Journal of Society Medicine
Research & Review Articles on Diseases
Journal of Society Medicine. 2023; 2(11)

Autoimmune Blistering Disease in Children

Ade Gustina Siahaan[1*], Cut Putri Hazlianda[2]

[1] *Departemen Dermatologi Venereologi dan Estetika Resident, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia / Haji Adam Malik General Hospital, Medan, Indonesia*
[2] *Departemen Dermatologi Venereologi dan Estetika, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia / Haji Adam Malik General Hospital, Medan, Indonesia*

***Corresponding Author**: Cut Putri Hazlianda, E-mail: cut.putri@usu.ac.id

ARTICLE INFO

Article history:
Received
28 September 2023
Revised
30 October 2023
Accepted
30 November 2023

Manuscript ID:
JSOCMED-280923-211-3

Checked for Plagiarism: Yes
Language Editor: Rebecca

Editor-Chief: Prof. Aznan Lelo, PhD

ABSTRACT

The skin is a particular organ that shields the body from physical stress and other external stresses. There are three layers of skin: epidermis, dermis, and subcutis. The three layers act as interrelated units in carrying out the above functions. One of the skin diseases that can be found is an autoimmune blister or bullous disease that can affect children. Autoimmune bullous or blisters are rare in children, but their quality of life is compromised if they suffer from this disease. Included in autoimmune bullous diseases in children are Linear Immunoglobulin A Bullous Dermatosis (LABD), Dermatitis Herpetiformis (DH), Pemphigus Vulgaris (PV), Pemphigus Foliaceus (PF), Paraneoplastic Pemphigus (PNP), Bullous Pemphigoid (BP), Mucous Membrane (cicatricial) Pemphigoid (MMP), Epidermolysis Bullosa Acquisita (EBA). Diagnosing and treating patients with autoimmune bullous diseases is challenging for clinicians. The skin of infants and children is anatomically thinner than adults, so they are more prone to develop bullae when traumatized.

Keywords

Autoimmune Blistering Disease, Autoimmune Bullous Disease, Children

How to cite: Siahaan AG, Hazlianda CP. Autoimmune Blistering Disease in Children. *Journal of Society Medicine*. 2023; 2(11): 366-376. **DOI: https://doi.org/10.47353/jsocmed.v2i11.100**

INTRODUCTION

The skin is a special organ in humans. Unlike other organs, the skin, which is located on the outer side of humans, makes it easier to observe, both in normal and sick conditions. The skin protects the body from various external pressures and protects the body from physical stress to keep the skin in a healthy condition.[1.2] The skin consists of three layers: epidermis, dermis, and subcutis. In carrying out the above functions the three layers act as a unit that is interrelated with one another.[3] fluids and electrolytes and provides several receptors, such as touch, pain, and pressure receptors.[2] Skin findings are relevant to the skin disease present and the patient's overall health.[4] One of the skin diseases that can be found is bullae or blisters which have an impact on both children and adults.

Bullae or blisters are rare in children, but their quality of life will be impacted if they have bullae.[5] Bullae or blisters in children are a diverse group of disorders that are challenging and complex to dermatologists.[6] Over a period of almost 15 years, the dermatological referral centers of the US and Singapore populations respectively recorded 23 and 12 incidences of autoimmune bullous disease in children, with the most prevalent being dermatitis herpetiformis (DH) in the United States and dermatosis bullous immunoglobulin A (IgA) linear (LABD) in Singapore.[5]

Bullae or blisters in children are very varied and are divided into 2 major groups, namely autoimmune bullae and non-autoimmune bullae. Included in autoimmune bull disease is linear Ig A disease or Chronic bullous disease in childhood (CBDC). This disease most often appears in children with an age range of 6

months-5 years, bullous pemphigoid is rare but can occur in children aged 1-8 years, epidermolysis bullosa acquisita (EBA) can appear at the age of fewer than 5 years, while those included in non-autoimmune bulla diseases include impetigo bullosa which often occurs and is caused by Staphylococcus aureus bacterial infection, varicella zoster virus (VZV) and herpes simplex virus often occurs also in children.[7,8]

It is still challenging for clinicians in determining the diagnosis and management of autoimmune bullae or blisters. The skin of infants and children is anatomically thinner than adults, so they are more prone to forming bullae when they are traumatized. Knowledge of autoimmune bull disease in children is very important considering that this disease is a rare condition, but can cause significant morbidity.[9,10]

Linear Immunoglobulin A Bullous Dermatosis (LABD)

Linear Immunoglobulin A Bullous Dermatosis (LABD), also known as linear IgA disease, is an autoimmune mucocutaneous disorder marked by subepithelial blisters caused by IgA autoantibodies against multiple antigens of different various weights, found in the basement membrane zone (BMZ) of skin and all mucosal tissues with stratified squamous epithelium.[9] The immunological analysis shows linear deposition of IgA along the BMZ and circulating IgA antibodies to various antigens, most commonly identified as 97- and 120- kD of BP antigen 2 (BPAG2 or BP180). LABD occurring in children is called chronic bullous dermatosis in children (CBDC), typically characterized as tense blisters arranged in an annular pattern ("crown of jewels" or "string of pearls") (Figure 1).[5]

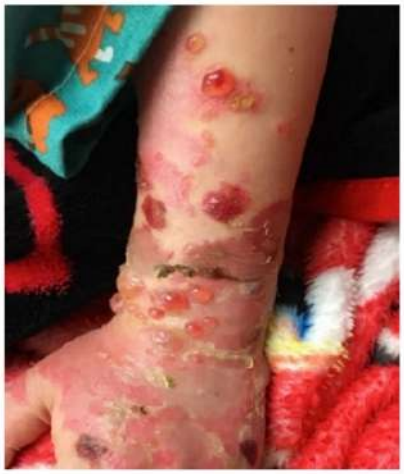

Figure 1. Linear Immunoglobulin A (IgA) [5]

Epidemiology

LABD can occur in both adults and children. LABD may appear after the age of 6 months and before 5 or 6 years; it rarely persists beyond puberty. In contrast, the adult onset occurs after puberty or after the age of 60 years.[5,6]

Genetic Relationship and LABD

Most previous studies of LABD in children and adults recently showed a correlation to human leukocyte antigen (HLA). In contrast to the populations of Polynesian, Japanese, and Chinese where this haplotype is absent, HLA B8 was prevalent in relatively high percentages in the UK. More recent studies in contrast have shown that children had significantly higher frequencies of HLA Cw7, HLA B8, and DR3. In adults, there were increasing frequencies of three haplotypes HLA Cw7, HLA B8, DR3, and DQ2.[5]

Clinical Features

Skin manifestations of LABD patients (Figure 2) are the same as those of Pemphigoid Bullosa, present as clear or hemorrhagic vesicles (or both) or bullae arising from normal skin, usually on an erythematous or urticarial

base. The bullae or vesicles are frequently tense and vary in size, and due to the coalescence of lesions, annular or polycyclic plaques frequently form. While in children, the lesions are localized primarily in the lower abdomen and perineal area, with extensive anogenital involvement. The blistering generally occurs in a "cluster of jewels" pattern, where new lesions develop at the margins of pre-existing lesions.[5,6]

Diagnosis

Overall clinical manifestations are needed to diagnose LABD, including patient history and physical examination, also histopathology, and immunofluorescence. The diagnosis is mostly determined by three parameters including clinical, histopathological, and immunological examination. The presence of subepithelial blisters represents the histopathologic appearance, with predominantly neutrophilic infiltration of the upper epidermis forming papillary microabscesses, whereas eosinophils and mononuclear cells may occasionally follow the inflammatory infiltrate. Direct immunofluorescence (DIF) examination on perilesional or healthy skin often shows IgA deposits along the BMZ in a linear pattern, while IgG, IgM, or C3 correlations are less frequently observed. DIF can sometimes be confused with DH when a linear IgA pattern is seen.[5]

Dermatitis Herpetiformis (DH)

Dermatitis herpetiformis (DH) is a **frequent chronic blistering rash that** occurs in people with celiac disease**.** In 1884, Louis Dühring identified the condition as a dermatological entity, four years before gastrointestinal manifestations of celiac disease were identified by Samuel Gee. Small intestinal biopsies from patients with DH in the 1960s revealed that the majority of them had villous atrophy, despite the absence of obvious gastrointestinal symptoms. In one-quarter of DH patients, the architecture of small intestinal villous is normal, with higher intraepithelial lymphocyte density, and this is later defined as celiac-type minor enteropathy.[12-14]

Epidemiology

Gastrointestinal symptoms are uncommon in DH, about 75% of patients showed villous atrophy in the small intestine, while celiac-type inflammatory alterations were present in the remaining 25%.11 In a series of studies involving 76 patients with DH during childhood, it was found that most cases occurred at the age of 2-7 years, and none occurred before the age of 10 months. DH is now recognized as a typical extraintestinal manifestation of celiac disease, which affects 10% of patients in Europe and North America.[11-13]

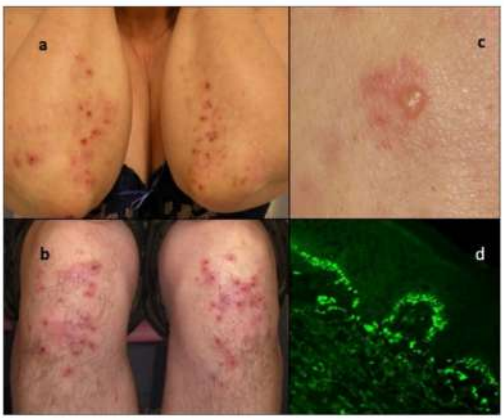

Figure 2. Dermatitis herpetiformis lesion on an elbow and knee: observed the symmetrical distribution and erosion from scratching; c) Close-up view of small blisters; d) Immediate immunofluorescence [10]

Clinical Features

The itchy rash that appears on the elbows, extensor surfaces of the forearms, knees, buttocks, and sacrum region, is one of the clinical symptoms of DH (Figure 3). It is polymorphic, erythematous small blisters and

papules; however, erosion, crusting, and post-inflammatory hyperpigmentation frequently dominate the clinical signs and symptoms induced by significant itching and excruciating scratching. The rash location is fairly typical, and an itchy rash on the predominant skin site typically indicates the presence of DH. The rash's severity tends to vary, and more severe rashes can also appear on other locations, such as the scalp, face, and upper back. Over the past few decades, the clinical features and the rash's severity appear to be unaltered as seen in celiac disease.[11-13]

Diagnosis

Diagnosis is based on the clinical picture, including patient history, physical examination, also histopathology, and immunofluorescence. Since 1969, granular IgA deposits in the dermal papillae of DH patients have been identified using direct immunofluorescence. After that, these findings have specifically proved that the existence of granular IgA deposits in the papillary dermis is now required for the diagnosis of DH. Skin biopsy is collected from normal-appearing skin near the rash, for example, perilesional skin, because IgA deposits are more prevalent close to active lesions. DH has easily suspected if the patient has celiac disease and also skin manifestations.[11,14]

Pemphigus Vulgaris (PV)

Pemphigus vulgaris (PV) is an immunobullous mucocutaneous eruption with loose blisters and erosions, and it is most frequently caused by autoantibodies to desmoglein (Dsg) 1 and 3.[5]

Epidemiology

PV is a rare, chronic autoimmune blistering condition that also affects skin mucosal. The estimated incidence is about 0.1-0.5% per 100,000 population per year.15 PV is rare in children but may occur in < 12 years of age and adolescents (13-18 years) in comparison to adult PV. As a result of maternal antibodies crossing the placenta, cases of neonates and stillbirths have also been reported. The average age of onset for patients with childhood PV was 8.3 years.[5]

Clinical Features

The clinical feature is manifested by the appearance of superficial, thin-walled blisters on healthy skin and/or mucosa, which easily rupture and progressively expand, leaving large open regions. Nikolsky's sign, epidermal detachment induced by intense linear pressure on normal skin, is a typical feature of PV, but not pathognomonic.16 Another possible manifestation is Asboe-Hansen's sign, an enlarged peripheral blister when pressed vertically. The predominant regions of skin lesions are on the urogenital, anus, palpebral, face, neck, chest, hands, and feet. PV begins in the oral cavity and spread to the gums and palate in more than 60% of cases. The nasal mucosa and conjunctiva are also frequently affected.[17]

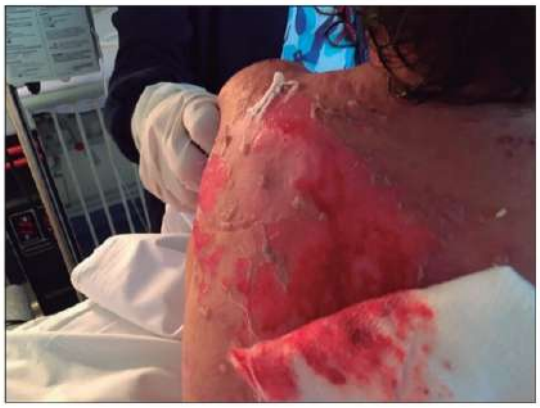

Figure 3. Extensive blisters on back [16]

Diagnosis

Comprehensive clinical features, including the patient's history and physical examination, also histology, and immunofluorescence, are needed to establish the diagnosis. PV should be diagnosed with a biopsy, as it is confirmed by histological studies and DIF. Intraepidermal blisters that contain eosinophils, and a superficial perivascular and deep inflammatory infiltrate, are characteristics of histopathological studies of PV. Linear intraepidermal intercellular IgG and C3 deposition are typically revealed by DIF examination. Circulating antibodies to hemidesmosome antigens are detected by indirect immunofluorescence using patient serum in 70% of cases. Upon skin biopsy, a distinctive row of tombstones is visible.[16]

Pemphigus Foliaceus (PF)

Pemphigus foliaceous (PF) is an immunobullous skin eruption without the involvement of the mucous membrane that is typically due to antibodies to Dsg1. DIF creates a similar pattern to PV, although the bullae or blisters are usually shallower. PF is an autoimmune bullous disorder due to autoantibodies targeting Dsg1, usually marked by crusted plaques, erosions, and loose vesiculobulae.[19]

Epidemiology

The age range of pediatric patients diagnosed with PF was 22 months to 14 years, with an average of 6.2 years. Boys comprise the majority of patients with a male-female ratio was 1.25:1.[19]

Clinical Features

Children and adults have an identical clinical presentation of PV, with superficial blistering and crusted skin erosions in a seborrheic distribution, despite childhood PF having a distinctive pattern of "arcuate, circinate, or polycyclic lesions". The diagnostic and immunological findings are the same across all age groups.[5]

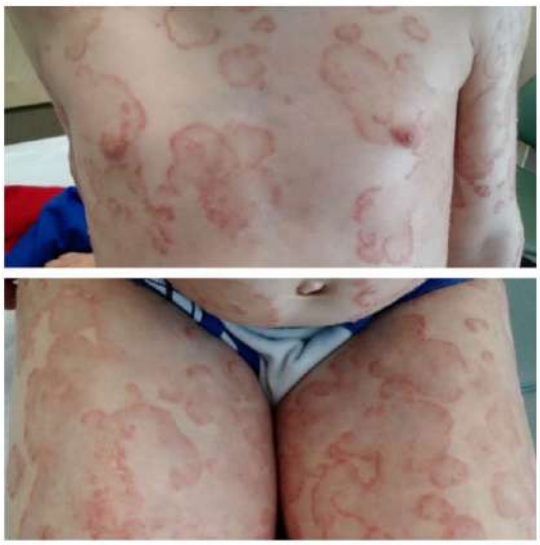

Figure 4. Erythematous annular and polycyclic plaques located on the trunk and proximal extremities.[19]

Diagnosis

The following criteria should be provided to diagnose PF, namely clinical symptoms, (patient's history and physical examination); histopathological examination; direct and indirect immunofluorescence studies to detect autoantibodies. Histopathologic analysis of early blisters shows acantholysis of the upper epidermis, frequently causing subcorneal fissures and midlevel epidermal detachment.19,20 Deposition of IgG and C3 in intercellular space (ICS) staining is found by DIF, and it is termed as 'chicken wire'.[15]

Paraneoplastic Pemphigus (PNP)

Paraneoplastic pemphigus (PNP) is defined as a clinical syndrome that is not associated with direct tumor invasion or compression, but secondary to tumor secretion of peptides and functional hormones, or associated with immune cross-reactivity with normal host tissues.21 PNP is a blistering disease, a rare autoimmune condition marked by polymorphous skin lesions and chronic mucositis, frequently linked to benign and malignant hematological neoplasms and solid tumors.[22]

Epidemiology

The incidence and prevalence are uncertain.21 The previous studies had reported 500 cases of PNP and about 3-5% of all cases of pemphigus. The median age of childhood PNP is 13–14 years, most commonly at age 16.5 However, it also affects children and adolescents, especially when related to Castleman's disease. Race, ethnicity, or geographic differences as the risk factors of PNP have not been recognized.15 Non-Hodgkin's lymphoma is the most frequent underlying malignancy that causes PNP in adults, while in children is Castleman's disease.[5,15]

Clinical Features

Severe stomatitis, which can affect adults and children, is the most common clinical symptom. However, the skin lesions in childhood PNP are more lichenoid than blistering, in contrast to the adult form.[5]

Diagnosis

The association between clinical presentations, histological analysis, and DIF will determine the diagnosis of PNP.24,25 In PNP, histopathological studies are various, including intraepidermal acantholysis (loss of cell-cell adhesion), and necrosis of keratinocytes. DIF of mucosa and skin biopsies may show deposits of immunoglobulin G and complement components throughout the epithelial BMZ. Therefore, the correlation of clinical evaluation, histopathological examination, and immunofluorescence will determine the diagnosis.[26]

Bullous Pemphigoid (BP)

Bullous pemphigoid (BP) is an acquired autoimmune subepidermal blistering disease that affects the elderly and infrequently presents in children, which identified by circulating autoantibodies that target antigenic components specific to the skin and mucous basement membranes such as the 180-kDa BP antigen (collagen type XV11).[27]

Epidemiology

It mostly appears in children above 8 years, and the mean age at onset of BP was 10 years, with female to male ratio was 2:1, and the 2-year-old patient was the youngest. Childhood BP is reported rapidly increasing and occurs in about 53% of cases within the first year of life.[28]

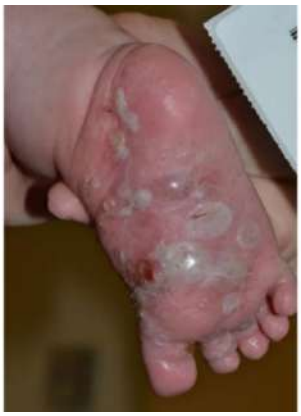

Figure 5. Pemphigoid bullosa 5

Clinical Features

Tense bullae and pruritus are the classic presentation of BP, which has a variable appearance in children. In one study of 78 patients reported two peaks of onset in childhood, with 53% of cases developing in the first year of life at a median age of 4 months, and the second peak occurring in 47% of cases at a median age of 8 years. Acral involvement is quite common in infantile BP, and an increased number of vulvar involvements is seen in childhood BP. Neonatal cases have been reported, typically with maternal gestational pemphigoid.[5]

Diagnosis

The diagnosis of BP is based on the association between clinical and histological examination, and also DIF. Biopsy showed well-demarcated subepidermal blisters, superficial dermis showing minimal chronic perivascular inflammation with few eosinophils. The majority of patients who had DIF test on their perilesional skin had linear IgG deposition, and almost all of them had C3c.[28]

Mucous Membrane (Cicatricial) Pemphigoid (MMP)

MMP is a group of immunobullous subepidermal diseases frequently with scarring which had mucosal involvement, and it is very uncommon in children.[5] Nasopharynx, larynx, genitals, rectum, and esophagus are some mucosal areas that may be affected. It can lead to blindness by scarring the affected eye mucosa. This disease is considered an autoimmune disease marked by the production of autoantibodies against BMZ antigens such as BP180, BP230, and laminin 5.[29]

Epidemiology

The estimated incidence of MMP in France and Germany is 1.3 and 2.0 per 1 million people-years, respectively. The disease presents earlier onset than bullous pemphigoid, with a mean age between 60 and 65 years. This disease is associated with HLA DQB1*0301.29 The age of onset of 18 cases in children with MMP in one review was 10.3 years (20 months to 18 years old).[5]

Clinical Features

The clinical manifestations of MMP affect the mucosa or mucous membranes of the conjunctiva and the oral cavity. In addition, it can also occur on the mucosa of the nasal cavity, esophagus, pharynx, and genitals.5 The oral cavity is the most typical location of MMP, and oral MMP is first presented as desquamative gingivitis. There have also been reports of ocular involvement, which can appear years after the first onset. The clinical manifestations of MMP in childhood are varied.[29]

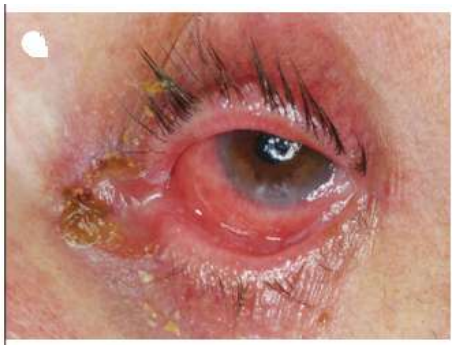

Figure 6. MMP on the conjunctival mucosa [29]

Diagnosis

Clinical characteristics, histological examination, and direct immunofluorescence are needed to make a diagnosis of MMP, based on a predominant mucosal lesion and also from DIF microscopy. It shows deposition of IgG, complement component 3, and IgA from perilesional specimens along the dermal-epidermal junction, and about 60% of serum samples may detect IgA autoantibodies.[29]

Epidermolysis Bullosa Acquisita (EBA)

EBA is a rare autoimmune blistering skin disease, mostly caused by the production of type VII collagen autoantibodies, a key protein that connects the epidermis and dermis. It occurs very rarely in childhood.[30]

Epidemiology

There are two main types of EBA. First, the classic non-inflammatory mechanobullous variant, which is more usual in adults presenting as acral blisters with scarring. The second one is the inflammatory type which is more likely in children, especially above 5 years of age.[5]

Clinical Features

The criteria of McCuaig et al. are used to support childhood EBA diagnosis: (a) onset at 18 years of age or younger and not congenital; (b) negative family history of epidermolysis bullosa; (c) exclusion of other bullous diseases; (d) relatively difficult to respond to therapy; (e) mucocutaneous bullae, (f) mild microscopic findings of subepidermal blisters and/or inflammation; (g) direct immunofluorescence (DIF) and indirect immunofluorescence (IIF) of perilesional skin showing linear deposits at the dermo-epidermal junction (DEJ) of IgG or IgM, IgA, C3, fibrinogen, while IgG is deposited on the dermal split side in human skin; and (h) serum antibodies against collagen type VII (EBA antigen) are detected using Western immunoblot or enzyme-linked immunosorbent assay (ELISA).[30]

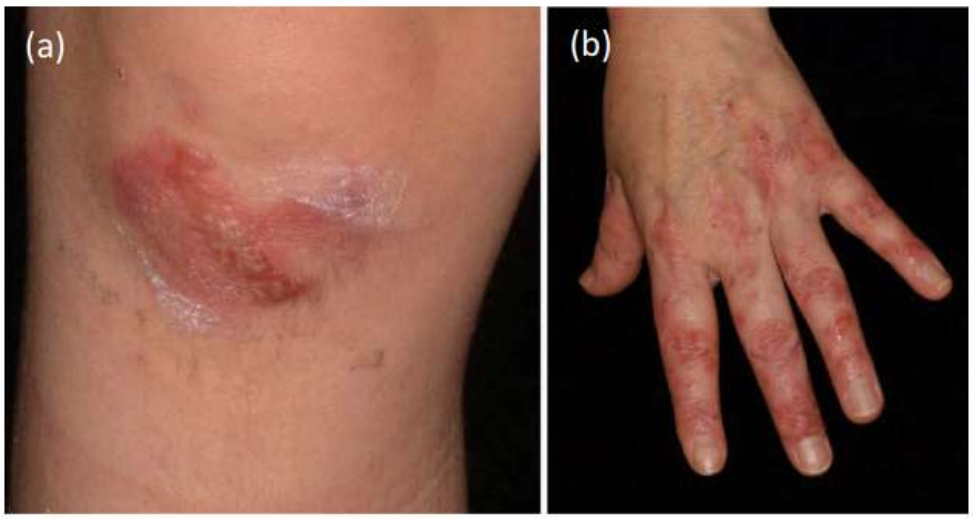

Figure 7. A classic variant of EBA. (a) Erythema and tension blisters on the knee B. Erythema and erosion on left hand.[32]

Diagnosis

Diagnosing EBA only from clinical features is not possible, because of the wide variety of clinical features.32 Diagnosis of EBA consists of histopathological analysis and direct immunofluorescence (DIF) and indirect immunofluorescence (IIF), in which the subepidermal bullous dermatosis can be diagnosed. Histopathological analysis of injured skin in EBA patients has shown subepidermal cleavage with varied degrees of inflammatory infiltration. Linear deposition of IgG and C3 along the BMZ can be seen from the DIF of perilesional skin. IgA and/or IgM may occasionally be found on examination.[31] The summary of the autoimmune bullous disease in children is presented in Table 1 below, also its target antigens and the common clinical presentation.[33]

Table 1. Autoimmune blister disease in children, target antigen and common clinical features.[33]

Disease	Target antigen	Clinical features
Pemphigus vulgaris	Desmoglein 3 Desmoglein 1	Flaccid blisters, erosions and crusts on the skin, painful erosions at the mucous membranes
Pemphigus foliaceus	Desmoglein 1	Only skin affected with scaly and crusted erosions, often pruritus
Bullous pemphigoid	BP180 BP230	Tense blisters, erosions and crusts, severe pruritus, mucous membranes rarely affected
Linear IgA dermatosis†	Soluble ectodomain of BP180 (LAD-1) BP230	Erythema, tense blisters and vesicles in a typical arrangement ('crown of jewels'), mucosal involvement possible
Mucous membrane pemphigoid	Soluble ectodomain of BP180 (LAD-1) BP180 BP230 Laminin 332	Only or predominantly mucous membranes affected with blisters and erosions, scarring of conjunctiv
Epidermolysis bullosa acquisita	Type VII collagen	Mechanobullous type: blisters, erosions, crusts and scars in exposed sites (Fig. 1) Inflammatory type: like BP or LAD

BP, bullous pemphigoid; LAD, linear IgA disease.
†Also termed chronic bullous dermatosis of childhood.

CONCLUSION

Autoimmune blistering or bullous disease is rare in children, but it can affect their long-term quality of life. Clinical knowledge regarding disease presentation and treatment are essential. Autoimmune bullae or blisters in children can be grouped into 8 diseases, namely: Linear Immunoglobulin A Bullous Dermatosis (LABD), Dermatitis Herpetiformis (DH), Pemphigus vulgaris (PV), Pemphigus Foliaceus (PF), Paraneoplastic Pemphigus (PNP), Bullous Pemphigoid (BP), Mucous Membrane (Cicatricial) Pemphigoid (MMP), and Epidermolysis bullosa acquisita (EBA). Clinical examination, histopathological, and immunological features often overlap, but diagnostic skills are needed as a clinician to provide appropriate management.

CONSENT FOR PUBLICATION

The Authors agree to publication in Journal of Society Medicine.

FUNDING

This article has received no external funding

COMPETING INTERESTS

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTIONS

All authors significantly contribute to the work reported. Contribute to drafting, revising, or critically reviewing the article. Approved the final version to be published, agreed on the journal to be submitted, and agreed to be accountable for all aspects of the work.

ACKNOWLEDGMENTS

I would like to thank all those who have supported me during the writing process of this article review.

REFERENCE

1. James WD, Elston DM, McMahon PJ. Andrews' Diseases of the Skin Clinical Atlas. Philadelphia: Elsevier. 2018. p. 1-10 3.
2. Kubo A, Amagai M. Skin Barrier. In: Sewon K, Masayuki A, Anna LB, et al. Fitzpatrick Dermatology 9th Edition. New York: The McGraw Hill Education. 2019. p. 206-231

3. Amy K. Forrestel & Robert G. Micheletti. Skin Manifestations of Internal Organ Disorders. In : Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, Orringer JS. Fitzpatrick's Dermatology 9th Edition. New York: McGraw-Hill Education. 2019: p.2425-2440.
4. Sampaio AL, Aline LB, Barbara NV, Alexandre CG. Skin manifestations associated with systemic diseases --- Part I. A Bras Dermatol. 2021. 96: p.655-671. DOI: https://doi.org/10.1016/j.abd.2021.02.008
5. Schultz B and Hook K. Bullous diseases in children: a review of clinical features and treatment options. Pediatric Drugs 2019; 21(5): 345-356. DOI: https://doi.org/10.1007/s40272-019-00349-3
6. Pradhan S, Jha K, Kumari P, Shrestha S, Jha AK. Chronic Bullous Disease of Childhood: A Case Report and Review of Literature of Bullous Diseases in Children. Nepal Journal of Dermatology, Venereology & Leprology 2022; 20(2): 69-75. DOI: https://doi.org/10.3126/njdvl.v20i2.47326
7. Mellyanawati. Laporan kasus: seorang anak dengan penyakit bula diduga Chronic Bullous Disease of Childhood. Jurnal Ilmiah Kedokteran Wijaya Kusuma 2021; 10 (2): 176-18
8. Bruckner AL. Inherited and Acquired Blistering Diseases. Neonatal and Infant Dermatology 3rd edition. Elsevier Saunders, USA. 2015. p: 151–154.
9. Oentari W, Mahadi IDR, Nababan KA. 2020. Kesulitan Diagnosis Penyakit Bulosa Pada Anak. MDVI 2020; 47 (3): 127-131.
10. Fortuna G and Marinkovich (MP). Linear immunoglobulin A bullous dermatosis. Clinics in dermatology 2012; 30(1): 38-50. DOI:10.1016/j.clindermatol.2011.03.008
11. Reunala T, Hervonen K, and Salmi T. Dermatitis herpetiformis: an update on diagnosis and management. American Journal of Clinical Dermatology 2021; 22(3): 329-338. DOI: https://doi.org/10.1007/s40257-020-00584-2
12. Salmi T and Hervonen K. Current concepts of dermatitis herpetiformis. Acta dermato-venereologica 2020; 100: 115-121. DOI: 10.2340/00015555-3401
13. Zingone F, Maimaris S, Auricchio R, Caio GPI, Carroccio A, Elli L, Galliani E., et al. Guidelines of the Italian Societies of Gastroenterology on the diagnosis and management of coeliac disease and dermatitis herpetiformis. Digestive and Liver Disease 2022; 54(10): 1304-1319. DOI: https://doi.org/10.1016/j.dld.2022.06.023
14. Cardones ARG and Hall RP. Pathophysiology of dermatitis herpetiformis: a model for cutaneous manifestations of gastrointestinal inflammation. Immunology and Allergy Clinics 2012; 32(2): 263-274. doi: 10.1016/j.iac.2012.04.006
15. Costan VL, Popa C, Hancu MF, Andrese EP, Toader MP. A comprehensive review of the pathophysiology, clinical variants, and management of pemphigus. Experimental and Therapeutic Medicine 2021; 22(5): 1-13. DOI:10.3892/etm.2021.10770
16. Lambogliaa ALC, Gubitosi AM, Bakerdijan CG, Larraz GG. Pemphigus vulgaris in pediatrics: a case report. Rev Chil Pediatr 2018; 89 (5): 650-654. DOI: 10.4067/S0370-41062018005000708
17. Didona D, Maglie R, Eming R, and Hertl M. Pemphigus: Current and future therapeutic strategies. Front Immunol 2019; 10: 1418. DOI: 10.3389/fimmu.2019.01418
18. Amber KT, Valdebran M and Grando SA. Nondesmoglein anti bodies in patients with pemphigus vulgaris. Front Immunol 2018; 9: 1190. DOI: 10.3389/fimmu.2018.01190
19. Evans MS, Culton DA, Diaz LA, George PB, Morrel DS. Childhood pemphigus foliaceus presenting as a polycyclic eruption: Case report and review of the literature. Pediatric Dermatology 2019; 36(2): 236-241. DOI: 10.1111/pde.13750
20. Stanley JR. The pathophysiology of pemphigus. Journal of Dermatological Science 2000; 24: 155-157
21. Grace MY MY, Chow JS, and Taylor GA. Review of paraneoplastic syndromes in children. Pediatric Radiology 2019; 49: 534-550. DOI: https://doi.org/10.1007/s00247-019-04371-y
22. Maruta CW, Miyamoto D, Aoki V, Carvalho RGR, Cunha BM, Santi CG. Paraneoplastic pemphigus: a clinical, laboratory, and therapeutic overview. Anais brasileiros de dermatologia 2019; 94: 388-398. DOI: http://dx.doi.org/10.1590/abd1806-4841.20199165

23. Czernik A, Camilleri M, Pittelkow MR, Grando SA. Paraneoplastic autoimmune multiorgan syndrome: 20 years after. Int J Dermatol 2011; 50: 905-14. DOI: https://doi.org/10.1111/j.1365-4632.2011.04868.x
24. Yong AA and Tey HL. Paraneoplastic pemphigus. Australas J Dermatol 2013; 54: 241-50. DOI: https://doi.org/10.1111/j.1440-0960.2012.00921.x
25. Ishii N, Teye K, Fukuda S, Uehara R, Hachiya T, Koga H., et al. Anti-desmocollin autoantibodies in nonclassical pemphigus. Br J Dermatol 2015; 173: 59-68. DOI: https://doi.org/10.1111/bjd.13711
26. Dias DRK, Ramos AF, Yamashita ME, Carcano CBM. Paraneoplastic pemphigus associated with chronic lymphocytic leukemia: a case report. Journal of Medical Case Reports 2018; 12(252): 1-4. DOI: https://doi.org/10.1186/s13256-018-1742-8
27. Kasperkiewicz M and Zillikens D. The pathophysiology of bullous pemphigoid. Clinical reviews in allergy & immunology 2007; 33: 67-77. DOI: 10.1007/s12016-007-0030-y
28. Veljic MG, Nikolic M, and Medenica L. Juvenile bullous pemphigoid: the presentation and follow‐up of six cases. Journal of the European Academy of Dermatology and Venereology 2010; 24: 69-72. DOI: 10.1111/j.1468-3083.2009.03264.x
29. Schmidt E and Zillikens D. Pemphigoid diseases. The Lancet 2013; 381: 320-332. DOI: http://dx.doi.org/10.1016/
30. Hignett E and Sami N. Pediatric epidermolysis bullosa acquisita: A review. Pediatric Dermatology 2021; 38: 1047-1050. DOI: 10.1111/pde.14722
31. Santi CG, Gripp AC, Roselino AM, Mello DS, Gordilho JO, Parsillac PF., et al. Consensus on the treatment of autoimmune bullous dermatoses: bullous pemphigoid, mucous membrane pemphigoid, and epidermolysis bullosa acquisita-Brazilian Society of Dermatology. Anais brasileiros de dermatologia 2019; 94: 33-47. doi: http://dx.doi.org/10.1590/abd1806-4841.2019940207
32. Vorobyev A, Ludwig RJ, and Schmidt E. Clinical features and diagnosis of epidermolysis bullosa acquisita. Expert review of clinical immunology 2017; 13(2): 157-169. DOI: http://dx.doi.org/10.1080/1744666X.2016.1221343
33. Hübner F, Konig IR, Holtsche MM, Zillikens D, Linder R, Schmidt E. Prevalence and age distribution of pemphigus and pemphigoid diseases among pediatric patients in Germany. Journal of the European Academy of Dermatology and Venereology 2020; 34(11): 2600-2605. DOI: 10.1111/jdv.16467