/12	92
Extremities	11/12	92

Duration of the diseases varied from 6 months to 3.4 years (mean 1.9 years). When stopping the medication during the courses, relapses of the diseases with a few blisters were noted in four cases and these cases required a longer duration of treatment. After three patients became adults, no recurrences were observed. The others were asymptomatic after 5 to 6 years' follow-up.

DISCUSSION

Our study revealed mean age of onset was 5.1 years with males outnumbering females in a ratio of 3:1. Compared with the English literature, patients with LAD of childhood usually develop the disease before the age of ten at a mean age of 4.5 years,[8,9] the male and female incidence is probably equal[3]. Clinical features and site of involvement in our patients were not different from reports from the U.S.A. and European countries[3,9]. Histopathology was suggestive (DH-like or BP-like) in about half of our cases. However, histopathology alone was difficult to distinguish between LAD of childhood and DH or BP. Smith et al[10] suggested

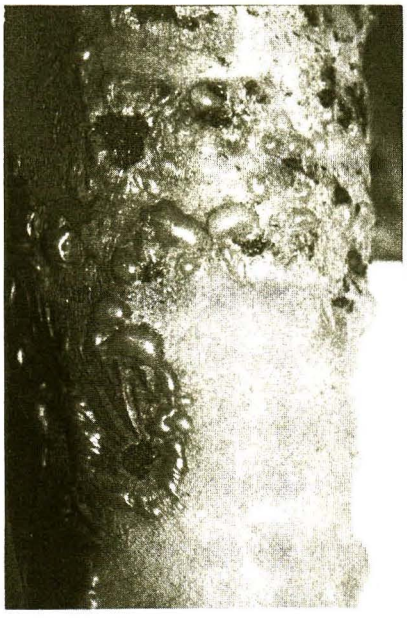

Fig. 1. Multiple tense bullae on the thigh of a patient with LAD shows the characteristic "cluster of jewels".

Fig. 2. Direct immunofluorescence study shows linear IgA staining at dermo-epidermal junction.

that diffuse infiltration with neutrophils in the basal vacuoles, along the basement membrane zone (BMZ) and involving the tip of the rete pegs favor LAD. The definite diagnosis is made by direct immunofluorescence (DIF) study, in which patients with DH show granular, not linear, IgA at the BMZ while patients with BP show linear IgG and IgA (not IgA alone) at the BMZ. All cases in our study showed a positive linear IgA band at the BMZ by DIF study that was a characteristic of this disease.

Only one of twelve cases had circulating IgA anti-BMZ antibody at the lower titer (1:10) (8%). Earlier studies showed only a few patients with circulating IgA anti-BMZ antibodies as detected by indirect immunofluorescence[1,9,11]. However, the recent study by Marsden et al[3] using human skin and rabbit esophagus as substrates demonstrated that twelve of sixteen tested sera of their patients had circulating IgA at low titer. However, a low serum dilution was used (five cases had circulating IgA at the titer lower than 10). In our laboratory, sera were tested at the beginning dilution of 1:10, and human skin was used as a substrate.

Treatment of our patients with dapsone resulted in control of the disease in most cases. The response was rapid, within a few days although lesions were clear in 2 weeks or more. For those patients who responsed partially with dapsone, adding prednisolone, in low doses brought about complete responses. Dapsone was contraindicated in one patient in which prednisolone alone could control the lesions. Because of the side effects of long term prednisolone treatment especially HPA-axis suppression, we suggest that prednisolone should not be used as the first line drug in this benign disease. Other treatment of LAD of childhood include sulphapyridine,[12] colchicine,[13] and dicloxacillin[14].

Mean duration of the disease that went into remission was 1.9 years in our study compared with 2 years as reported by Wojnarowska et al[8]. Our three cases had no recurrences as the patients have been followed through puberty. The others have had no recurrences after 5 to 6 years follow-up. In the literature, almost all patients went into remission before puberty but persisting lesions beyond puberty have been observed[15]. However, the symptoms became less severe with time.

Bhogal et al[16] studied the ultrastructural localization of IgA deposits in the skin of 15 patients with LAD of adults and 13 patients with LAD of

childhood. They reported that in all patients, the IgA was located predominantly at sublamina densa. Yamane et al[17] reported a girl with immunoelectron microscopic study which revealed deposition of IgA in the lamina lucida of the BMZ. Zone et al[18] reported that IgA antibodies in eight of twelve sera of LAD of childhood recognized 97 kDa BMZ antigen present on the epidermal side of BMZ split skin that co-migrated with the antigen previously identified in LAD of adults. Their findings suggest that LAD in children and in adults is an immunologically related disorder occurring in different age groups. By immunoblotting or immunoprecipitation, other BMZ proteins reported in LAD were 100, 145 kDa,[17] 230 kDa,[19] 255 kDa,[20] 285 kDa (or 250 kDa, using non-collagenous standard),[21] 290 kDa type VII collagen[22]. Recently, a novel protein called ladinin, which is associated with anchoring filaments, is known to have served as an autoantigen in LAD. The corresponding gene, LAD1, has been mapped to human chromosome 1[23].

In conclusion, our study of LAD of childhood in Thai patients revealed data similar to previous studies carried out in Caucasians. Even though we have not studied the HLA-linkage, we think that the genetic background will be similar.

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โรคตุ่มน้ำพองเรื้อรังในเด็กไทย

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คณะผู้วิจัยได้ทำการศึกษาลักษณะทางคลินิก พยาธิวิทยา พยาธิอิมมูนวิทยา การตอบสนองต่อการรักษา และการดำเนินโรคของผู้ป่วย 12 ราย ซึ่งได้รับการวินิจฉัยว่าเป็นโรค Linear IgA bullous dermatosis of childhood ที่สถาบันโรคผิวหนัง ตั้งแต่ปี พ.ศ. 2527-2533 พบว่าอายุเฉลี่ยของผู้ป่วยเมื่อเริ่มมีอาการ คือ 5.1 ปี ผู้ป่วยส่วนใหญ่มีตุ่มน้ำพองตึงขึ้นบนผิวหนังที่ดูปกติ และมีกลุ่มของตุ่มน้ำที่มีลักษณะเฉพาะที่เรียกว่า cluster of jewels บริเวณที่เกิดรอยโรคบ่อย คือ รอบปาก ลำตัวด้านล่าง รอบอวัยวะสืบพันธุ์ ก้น ต้นขาด้านใน การศึกษาพยาธิวิทยาของตุ่มน้ำมีลักษณะคล้าย dermatitis herpetiformis หรือ bullous pemphigoid ใน 50% ของผู้ป่วย การศึกษาพยาธิอิมมูนวิทยา พบว่าผู้ป่วยทุกรายมี IgA ติดที่บริเวณ basement membrane (BMZ) แบบเส้นตรง (linear pattern) ผู้ป่วย 1 ราย มีแอนตีบอดีชนิด IgA ต่อ BMZ ในเลือด ในระดับ 1:10 ผู้ป่วยส่วนใหญ่ตอบสนองดีต่อยา dapsone มีบางรายที่ต้องเพิ่ม prednisolone ในขนาดต่ำร่วมด้วย ระยะเวลาที่โรคเข้าสู่ภาวะสงบ คือ 1.9 ปี ผู้ป่วยที่เหลือหลังจากที่ติดตาม 5-6 ปี ไม่พบว่ามีผู้ป่วยรายใดกลับเป็นซ้ำ

คำสำคัญ : โรคตุ่มน้ำพอง, เด็กไทย

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