Linear IgA bullous dermatosis

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Introduction and AIMS

Short Definition in Layman Terms

Linear IgA bullous dermatosis (LABD) is an itchy blistering skin disease with grouped vesicles on erythematous patches caused by linear IgA depositions in the epidermal basement membrane zone (EBMZ).

LABD is characterized by exclusively IgA autoantibodies targeting components of EBMZ

Learning Objectives

After reading this chapter you will be familiar with the clinical presentation of LABD, you will be able setup a diagnostic algorithm, and to propose a therapeutic plan.

Case Study: Part 1

A 44-year old female presented with itchy erythematous plaques with tense blisters, erosions and crusts at the periphery, on the head, trunk and extremities. She developed erosions at the vaginal mucosa, but other mucosal surfaces were spared. Previous medical history reported primary Sjögren's syndrome and idiopathic hyperhidrosis. There was no medication previously administered.

Didactical Questions; Cross Section of Questions to Prime the Readers Interest

How can you diagnose LABD? What would you see in the histopathological section? How can you make de difference between LABD and other autoimmune bullous diseases? What is the drug of choice for LABD?

Facts and Figures

Definitions and Classification

LABD is a heterogeneous group of subepidermal autoimmune blistering diseases characterized by

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autoantibodies exclusively from the IgA class targeting different antigens of the EBMZ. According to age LABD can be divided in juvenile and adult forms, which differ slightly in their clinical presentations but share common immunopathological features.

According to the splitting there are two different forms of LABD. In the lamina lucida-type LABD the two most common antigens are the 120 kDa molecular mass LAD-1 antigen, and the 97 kDa molecular mass LABD antigen 1 (LABD97) with BP180 being recognized by a minor subset. Laminin 332 and p200 are rare autoantigens in lamina lucida-type LABD [1]. In the sublamina densa-type LABD, also called IgA epidermolysis bullosa acquisita (EBA), the splitting level is deeper and the target antigen is type VII collagen (Chap. 16).

The LABD autoantigens are LAD-1, LABD97, BP180, laminin 332, p200 and type VII collagen

Epidemiology

LABD is a rare disease with an estimated incidence rate of 0.2–2.3/million/year depending of the geographical region [2]. The distribution in the population is biphasic affecting primarily young children at age of 4–5 years and adults in the fifth decade. The childhood form seems to be chronic but self-limiting with disease duration of 1–5 years [3]. The adult form is more chronic and recalcitrant to different treatments.

Although LABD is mostly idiopathic there are some known triggers such as drugs (mostly reported vancomycine), malignancies, UV-light and internal diseases (ulcerative colitis, collagen diseases). For drug-induced LABD we refer to Chap. 19.

LABD or chronic bullous dermatosis of childhood is the most common autoimmune blistering disease in children

Pathogenesis

The two most common LABD antigens are LAD-1 and LABD97 (Fig. 18.1). Both are cleaved from the extracellular domain of BP180 by ADAM9 and 10, and plasmin, respectively. The first cleavage is just in the NC16A domain of the BP180, and this explains that only 20% of the sera of LABD patients react with the NC16A domain [1]. IgA is a chemoattractant of neutrophilic granulocytes, leads to blister formation. In an animal model with passive transfer of murine IgA monoclonal antibodies against LABD autoantigens in a SCID mouse resulted in subepidermal vesicle formation with neutrophil influx [4].

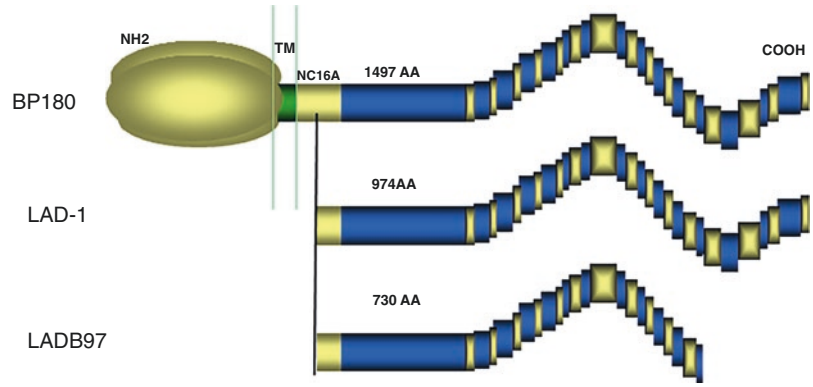


Fig. 18.1 Diagram of BP180 and shed derivates of its extracellular domain: LAD-1 and LABD97 proteins. BP180 is a transmembrane protein of the hemidesmosome containing an intracellular (N-terminus), transmembrane and extracellular (C-terminus) domain. The extracellular domain consists 15 collagenous domains (C1–15) at the C-terminus end and a non-collagenous NC16A domain downstream from the transmembrane domain (TM). LABD97 is a proteolytic product of the extracellular domain containing 1209 amino acids and the N-terminus is just within the domain 3 of the NC16A. The N-terminus of LAD-1 seems to be near the N-terminus of LABD97 but the C-terminus is the same as in the full BP180 protein (1497 amino acid)

Diagnosis Paths

History and Physical Examination

According to the biphasic population distribution, LABD has different phenotypes in adults and in children, the latter was previously called chronic bullous dermatosis of childhood (CBDC). In adults some cases resemble dermatitis herpetiformis (DH) with pruritic papulovesicular eruption on the extensor surfaces. The unique presentation of LABD are tense circinate vesicles and blisters on urticarial plaques on the trunk and limbs. The blistering in LABD is more grouped peripheral (circinate) to the plaques, and unlike BP where blistering is more to the spread over the urticarial plaque. The circinate configuration forms in a ring a "crown of jewels" (Fig. 18.2) or more serpenginous a "string of pearls" (Fig. 18.3b) [5]. In children the predilection sites are legs, lower arms and genitals (Fig. 18.3), or localized and exclusively on the lower eyelid (Fig. 18.4). Mucous membrane involvement occurs up to 80% of cases.

Moreover, drug induced cases are more atypical in the clinics with more severe course, especially cases mimicking toxic epidermal necrolysis (TEN) [6]. Careful medical history according medication in the last weeks is mandatory.

Several cases report associations with other diseases as hematological malignancies (Hodgkin's disease and B-cell lymphomas), different solid cancers (esophagus and bladder), other autoimmune diseases as SLE, multiple sclerosis, dermatomyositis, rheumatoid arthritis, Sjögren's syndrome and Crohn's disease. Whether these are true associations or coincidences needs confirmation [5].

In juvenile LABD the skin lesions are located on the legs, lower arms and perineum in a configuration known as a "crown of jewels"

Another presentation with grouped vesicles in circinate configuration and arciform erythema resembles linear IgA bullous dermatosis, and is called IgA epidermolysis bullosa acquisita (IgA-EBA) with exclusively IgA deposits along the epidermal BMZ. IgA-EBA patients had widespread or localized vesicles, mostly without larger bullae formation (Fig. 18.5). Mucosal involvement is present in five out of eight patients with vesicular pemphigoid-like IgA-EBA but scarring of mucosal surfaces is absent.

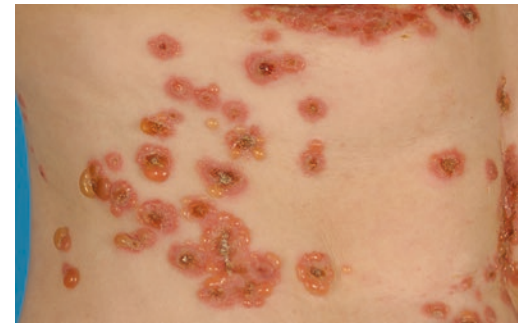


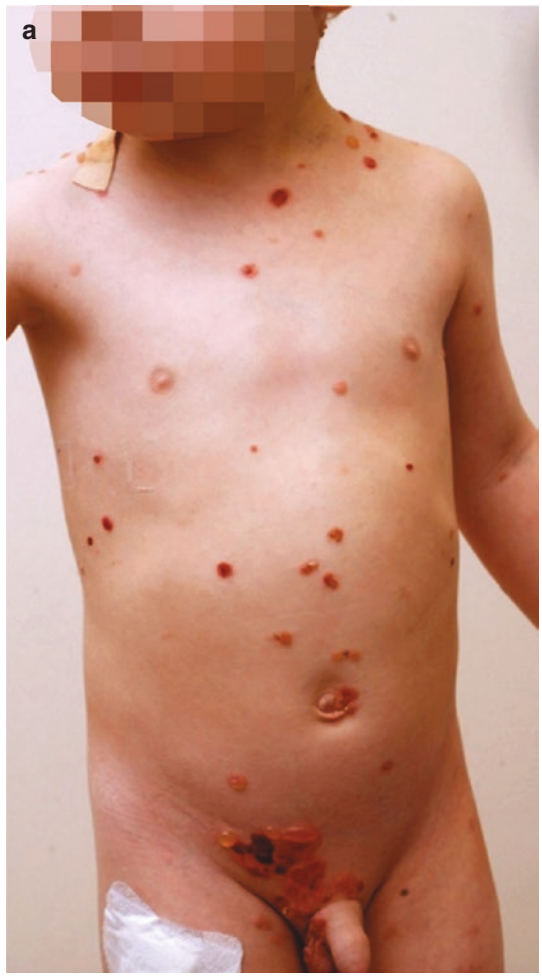
Fig. 18.2 Linear IgA bullous dermatosis in an adult presenting circinate grouped vesicles and bullae ('crown of jewels') on the abdomen

General Diagnostics

Histological examination of perilesional and lesional skin shows subepidermal blister formation with predominantly neutrophil infiltrate in the papillary dermis with occasionally some eosinophils or mononuclear cells.

Specific Diagnostics

The gold standard for the diagnostics of LABD is the linear deposition of IgA along the EBMZ by direct immunofluorescence (DIF) (Fig. 18.5). The autoantibodies are mainly from IgA1 class [7]. Indirect immunofluorescence (IIF) on monkey esophagus fails to detect autoantibodies in most cases due to the low circulating autoantibody titers. Using salt-split skin can raise the sensitivity of the serology, where the majority of the patients show epidermal bindings (lamina lucida-type LABD) and in a minority of the cases is the signal on the dermal side of the split (sublamina densa-type LABD). However some cases show a mixed pattern. Interestingly in drug-induced LABD circulating IgA against the EBMZ on salt-split skin is mostly not was detectable [8]. Western blotting seems to be more sensitive to detect circulating IgA autoantibodies against LABD97 and LAD-1.



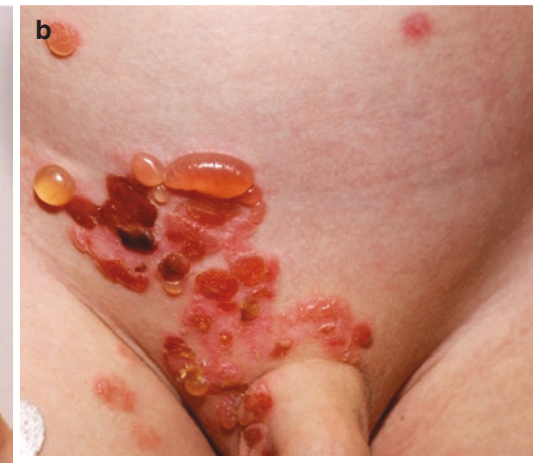


Fig. 18.3 (**a**) Juvenile linear IgA bullous dermatosis in a young boy presenting with serous bullae and hemorrhagic crusts on the trunk, and (**b**) a serpenginous configuration in pubic and genital area ('string of pearls')

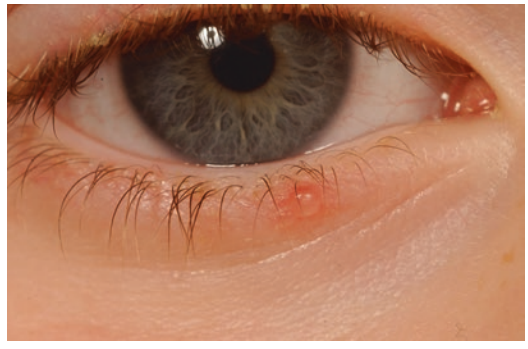


Fig. 18.4 Solitary vesicle on lower eye lid in a boy with localized linear IgA bullous dermatosis

It should be mentioned here, that in minority of the cases also IgG may be seen by DIF parallel to IgA, although in less intensity. These cases should be considered rather as overlap syndromes and designated mixed IgG/IgA bullous pemphigoid.

The linear deposition of IgA along the EBMZ in the lamina lucida-type of LABD has an n-serrated pattern (Fig. 18.6), whereas an u-serrated pattern in the sublamina densa-type LABD

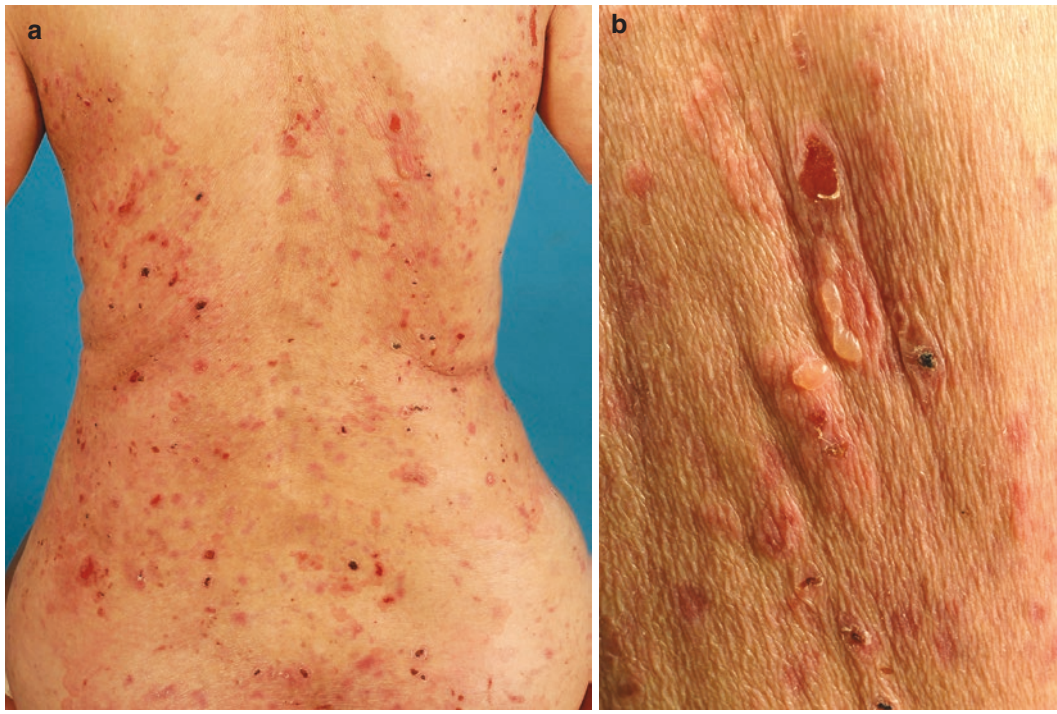


Fig. 18.5 Vesicular sublamina densa-type linear IgA bullous dermatosis (IgA-EBA) showing (**a**) multiple excoriated papules and macules on the trunk (**b**) with some small vesicles

Case Study: Part 2

Routine histopathology taken from the border of a blister showed subepidermal blister filled with almost neutrophils. DIF reveals exclusively IgA deposits in a linear n-serrated pattern along the EBMZ. IIF showed no binding of serum IgA to salt-split skin.

Treatment Tricks

Initial Treatment and Therapeutic Ladder

Dapsone is the first line treatment. Before starting glucose-6-phosphate dehydrogenase (G6-PD) deficiency should be excluded. Starting dose is 0.5 mg/kg daily slowly rising up to maximum 2.5–3.0 mg/kg until itch and blistering is controlled. The average dose to control the disease is about 100 mg daily, sometimes higher doses are needed, but hemolysis is obligate above doses of 100 mg [9]. The mechanism of dapsone to inhibit neutrophil chemotaxis on the site on IgA deposition is not well understood yet. It is known that dapsone inhibits neutrophil lysosomal activity and myeloperoxidase-mediated iodination, however it does not have any effect on antibody or complement deposition [4]. Further it was shown that dapsone inhibits neutrophil adherence to EBMZ antibodies on a dose dependent manner, which covers the pharmacological range of serum dapsone levels [4].

Alternatives are sulfonamides (sulfapyridine in a dose of 15–60 mg/kg/day) alone or in combination with dapsone. Combination of these two drugs has cumulative efficacy without additive toxicity [10]. In partial effect both can be combined with topical or oral corticosteroids [9]. There are several other treatment options reported as mycophenolate-mofetil, mycophenolic acid, colchicine, cyclosporine, methotrexate, HIVIG, cotrimoxa-

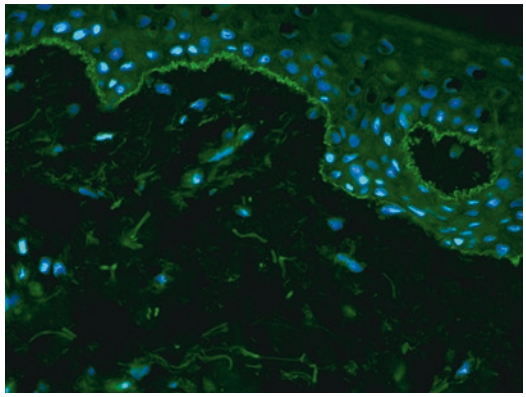


Fig. 18.6 Direct immunofluorescence in lamina lucida-type linear IgA bullous dermatosis shows linear, n-serrated, deposition of IgA along the EBMZ

zole, different antibiotics and immunoadsorption, most of them single or small case series [9].

First line treatment for LABD is dapsone

Follow-Up and Tapering

Patients on dapsone therapy should be carefully monitored for hemolysis and methemoglobinemia. Read more in Chap. 20. In cases with intolerance consider extreme low dapsone doses such as 12.5 mg daily (1/8 of tablet).

Case Study: Part 3

Patient was treated with dapsone climbing up to 200 mg daily without achieving remission. Later adalimumab and rituximab were tried in an off-label set-up without success. Systemic high dose corticosteroids and colchicine could not also book any success. Importantly patient developed several side effects from these systemic medications. From the chronic high dose dapsone usage she developed serious methemoglobinemia up to 21% MetHb in the peripheral arterial blood. Patient should receive several times methylene blue intervention to treat methemoglobinemia. Under adalimumab treatment patient developed an interstitial pneumonitis, which was considered as a side effect of the TNF-alpha blocker, however the underlying Sjögren disease could not be excluded. As a side effect of high dose steroid, patient developed Cushing syndrome with weight gain and diabetes. At the end patient was treated with mycophenolic acid in a dose of 360 mg QID, and she achieved at least partial remission.

Review Questions

1. What is the most common location of LABD in childhood?
   a. Perineum
   b. Head
   c. Pals and soles
2. The most important characteristics on DIF in LABD is
   a. IgA deposition in epithelial cell surface pattern
   b. Linear IgA deposition along the EBMZ
   c. Granular IgA deposition along the EBMZ
   d. Granular IgA deposition in dermal vessels
3. Mucosal involvement occurs in …% of the patients with LABD
   a. 10%
   b. 30%
   c. 80%
   d. 100%
4. First line treatment of LABD is
   a. superpotent topical corticosteroids
   b. systemic corticosteroids
   c. *dapsone*
   d. rituximab

Answers

1. a.
2. b.
3. c.
4. c.

On the Web

DermNet NZ: http://www.dermnetnz.org/immune/linear-iga.html

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