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Chronic Bullous Disease or Linear IgA Dermatosis of Childhood -Revisited

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Abstract

Linear IgA dermatosis or chronic bullous disease of childhood (CBDC) is a nonhereditary, autoimmune subepidermal bullous disease, characterized by the presence of continuous linear deposits of IgA autoantibodies along the basement membrane zone. Antigens mainly involved in the pathogenesis of CBDC are a 97-kDa and a 120 –kDa protein, which represent fragments of the extracellular domain of collagen XVII (BP180), a transmembrane protein playing a critical role in maintaining the linkage between the intracellular and the extracellular structural elements involved in epidermal adhesion. Humoral and cellular response contributes to the pathogenetic mechanism leading to blister formation. CBDC is characterized by a clinical polymorphism in each patient, with the "cluster of jewels" pattern being the most typical clinical lesion. For the establishment of CBDC diagnosis, combination of histology and immunofluorescence studies are of utmost importance. The majority of patients respond to dapsone, sulfapiridine or systemic steroids in cases of widespread disease. CBDC tends to resolve spontaneously within several months to 5 years after its onset. In this review article, the key features of this rare autoimmune bullous disease are revisited.

Keywords: Chronic bullous disease of childhood; Linear IgA dermatosis

Introduction

Linear IgA dermatosis or chronic bullous disease of childhood (CBDC) is generally a rare, nonhereditary, autoimmune disease. It is, though, the most common chronic bullous disease during the first decade of life.

Bowen described in 1901 the first six cases of linear IgA bullous disease of childhood, by that time considered as dermatitis herpetiformis [1].

A changing terminology for this entity existed for almost 80 years. In 1979, chronic bullous disease of childhood or linear IgA dermatosis of childhood was classified as a subepidermal bullous disease characterized by the presence of continuous linear deposits of IgA along the basement membrane zone and as a separate entity from bullous pemphigoid or dermatitis herpetiformis [2].

Controversies on this disease continue regarding the age - related forms. Recently, Haneef et al. [3] proposed that all pediatric cases showing the typical clinical picture of 'cluster of jewels' or 'string of pearls' sign to be included under the broad term 'chronic bullous disease of childhood,' irrespective of the nature of the immune deposits, as there are cases which share this clinical features but show IgG predominance. The authors claim that linear IgA dermatosis of childhood is a separate entity with variable immune deposits but unique clinical features, while the adult disease has variable clinical features and the linear deposition of predominantly IgA is an essential diagnostic finding [3].

Linear IgA dermatosis with adult onset and linear IgA dermatosis of childhood share the same basement membrane zone antigens and thus, they are currently considered as variants of the same disease [4,5].

Epidemiology and Genetics

There is a heterogenicity of the epidemiologic data on CBDC. For example, in 1991, 25 cases in 3 years were reported in South Africa while in 2008, 38 cases in 30 years were reported in Japan [6]. In our center, we estimate to see one case every 10 years.

CBDC is relatively frequent in Africa. In a 32-year retrospective study in Tunisia, from the 47 children of all ages with confirmed bullous dermatosis, CBDC was by far the most common disease with up to 31 cases (65.9%). The other cases were distributed as follows: eight cases of bullous pemphigoid, five cases of dermatitis herpetiformis, and three cases of pemphigus [7]. The mean age of onset of CBDC was 5.5 years and the sex ratio (M/F) was 2.4/1 [7].

The limited number of cases worldwide, as well as missing genetic data do not allow to define the genetic background of this disease. Collier et al. [8], performed Class I and II major histocompatibility locus (MHC) antigen typing in 60 patients (26 children with CBDC and 34 adults with linear IgA disease), and correlated the findings with the clinical course. The authors reported that the presence of HLA B8, DR3 and DQ2 may enforce the susceptibility to an early onset of linear IgA dermatosis [8]. An additional role for the duration of the disease and for a worse prognosis may be attributed to the TNF2 gene [8].

Pathophysiology and Autoimmunity

CBDC is an autoimmune disease with the targeted antigens localized in the basement membrane of squamous epithelium. Antigens mainly involved in the pathogenesis of CBDC are an 97-kDa (LABD97) [9] and an 120 –kDa (LAD-1) [10] antigen, which represent fragments of the extracellular domain of collagen XVII (BP180), a transmembrane protein playing a critical role in maintaining the linkage between the intracellular and the extracellular structural elements involved in epidermal adhesion [11].

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The targeted dermal-epidermal junction antigens have been identified in the lamina lucida, sublamina densa, or both locations simultaneously. The 97 kDa and the 120 kDa, the best characterized antigens binding IgA antibodies in CBDC patients'sera, are localized in the lamina lucida. These proteins may represent a cleaved portion of the extracellular domain of bullous pemphigoid antigen (180 kDa), or could also be alternative splicing products of the same antigen. A small number of patients present with antibodies directed against different antigens located on both lamina lucida and lamina densa, such as the 280 kDa antigen, the collagen VII (250 kDa) antigen, and many more [12-15].

The variety of target antigens in CBDC may be caused by epitope spreading, by which the primary autoimmune process is extended to neighboring molecules, generating new autoantigenic epitopes [16].

Production of IgA against the above antigens and deposition in a linear pattern along the basement membrane determines the humoral response in CBCD. A cellular response is also involved with complement activation, recruitment of inflammatory cells and release of proteolytic enzymes [17,18].

Blister formation in CBDC mainly results from the plasminogen activation by keratinocytes and the activation of neutrophils leading to the activation of promatrix metalloproteinase 9 (MMP-9) and neutrophil elastase. Plasmin is formed by the activation of plasminogen and is able to cleave type XVII collagen. Thus, fragments may be recognized as immunogenic epitopes (including a 97-kDa fragment) by the sera of patients with CBDC [19,20].

Another pathway resulting in blister formation in CBDC may proceed through activation of pro-MMP-9 into MMP-9/gelatinase B. This enzyme is essential for the inactivation of α1- proteinase inhibitor leading to chemoattraction of neutrophils and allowing neutrophil elastase to induce epithelial – dermal detachment [20,21].

In CBCD, there are no convincing data on precipitating factors like hematologic malignancies, bladder cancer, ulcerative colitis and systemic lupus erythematosus, which, on the contrary, are associated with the adult onset linear IgA dermatosis.

Drug-induced CBDC is rarely described in children. Drugs that have been associated with CBDC include antibiotics, such as the combination of amoxicillin with clavulanic acid, vancomycin or nonsteroidal inflammatory agents [16,22].

In a series of 25 cases of childhood CBDC, 38% of them had either preceding infection or ingestion of drugs [23]. Drugs may serve as haptens, completing complexes with dermal/epidermal proteins, and eliciting an autoimmune response. Immunoglobulin A-stimulated neutrophil chemotaxis then results in the formation of neutrophilic microabscesses at the dermoepidermal junction [16].

The causative relationship between CBDC and infections is not adequately supported. Salmonella enteritis, nonspecific gastrointestinal infections, upper respiratory tract infections and Epstein-Barr virus infection have been associated with the development of CBDC lesions [24-26].

CBDC most commonly affects preschool aged children. In the literature there are 7 neonatal reports, most of which have had life threatening aerodigestive complications. Mother's exposure to infectious agents or antibiotics (e.g penicillin) has been reported to act as a possible trigger factor for neonatal CBDC [27].

Clinical Features

The "cluster of jewels" pattern is typical of CBDC. In this pattern of distribution tense vesicles arise at the periphery of old lesions. Predilection sites are the lower extremities, especially the perineal area. Tense bullae on or without urticarial base may also be present symmetrically or asymmetrically. The lesions may coalesce to form annular or polycyclic plaques. Face, trunk and upper extremities may also be involved, to a lesser extent. Pruritus may vary from mild to severe.

There is a polymorphism of the cutaneous lesions in each individual patient, as several types of lesions at different stages of the disease may coexist (Figures 1- 3). Tense pruritic blisters of variable sizes, small clear-filled vesicles normal appearing skin, or at the periphery of an

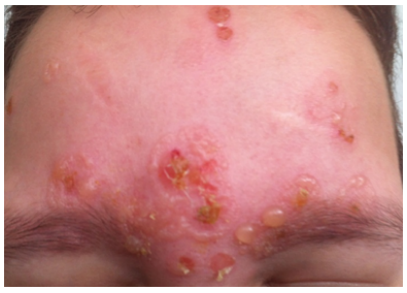

Figure 1: Vesicles, erosions and crusts on the face.

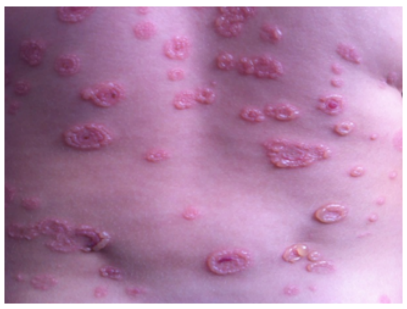

Figure 2: "cluster of jewels" pattern of lesions.

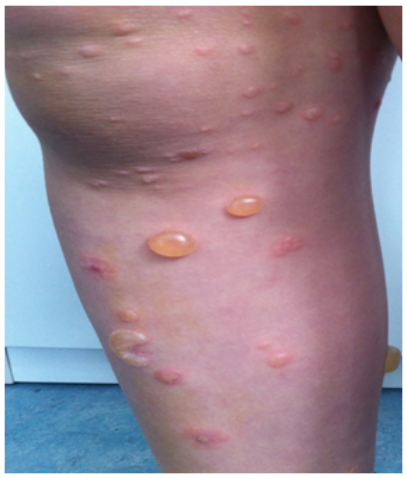

Figure 3: tense bullae on lower extremities.

annular erythema, along with crusts, excoriations, and erosions may be present in the same patient. Large and tense bullae are indistinguishable from bullous pemphigoid lesions [12,28]. Cutaneous lesions heal without scarring.

Mucous membranes may also be involved with painful erosions [29]. In a study from Tunisia, 12.9% of children had evidence of oral or genital lesions [28]. Oral cavity, especially the soft and hard palate and the buccal mucosa is more commonly involved than the conjuctiva, larynx, pharynx, trachea, vaginal mucosa or balanopreputial sulcus. Even if no signs of mucosal affection are reported, it is suggested that an ocular examination is necessary for the detection of signs which may lead to subconjunctival fibrosis, symblepharon formation, and cicatricial entropion [28,29].

Diagnosis

Differential diagnosis most notably includes bullous pemphigoid, dermatitis herpetiformis and erythema multiforme (Table 1). For the establishment of CBDC diagnosis, combination of histology and immunofluorescence studies are of utmost importance.

On histology from lesional skin, a subepidermal cavity with eosinophils and neutrophils is commonly seen. Cell poor CBDC has been rarely reported [30]. Direct immunofluorescence reveals a smooth linear pattern of IgA deposition along the basement membrane, which is a typical finding for CBDC (Figure 4). Associated deposits of IgG, IgM, and C3 have been reported in cases of CBDC in the literature [31,32]. Direct immunofluorescence on salt-split lesional skin, incubated in 1 m sodium chloride solution, shows typically linear deposition of IgA along the roof of the cavity.

Indirect immunofluorescence may not be diagnostic in almost half of cases, although circulating IgA BMZ antibodies have been reported in up to 80% of patients [33]. Monia et al. reported indirect immunofluorescence to be negative in 67% of cases [28].

Prognosis

CBDC resolves spontaneously within several months to 5 years after its onset or by the age of 6-8 years. In a series of 25 children with CBDC, 16 cases presented remission within 2 years, while three patients still had persistent disease post puberty [23,30].

The mean duration of the disease, in a study of 31 Tunisian Children with CBDC, was 14 months. In the same study a long-term remission period was achieved in 76.1% of patients [28].

Treatment

CBDC is a recurrent disease with a potential to become generalized or to severely affect mucosa, especially the conjuctiva. Aim of each therapeutic decision is to achieve a long lasting remission with the

Disease	Clinical Features	Histology	Direct Immunofluorescence(perilesional skin)	Indirect Immunofluorescence	Antigen
Chronic Bullous Disease of Childhood (CBDC)	"cluster of jewels" pattern, vesicles or bullae on perigenital area, extremities, trunk, face	Subepidermal cavity with neutrophils along the basement membrane vacuolar degeneration, eosinophils may be present	linear deposition of IgA along the basement membrane, rare associated deposits of IgG, IgM, and C3	negative in the majority of cases	97-kDa, 120-kDa antigen
Bullous Pemphigoid	tense vesicles or bullae on erythematous base on the inner surface of the thighs, forearms, axillary folds, palms, soles	subepidermal cavity with an inflammatory infiltrate, predominantly of eosinophils	linear deposition of C3 and IgG along the basement membrane	linear deposition of C3 and IgG along the basement membrane	230-kDa, 180-kDa
Dermatitis Herpetiformis	pruritic papules and vesicles on the extensor surfaces of the limbs, buttocks, shoulders, nape of neck, scalp	subepidermal cavity with neutrophils in the dermal papillae, edema of the papillary dermis, eosinophils may be present	granular deposition of IgA in dermal papillae	negative	epidermal transglutaminase
Erythema multiforme	Papules, vesicles, targetoid lesions on palms, soles, extremities, trunk, oral mucosa	subepidermal blister with infiltrate of lymphocytes in the underlying dermis, a few eosinophils, the epidermis overlying the blister may show necrosis, apoptotic keratinocytes present in the epidermis adjacent to the blister	negative	negative	-

Table 1: Differential Diagnosis of CBDC.

Age and Gender: First decade, more common to males
Clinical features: Tense vesicles or bullae at different stages of evolution, on normal or erythematous base, "cluster of jewels" pattern of distribution
Predilection Sites: Perigenital area, extremities, face
Pruritus: Mild to intense
Among diagnostic procedures: Direct immunofluorescence from perilesional skin is the gold standard, linear IgA deposition along the basement membrane being the typical finding
Treatment: Dapsone if possible
Prognosis: Recurrences are frequent, remission expected in 2 - 5 years

Table 2: A clinician's algorithm for Chronic Bullous Disease of Childhood.

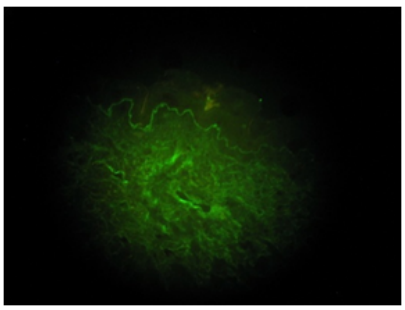

Figure 4: Linear IgA deposition along the basement membrane zone in perilesional skin.

minimum of systemic agent – related side effects. Low incidence of CBDC has not allowed the performance of large, randomized, placebo – controlled studies on different treatment modalities. The majority of patients responded to dapsone, sulfapiridine or systemic steroids in cases of widespread disease [6]. Dapsone is used as a first-line therapy at an initial dose from 25 mg to 100 mg/day. Duration of treatment is individualized, although most authors keep the patients on maintainance treatment for 3-21 months. Dapsone may be combined with oral steroids or steroids may be used as monotherapy in generalized CBDC at a dose 0.5-2 mg/kg/day and with a mean maintenance period of 20 months [28]. Levels of glucose -6- phosphate- dehydrogenase must be measured to avoid hemolytic anemia in all cases treated with dapsone. Erythromycin, mycophenolate mofetil, colchicine and intravenous immunoglobulins are less used but reported as successful treatment options [34,35]. Colchicine at a dose of 0.5 mg twice daily may be introduced in cases with G6PD deficiency or when there is failure or side effects of the first line therapeutic regimen [36]. Flucloxacillin, erythromycin, cotrimoxazole and miocamycin have also been administered in young patients with CBDC as monotherapy or in combination with dapsone or topical steroids, achieving a good response due to their antinflammatory properties [24,37-39]. In dapsone resistant cases of CBDC, tacrolimus has showed benefit as an adjunctive topical medication [40]. As a closing remark, initiation of treatment early on in the course of the disease (within 1 month) may be the decisive factor in inducing early remission [24]. The key features of CBDC are summarized in Table 2.

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