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Breaking Through the Blister : Exploring Chronic Bullous Disease of Chidhood

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ABSTRACT

Background: One of the autoimmune disease occurs on the first decade of life is Linear Immunoglobulin A Bullous Disease now referred to as Chronic Bullous Disease of Childhood is an infrequent and nonhereditary skin disorder defined by a linear accumulation of immunoglobulin A. The lesions present as clear or hemorrhagic vesicles (or both) or bullae that emerge from otherwise normal skin, occasionally accompanied by an erythematous or urticarial base. The bullae or vesicles are typically tense, vary in size, and often develop into annular or polycyclic plaques as a result of the lesions merging together. CBDC is a self-limiting disease, with most children experiencing recovery within two years of the symptom beginning, in some cases, the disease continues into puberty, but it is typically less severe than the initial eruption. **Objective:** This literature review aims to provide a comprehensive understanding of CBDC, including its pathogenesis, diagnosis and appropriate therapeutic approaches for managing the disease. **Methods:** Herein, using the key terms: "Chronic Bullous Disease of Chidhood", "Linear Immunoglobulin A Bullous Disease", "autoimmune bullous disease", we carried out a review of the literature, using Google Scholar, PubMed and book in last 10 years. **Conclusion:** CBDC is a chronic bullous disease that appears in pediatric age. The pathogenesis of this disease is not yet known with certainty. Although the disease is capable of self-healing, dapsone is the recommended first-line treatment. If spontaneous recovery takes place, the prognosis is often optimistic. Accurate diagnosis and therapy are important for a prognosis.
Keyword: Chronic Bullous Disease of Childhood, autoimmune, bullous disease, skin disease, children

ABSTRAK

Latar Belakang: Salah satu penyakit autoimun bulosa yang muncul pada decade pertama kehidupan adalah Penyakit Linear Immunoglobulin A yang sekarang disebut Chronic Bullous Disease of Childhood, merupakan kelainan kulit yang jarang terjadi dan tidak bersifat keturunan ditandai dengan akumulasi linear IgA. Lesi muncul sebagai vesikel bening atau hemoragik (atau keduanya) atau bula yang muncul dari kulit normal, kadang-kadang disertai dengan dasar eritematosa atau urtikaria. Bula atau vesikel biasanya tegang, ukurannya bervariasi, dan sering berkembang menjadi plak anular atau polisiklik akibat bergabungnya lesi. CBDC merupakan penyakit yang dapat sembuh dengan sendirinya, dengan sebagian besar anak mengalami pemulihan dalam waktu dua tahun sejak gejala muncul, dalam beberapa kasus, penyakit ini berlanjut hingga masa pubertas, namun biasanya tidak separah gejala awal. **Tujuan:** Tinjauan pustaka ini bertujuan untuk memberikan pemahaman yang komprehensif tentang CBDC, termasuk patogenesis, diagnosis dan pendekatan terapi yang tepat untuk penyakit ini. **Metode:** Dalam penelitian ini, menggunakan istilah kunci: "Penyakit Bulosa Kronis pada Anak", "Penyakit Bulosa Imunoglobulin A Linear", "penyakit bulosa autoimun", kami melakukan telaah pustaka, menggunakan Google Scholar, PubMed dan buku dalam 10 tahun terakhir. **Kesimpulan:** CBDC merupakan penyakit bulosa kronis yang muncul pada usia anak-anak. Patogenesis penyakit ini belum diketahui secara pasti.

Meskipun penyakit ini mampu sembuh sendiri, dapson merupakan pengobatan lini pertama yang direkomendasikan. Jika terjadi pemulihan spontan, prognosisnya sering kali optimis. Diagnosis dan terapi yang akurat penting untuk prognosis.
Keyword: Penyakit Bulosa Kronik Anak, autoimun, penyakit bulosa, penyakit kulit, anak

1. Introduction

Linear Immunoglobulin A Bullous Disease abbreviated as LABD is an infrequent, nonhereditary, autoimmune skin disorder defined by a linear accumulation of immunoglobulin A beneath the epidermis along the basement membrane region on the first decade of life.[1,2] The disease that occurs in pediatric patients was initially referred to as Chronic Bullous Disease of Childhood (CBDC) in the late 1970s.[1]

There are two variants of the disease : one that affects children and another that occurs in adults, exhibit distinct clinical characteristics however have a similar immune pathogenesis and microscopic appearance.[1,2] The pediatric onset most often presents before the age of 5 years, while the adult onset typically manifests after puberty, with most cases occurring after the fourth decade of life. The adult-onset form is referred to as Linear Immunoglobulin A Bullous Disease (LABD).[1,2,3] As with patients with LABD, there is a minor predominance of females among patients with CBDC in some studies, but not all studies have noted the same.[3]

2. Discussion

DEFINITION

Chronic Bullous Disease of Childhood (CBDC) is an autoimmune skin condition that typically affects children under the age of 5, characterized by the formation of bullae and the finding of homogeneous linear IgA deposits on the at the dermal–epidermal basement membrane.[3,4]

EPIDEMIOLOGY

There is heterogeneity in the epidemiological data on CBDC. Twenty five cases were reported over 3 years in South Africa in 1991, while in 2008, thirty eight cases were reported over a span of 30 years in Japan. Meanwhile in Papageorgiou General Hospital, Thessaloniki, Greece only one case every 10 years.[1] The incidence is estimated to be between 0.2 and 2.3 cases per million per year, with a higher prevalence noted in Africa and Asia. In Western Europe, the incidence is approximately 1 in 500,000, and no ethnic or gender predisposition has been observed.[2,5]

ETIOLOGY AND PATHOGENESIS

Chronic Bullous Disease of Childhood (CBDC) is an autoimmune disorder with the targeted antigens localized in the basement membrane of the squamous epithelium. A 120-kDa (LAD-1) antigen and 97-kDa (LABD97) antigen are the primary antigens that involve the pathogenesis of CBDC, as they are both parts of the extracellular domain of collagen XVII (BP180). This protein is crucial for preserving the link between intracellular and extracellular structural components necessary for epidermal adhesion.[1,2]

Antigens targeting the junction of dermal-epidermal have been identified in the lamina lucida, sublamina densa, and in both layers. The 97 kDa and 120 kDa antigens, which are most well-characterized for attaching IgA antibodies in the serum of CBDC patients, are localized to the lamina lucida.[1]

The majority of childhood LABD are unknown causes; however, medications, infections, skin injuries, and also malignancies may act as possible triggers for this disease. Several drugs, including antiepileptics, antibiotics, antiretrovirals, NSAIDs, ACE inhibitors diuretics, cyclosporine, amiodarone, statins, influenza vaccination, have been reported to be responsible for drug induction in adults.[2] In contrast, drug-induced CBDC is uncommon in children.[6] Infection caused by Salmonella enteritis and Epstein-Barr virus infections have been linked to the formation of CBDC lesions. Other infections including nonspecific gastrointestinal infection and upper respiratory tract infections also take effect.[2]

CLINICAL MANIFESTATIONS

The clinical symptoms of immunoglobulin A (IgA) bullous dermatosis patients are similar to bullous Pemphigoid. The lesions appear as clear or hemorrhagic vesicles, or both, or as bullae emerging from otherwise normal skin, often on an inflammatory base.[3,7] The bullae or vesicles are typically tense, vary in size, and often develop into annular or polycyclic plaques as a result of the lesions merging together.[6,7] These lesions most commonly appear in the perineum and perioral region, and they often occur in clusters, creating a "cluster of jewels" appearance (Figure 1). New lesions may occasionally emerge around the edges of existing lesions,

resulting in a "collarette" of blisters.[3] Typical locations are the limbs, particularly the perineal region, while mucosal involvement is less common.[2,6] Patients frequently experience significant itching and/or a burning sensation in the skin as skin lesions develop.[3]

The skin manifestations of LABD induced by drugs typically present as typical tense bullae in annular pattern, however, up to 20% of cases in a French research have documented a toxic epidermal necrolysis-like pattern.[6]

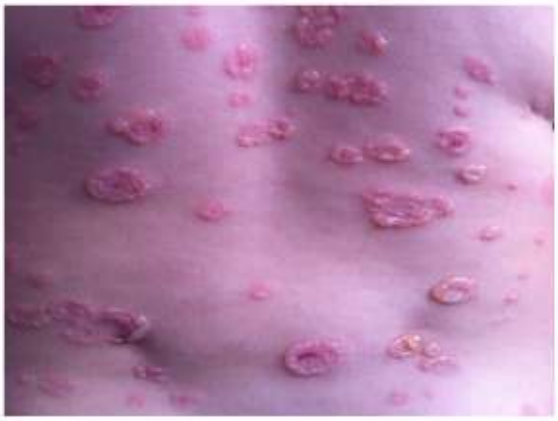

Figure 1 : “Cluster of jewels” pattern.[2]

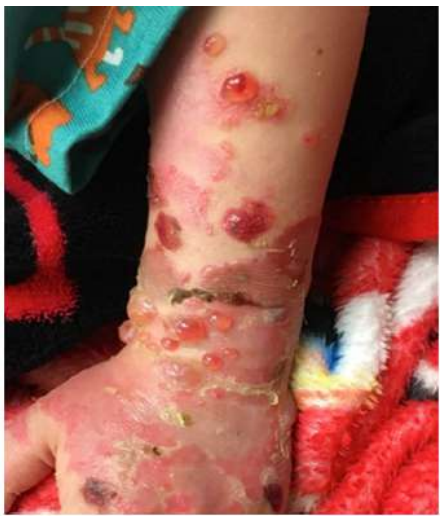

Figure 2 : Appearance of skin on Chronic Bullous Disease of Chidhood**.** [8]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

There are three criteria to diagnose bullous dermatosis, the presence of vesicular or bullous eruptions affecting the skin or mucous membranes, dominant subepidermal neutrophil infiltration on histological examination, and the existence of linear IgA deposits beneath the epidermis along the basement membrane region.[9] Chronic Bullous Disease of Childhood diverges from linear IgA bullous dermatosis of adults in its typical clinical presentation and the relative scarcity of severe mucosal involvement.[3]

On histology of the lesion, along the vacuolar degeneration of the basement membrane are commonly seen subepidermal cavities with eosinophils and neutrophils, often gathering at the tips of the papillae.[2,3] Combination of histology and immunofluorescence studies are crucial to diagnose CBDC.[2] Direct immunofluorescence reveals linear IgA deposition, and studies have also reported the existence of deposits of IgM, IgG, and C3.[9]

Mucosal involvement is a notable clinical feature in patients with linear IgA dermatosis and CBDC. It can range from mild, asymptomatic oral ulcers and erosions to severe isolated oral disease or even extensive conjunctival and oral involvement, resembling cicatricial pemphigoid.[3] Oral lesions occur in up to 70% of patients with linear IgA disease, with the oral cavity—particularly the soft and hard palate and buccal mucosa—being more frequently affected than the conjunctiva, larynx, pharynx, trachea, vaginal mucosa, or

balanopreputial sulcus.[2,3] An eye examination is advised, even in the absence of visible signs of mucosal damage, to identify any signs that could lead to subconjunctival fibrosis, formation of symblepharon, and entropion scarring.[2]

Chronic Bullous Disease of Childhood (CBDC) often closely mimics the clinical pattern seen in patients with Dermatitis Herpetiformis (DH).[3] Other differential diagnosis of CBDC includes bullous impetigo, hand-foot-and-mouth disease, Bullous Pemphigoid (BP), Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and erythema multiforme (Table 1).[2,9,10]

Linear IgA deposits at the basement membrane, detected by direct immunofluorescence and typically absent of IgG and C3, serve as a distinguishing feature of this disease from BP, cicatricial pemphigoid, and Epidermolysis Bullosa Acquisita (EBA). In contrast, patients with DH exhibit granular IgA deposits at the basement membrane.[2,3]

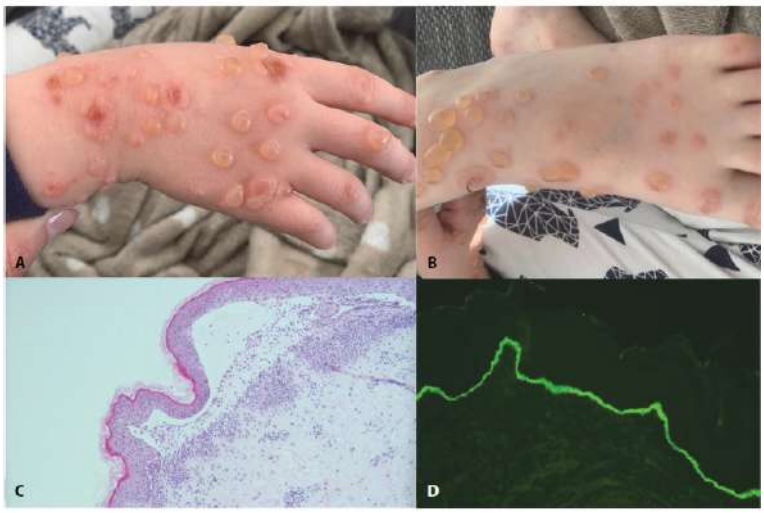

Figure 3 : A, B. Clinical manifestation of the patient´s extremities C. H&E histopathology reveals a subepidermal blister accompanied by neutrophilic infiltration at 10× magnification. D. Direct immunofluorescence displays a smooth, linear pattern of immunoglobulin A deposition along the basement membrane at 10× magnification.[6]

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 erythemat	subepidermal cavity with an inflammator	linear deposition of C3 and IgG along the basement membrane	linear deposition of C3 and IgG along the basement membrane	230-kDa, 180-kDa

	ous base on the inner surface of the thighs, forearms, axillary folds, palms, soles	y infiltrate, predominantly of eosinophils			
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 : Table of differential diagnosis of CBDC.[2]

THERAPY

The majority of children experiencing recovery within two years of the onset of symptoms, and it is exceptionally rare for the disease to persist beyond puberty, even after undergoing various treatment approaches.[11] Patients with CBDC well respond to dapsone or sulfapyridine.[8,11]

The first choice of therapy of LABD and CBDC is dapsone with initial dose 0,5mg/kg/day, this dose is gradually increased until symptoms are resolved and controlled, usually reaching up to 2 mg/kg/day.[8,9] The duration of treatment is adjusted individually, most authors provide treatment for 3-21 months.[7] This treatment

can be given either as monotherapy or in combination with corticosteroids, antibiotics, or colchicine.[1,2] Regular laboratory monitoring is necessary while taking dapsone, because of potential adverse effects like hemolysis or agranulocytosis, [10] In instances of dapsone-resistant CBDC, tacrolimus has demonstrated efficacy as a supplementary topical treatment.[2]

Systemic steroid can be used as monotherapy in generalized CBDC for temporary treatment, but they should be generally avoided in children due to the side effects associated with long-term use.[8,9] Some patients require low-dose prednisone therapy to control and suppress the formation of blisters.[3] Sulfapyridine can be used in patients with G6PD deficiency. For those who are intolerant to dapsone or sulfapyridine, or have G6PD deficiency, colchicine may be considered as an alternative. The typical dose of colchicine is 0.5-0.6 mg twice daily.[8,10]

Antibiotics such as erythromycin, dicloxacillin, and oxacillin are less used but can be helpful in treating CBDC due to their antinflammatory properties.[2,8] However, tetracyclines are not advised for children under 8 years of age due to the risk of irreversible tooth discoloration.[8] In difficult-to-treat cases, various treatments including methotrexate, nicotinamide, IVIG, ciclosporin, mycophenolate, azathioprine, and immunoadsorption have been used with success.[11]

Recent studies suggest that rituximab can effectively manage recalcitrant adult-onset linear IgA disease. Rituximab is typically safe and well-tolerated in most pediatric patients and has been widely used in conditions such as B-cell non-Hodgkin's lymphoma, pediatric nephrotic syndrome, and various autoimmune diseases in pediatric rheumatology. However, some studies report rituximab appears to be less effective in adult patients with IgA-dominant diseases, making it potentially less beneficial for treating CBDC.[8,11]

A case report of a 2-year-old male child who presented with chronic, recurrent bullous lesions over 18 months, involving the face, trunk, extremities, perineal region, and oral mucosa, with spontaneous blister rupture and peripheral progression of lesions. The presence of oral ulcers, conjunctival involvement, and the characteristic 'string of pearls' sign suggested a bullous dermatosis, with histopathological and direct immunofluorescence findings confirming chronic bullous disease of childhood (CBDC). The patient was treated with rituximab, administered in two doses at 15-day intervals, following the Oxford Pediatric Rheumatology protocol. The treatment led to complete resolution of skin lesions without scarring within 15 days (Figure 4). The patient remained disease-free during a 12-month follow-up period, indicating successful long-term remission with rituximab in this refractory CBDC case.[11]

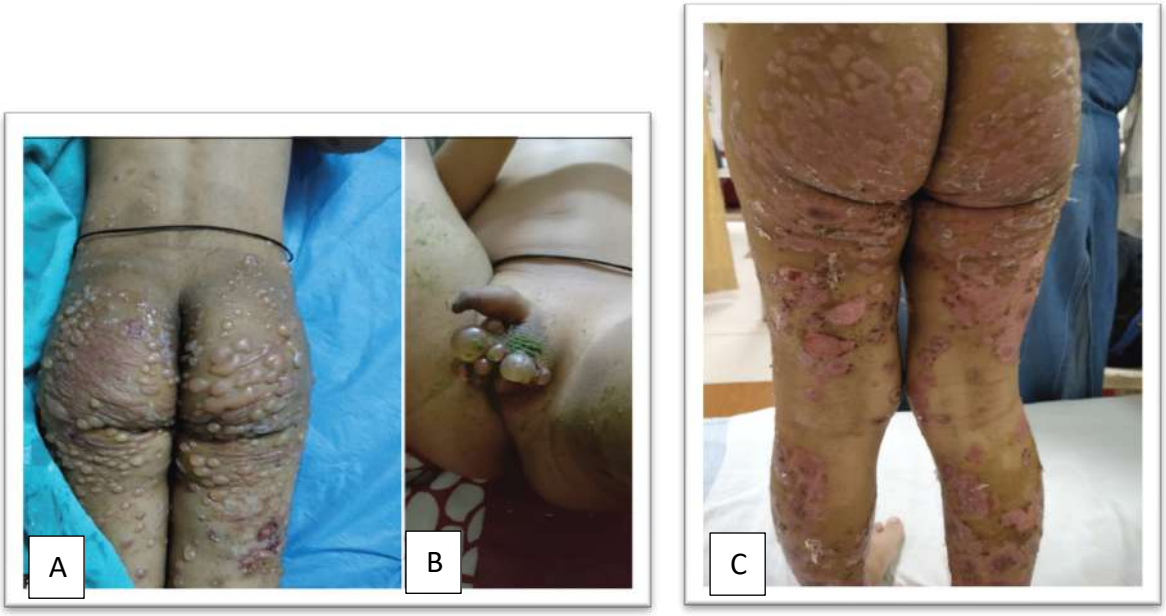

Figure 4 : A. Bullae on the perineal area, buttocks, and lower limb. B. Clustered pattern bullae on the scrotum. C. The lesions resolved following 15 days of rituximab therapy.[11]

PROGNOSIS

CBDC can healed spontaneously within a few months to five years after the onset of symptoms, commonly two years of the symptom beginning, leading to the loss of clinical features of the disease and the disappearance of linear IgA deposits in the skin.[2,3] In a study of 31 Tunisian children with CBDC , the mean duration of disease was 14 months. In the same study, 76.1% of patients achieved long-term remission.[2] Patients with severe mucosal disease, particularly involving the eyes, may experience ongoing issues with the formation of symblepharon and resulting structural problems with the eyelids and cornea, even after blister has resolved. [3]

4. Conclusion

The result CBDC is a chronic bullous disease that appears in pediatric age. The pathogenesis of this disease is not yet known with certainty, some studies say that various stimuli (eg, infection, drugs, trauma, malignancies) can activate autoimmune responses first choice of therapy of LABD and CBDC is dapsone treatment with initial dose is gradually increased until the symptoms are resolved and controlled. Occasionally, patients may experience spontaneous remission, leading to the loss of clinical features of the disease and the disappearance of linear IgA deposits in the skin. Rapid and accurate diagnosis is useful for identifying triggering factors and administering therapy as early as possible is very important to produce a better prognosis. This literature review aims to provide a comprehensive understanding of CBDC, including its pathogenesis, diagnosis and the most appropriate therapeutic approaches for managing the disease.

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