Autoimmune bullous diseases in childhood

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Introduction and Aims

Short Definition in Layman Terms

Autoimmune bullous diseases (AIBDs) in childhood encompass the same spectrum of subtypes as the group of AIBDs in adults, both from the pemphigoid group, the pemphigus group and dermatitis herpetiformis (DH). Linear IgA disease (LAD) is the most common AIBD in children, followed by DH and bullous pemphigoid (BP). Neonatal AIBD variants exist, in which passive transfer of autoantibodies from the mother to the child has occurred. These types are usually self-limiting in a few weeks.

Learning Objectives

After reading this chapter, you will be able to recognize clinical features of different AIBDs in childhood and know the differential diagnosis of bullous diseases in childhood. You will also be aware of differences between childhood and adult AIBDs, treatment options and prognosis.

Case Study: Part 1

A 3-month-old girl was referred by a pediatrician because of vesicles evolving to blisters on the feet and hands and spreading to the trunk (Fig. 24.1). The mucosal surfaces were unaffected. The girl was the first child of non-consanguineous parents. Pregnancy and childbirth were uneventful. No exogeneous factors were involved. Family history was negative for skin fragility disorders. The lesions started several days after vaccination (diphtheria, tetanus, pertussis, polio, hepatitis B, haemophilus influenza type b, pneumococcal vaccine). Because PCR for coxsackievirus and enteroviruses were negative, the working diagnosis of hand-foot-mouth disease was discarded, and the girl was referred to our dermatology clinic.

Didactical Questions

Are there specific clinical features in the different AIBDs in childhood? What is the most frequent AIBD in children? How are AIBDs in children diagnosed? What is the course and long-term prognosis of the different forms of AIBDs in childhood? Does therapy in AIBDs in children differ from that in adults? Are comorbidities associated with AIBDs in children?

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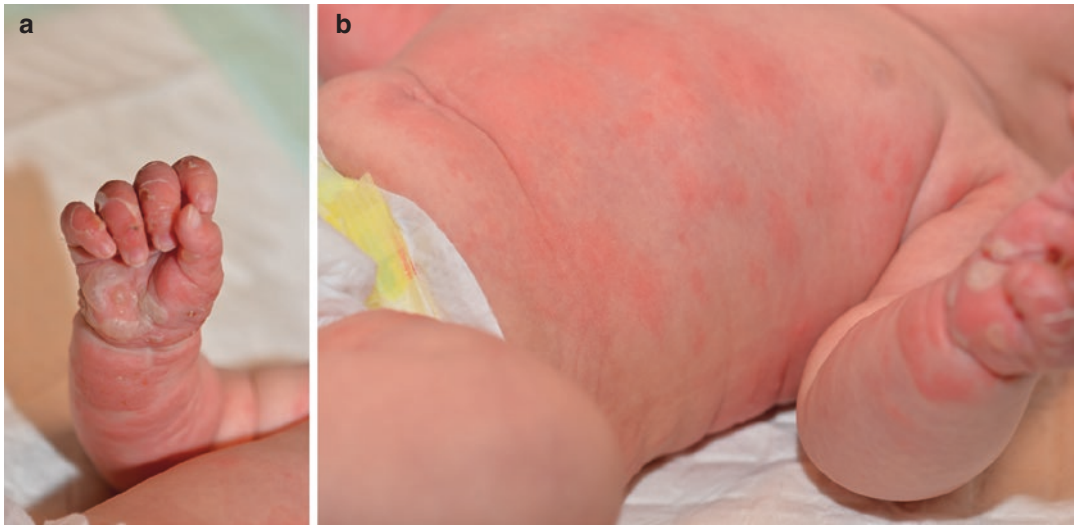

Fig. 24.1 A 3-month-old with tense blisters, vesicles, crusts and erythematous plaques on the hand and lower arm (**a**), and erythematous papules and plaques on the trunk (**b**)

Facts and Figures

The spectrum of AIBDs in children comprises the same subtypes as in adults, as also the recognized autoantigens in the different forms of AIBDs in children (see also the respective chapters of the different AIBDs). AIBDs in childhood are very rare. The prevalence in the German population was estimated to be around 100 cases per million children [1]. In most of the reported pediatric AIBD populations LAD was reported to be the most frequent AIBD in childhood followed by DH and BP [2, 3]. Neonatal forms of LAD, BP, pemphigus vulgaris (PV) and pemphigus foliaceus (PF) due to transplacental maternal antibodies have been reported with the majority having a self-limiting course in several weeks when maternal antibodies subside, or only minor treatment [4]. A few neonatal LAD cases have been reported with a more severe and prolonged course requiring systemic immunosuppressive therapy.

Vaccinations and antibiotics have been reported in several cases as eliciting factors for LAD and BP in children, although the exact correlation remains difficult to establish [5]. Epidermolysis bullosa acquisita (EBA) in children has been associated with inflammatory bowel disease [6]. The underlying neoplasm in paraneoplastic pemphigus (PNP) in children is most often Castleman's disease.

LAD is the the most frequent childhood AIBD

Diagnosis Paths

History and Physical Examination

The presenting clinical features of AIBDs in childhood may vary from the adult variants [7]. The clinical features of the different AIBD types in children are summarized here.

Clinical features of LAD in childhood include pruritus and annular configuration of blisters on the skin in a "crown of jewels" or "string of pearls" pattern. Primary lesions are clear and/or hemorrhagic firm vesicles and bullae on normal or erythematous maculae or plaques. New lesions are formed at the edges of the older lesions (Fig. 24.2a). They typically appear on the abdomen, groin and thighs, the anogenital skin, feet, hands, face and perioral area. The mean age of onset of childhood LAD is around 5–6 years.

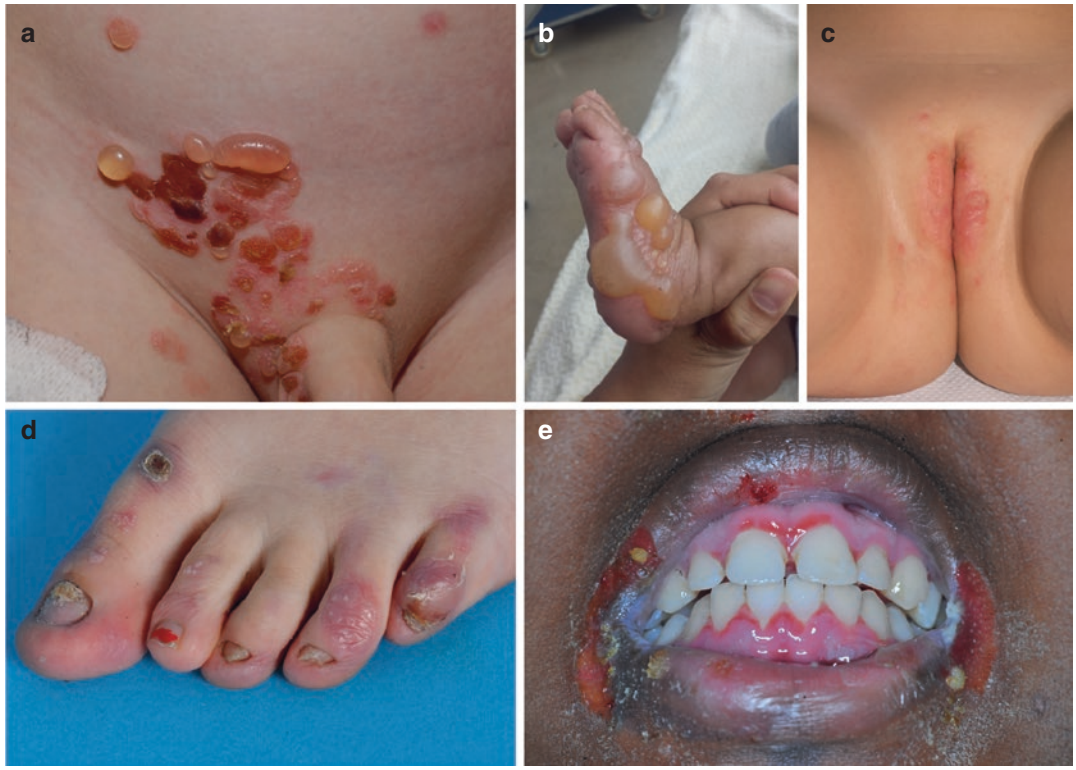

Fig. 24.2 LAD in a young boy presenting with serous bullae and hemorrhagic crusts in a serpiginous configuration in the pubis/genital area (**a**). BP in an infant with multiple tense, serous blisters and vesicles on the foot (**b**). LVP in a young girl, presenting with vulvar erythema and erosions (**c**). EBA in a 12-year-old girl with scars, milia and crusts on the dorsum of the foot and toes, and partly absent, partly dystrophic toenails (**d**). Pemphigus vulgaris in a 10-year-old girl with a desquamative gingivitis and erosions peri-oral and on the lips and (**e**)

The clinical manifestations of DH are similar in children and adults, classically presenting as intensely pruritic polymorphous eruption favoring extensor surfaces (see also Chap. 20).

BP in childhood may present at different ages. Commonly involved body site in infantile BP (<1 year of age) are the palms, soles and head (Figs. 24.1 and 24.2b) [8]. Childhood BP (>1 year of age) has a more diffuse distribution of lesions, including the mucosae. The vulvar area is often involved as well. Firm vesicles and blisters on erythematous or normal-appearing skin can be seen. In addition, pruritic, erythematous papules and plaques with irregular, annular and polycyclic configurations are usually present, and may precede or coexist with blisters. Blisters may vary in size, are usually symmetrical and ungrouped with serous and/or hemorrhagic contents. Lesions of childhood BP are non-scarring and usually pruritic.

EBA can be divided in two clinical variants: a classic mechanobullous phenotype (more common in adults and older children) which has clinical similarities with hereditary dystrophic epidermolysis bullosa, and an inflammatory phenotype which shows similarities in presentation to bullous pemphigoid (more common in children younger than 5 years of age). In mechanobullous EBA clinical characteristics include clear or hemorrhagic blisters on extensor surfaces of extremities at sites of trauma that heal with scarring (Fig. 24.2d). Mucosa (oral and genital) are often affected in childhood EBA. Furthermore, nail dystrophy, milia, and alopecia may be seen. The lesions of EBA may heal with scarring.

Mucous membrane pemphigoid (MMP) may present in childhood, although it is one of the least frequent childhood AIBDs. Only few case reports have been published. The clinical presentation of MMP in childhood is comparable to that in adulthood. It may likewise vary in presentation, mucosal sites involved, and severity (see also Chap. 15). The oral mucosa is the most common site involved, with a desquamative gingivitis as presenting sign. Affection of the vulvar mucosa and skin may be the only site involved in juvenile localized vulvar pemphigoid, Fig. 24.2c and see Chap. 15).

The clinical presentation of PV usually starts with painful mucosal blisters and erosions. Oral mucosal lesions, most often the gingiva, occur in 50–70% of childhood patients (Fig. 24.2e). Mainly non-pruritic flaccid blisters that easily erode on skin will develop after a period of weeks to months. Preferred locations of PV in both adults and children are the mucous membranes, upper torso (in a V-shape), the face including the eyelids, the scalp and the flexural areas. PF presents similar in children as in adults, with erythematosquamous plaques with a predilection for the scalp, face and upper trunk (see also Chap. 9). It may mimic seborrheic dermatitis. A clue to the diagnosis (also for pemphigus vulgaris) is the positive Nikolsky sign. Pemphigus variants may present at any age in childhood.

PNP in children has a severe stomatitis as its most frequent clinical presentation. In addition, erythematosquamous papules and plaques with lichenoid appearance are observed. In children, PNP is often accompanied by pulmonary involvement leading to bronchiolitis obliterans and subsequent high morbidity.

A baby with acral vesicles and blisters with negative skin swabs should be suspected of infantile BP

Diagnostics

The differential diagnosis of blistering in children may differ per age group and depending on the localization (mucosa, skin) and distribution. Most often AIBDs in children are confused with infectious causes like impetigo bullosa and hand-foot-mouth disease. The differential diagnosis comprises genetic diseases (forms of epidermolysis bullosa and related skin fragility disorders, keratinopathic ichthyoses, bullous mastocytosis, acrodermatitis enteropathica (may be acquired as well), autoinflammatory syndromes, m. Behcet), infectious diseases (like candida, herpes, varicella, impetigo bullosa, staphylococcal scalded skin syndrome, hand-foot-mouth disease ad scabies), inflammatory diseases (lichen planus, lichen sclerosus, erythema multiforme), acropustulosis of infancy, and exogenous causes. Childhood vulvar pemphigoid may be confused with sexual abuse.

Diagnosis of AIBDs in children is made based upon clinical features, direct immunofluorescence (DIF) microscopy of perilesional skin and serology screening for tissue bound and circulating autoantibodies respectively, similar as in AIBD in adults (see the respective chapters). In childhood BP the serology seems to be more sensitive than in adults. In neonates with a suspicion for an AIBD it is important to pay attention to skin complaints of the mother during pregnancy and right afterwards that may point to an AIBD in the mother and the possibility of transplacental transfer of autoantibodies. Bacterial and yeast swabs, and PCR swabs of affected/eroded skin may help in differentiating with infectious causes. In case PNP is diagnosed, screening for underlying neoplasms should initiated. Careful history should be taken for bowel complaints, and, if indicated, the child should be referred for screening for inflammatory bowel diseases.

Childhood AIBD is diagnosed with DIF of perilesional skin for tissue bound autoantibodies and serology for circulating autoantibodies

Case Study: Part 2

Physical examination revealed multiple vesicles and bullae on erythematous and urticarial plaques, mainly on hands and feet, but also on proximal extremities and trunk (Fig. 24.1). Mucosal surfaces were unaffected. No scars or milia were

seen. A differential diagnosis was considered of acropustulosis of infancy, viral infection (herpes simplex/zoster), bacterial infection (impetigo bullosa), bullous scabies, linear IgA disease, neonatal bullous pemphigoid or epidermolysis bullosa acquisita, epidermolysis bullosa (simplex) or diffuse cutaneous mastocytosis.

Skin swabs were negative. A skin biopsy for histopathology showed an eosinophilic spongiotic dermatitis and subepidermal blister formation. A skin biopsy for DIF showed IgG 3+, IgA 1+ and complement C3 3+ along the EBMZ in a linear n-serratted pattern. Indirect IF on salt-split skin showed positive IgG 2+ roof staining, with also a positive BP180 NC16A ELISA (titer 116 U/ml). The diagnosis of **neonatal bullous pemphigoid** was made, possibly triggered by vaccination. The positive DIF biopsy with IgG, IgA and C3c depositions in an n-serrated pattern and findings of indirect IF on salt-split skin exclude linear IgA disease and epidermolysis bullosa acquisita.

Treatment Tricks

Initial Treatment and Therapeutic Ladder

No treatment guideline is available specific for AIBDs in childhood, the treatment and medication is similar to adults, but dosages taken into account. The various AIBDs in childhood may require specific treatments, such as dapsone in LAD, a gluten-free diet combined with dapsone in DH, topical tetracycline cream in juvenile LVP and treatment with topical and/or oral corticosteroids with potential adjuvant immunosuppressive agents in subtypes of pemphigoid and pemphigus. In general, topical corticosteroids (class III–IV) alone is a first step in treatment and often sufficient in milder forms of AIBD. The use of oral corticosteroids remains a treatment for moderate and severe forms of bullous pemphigoid, mucous membrane pemphigoid, epidermolysis bullosa or pemphigus. Especially in recalcitrant cases, adjuvant immunosuppressive agents may be considered, such as mycofenolate mofetil, colchicine or rituximab. Colchicine is a treatment option for childhood EBA with relative mild side effects, and suitable for mild cases or when other immunosuppressive agents fail.

Follow-Up and Long-Term Prognosis

AIBDs in childhood in general have a milder course, a good treatment response and a better long-term prognosis than AIBD in adults [2, 7]. Nevertheless, large areas of eroded skin always pose a threat for superinfection, and loss of fluid and electrolytes. Therefore, AIBDs in children should be considered a serious condition that requires fast treatment and adequate and hygienic skin care (see also Chap. 25). Long term follow-up of our own cohort of childhood AIBD (44 patients) did not reveal any associated diseases in a mean time of follow-up of almost 9 years.

EBA and MMP may have a more prolonged and therapy resistant course, similar as in adults. PNP in children, as in adults, has a poor prognosis with high mortality due to bronchiolitis obliterans.

Case Study: Part 3

The initial treatment of lesional clobetasol cream once a day did not lead to disease control. Therefore, in conjunction with a pediatrician, prednisolone 0.5 mg/kg/day (3 mg) was started, and dosage increased to 1.0 mg/kg/day (5 mg) because of active disease. Topical steroids were maintained. Pain management was optimized, and osteoporosis prophylaxis (vitamin D) and proton pump inhibitor were prescribed during prednisolone treatment, with also regular check-ups of blood glucoses and blood pressure. After 1 month of treatment, prednisolone was tapered to stop in the follow-

ing 2 months. Three months after the initial lesions, she was in complete remission and the topical corticosteroids tapered and ultimately stopped after 4 months, without signs of skin atrophy. No relapse occurred.

Review Questions

1. What is the most frequent AIBD in children?
   a. BP
   b. LAD
   c. PV
   a. MMP
2. The AIBD with the most favorable clinical course and prognosis is:
   a. MMP
   b. EBA
   c. BP
   d. PV
3. Diagnostics of a child with suspicion of an AIBD should include (more than 1 is right):
   a. DIF biopsy.
   b. Serology for circulating autoantibodies.
   c. Hb, MCV, leucocytes.
   d. Gastroduodenoscopy and colonoscopy.
4. First line therapy of mild infantile BP consists of:
   a. Topical superpotent corticosteroids.
   b. Topical tetracycline cream.
   c. Oral corticosteroids (0.5 mg/kg/day).
   d. Dapsone.
5. Which statement about childhood mechanobullous EBA is incorrect?
   a. Oral mucosa is affected in most of the patients.
   b. It responds well to treatment.
   c. It resembles dystrophic epidermolysis bullosa.
   d. It can be associated with inflammatory bowel disease.

Answers

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

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