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Autoimmune Bullous Disease in Childhood

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Abstract

Background:

Autoimmune bullous disorders (AIBDs) are a heterogeneous group of diseases which are rarely seen in children. Studies concerning the immunobullous diseases in pediatric patients are scarce.

Aims and Objectives:

In this study, we aimed to investigate the clinical features and treatment outcomes of AIBDs in children.

Materials and Methods:

The electronic records of the patients in our AIBDs outpatient clinic were retrospectively reviewed. All cases diagnosed before the age of 16 years were included in the analysis of clinical features, treatment outcomes, and follow-up data.

Results:

Of the 196 patients with immunobullous diseases, 9 (4.6%) were diagnosed before the age of 16 years. Mean age of the patients at the time of diagnosis was 7.72 ± 5.66 years. Among nine patients, linear immunoglobulin A disease (LAD), pemphigus vulgaris (PV), and bullous pemphigoid (BP) were seen in 5, 2, and 2 children, respectively. All patients were treated with at least two systemic agents (including methylprednisolone, dapsone, methotrexate, salazopyrine, intravenous Ig [IVIg], and rituximab) leading to clinical remission in all of them after a mean period of 31.77 ± 27.99 months.

Conclusion:

In line with earlier studies, LAD was the most common immunobullous disease and in general, associated with a favorable response to dapsone. This study was noteworthy in that the patients with PV and BP demonstrated a relatively more recalcitrant course, requiring rituximab and IVIg for remission,

respectively. Overall, patients had a good prognosis.

Key Words: *Autoimmune bullous disease*, *bullous pemphigoid*, *childhood*, *linear immunoglobulin A disease*, *pemphigus vulgaris*

What was known?

- Autoimmune bullous disorders comprise a heterogeneous group of diseases rarely seen in children
- In studies from different regions of the world, linear immunoglobulin A disease was found to be the most common immunobullous disease of the pediatric age, usually associated with a favorable prognosis
- Pemphigus and bullous pemphigoid may follow a more recalcitrant course, requiring intravenous immunoglobulin and/or rituximab for remission.

Introduction

Autoimmune bullous disorders (AIBD) encompass a wide variety of diseases such as pemphigus vulgaris (PV), bullous pemphigoid (BP), linear immunoglobulin A disease (LAD), and dermatitis herpetiformis (DH). They are all characterized by mucosal and/or cutaneous blister formation caused by autoantibodies targeting specific adhesion molecules of the skin. Due to the rarity of AIBDs during pediatric age, studies regarding their prevalence, clinical characteristics, and treatment outcomes in children are sparse.[1,2] In an attempt to contribute to the existing literature data on AIBDs in childhood, we embarked on a retrospective study.

Materials and Methods

A retrospective study was performed to identify the clinical features and parameters related to the treatment and follow-up of pediatric patients diagnosed with AIBD at our institution between the years of 2005 and 2014. In all patients, diagnosis was based on typical clinical and histopathological findings, confirmed by direct immunoflourescence, as outlined elsewhere.[2,3]

Patients who are regularly being followed up in our AIBD outpatient clinic were reviewed. All cases diagnosed before the age of 16 years were extracted. Electronic medical records of these patients were analyzed, with emphasis on clinical data such as demographic information, diagnosis, time until diagnosis, extent of lesions, treatment-related parameters (duration, adverse effects, and response), prognosis, and elapsed time until remission. Comorbidities and concomitant medications were also recorded. Final outcome of the patients was classified into three categories: active disease, remission on treatment, and remission off treatment. Active disease was defined as the development of new vesiculobullous lesions despite adequate treatment. Remission was defined on clinical grounds as reepithelialization of all eroded areas and cessation of new lesion development, either under systemic treatment or off therapy. Results were compared with the relevant data from the literature.

This study was approved and accepted by our Institution's Review Board and has been performed in accordance with the Declaration of Helsinki.

Results

Analysis of 196 patients revealed nine children diagnosed with immunobullous disorders (4.6%). Mean age of the patients at the time of diagnosis was 7.72 ± 5.66 years (range: 5 months–16 years) and female/male ratio was 1/2. Five children (55.6%) had LAD, whereas PV and BP were seen in two patients, each 22.2%. The elapsed mean time until diagnosis was 1.77 ± 0.97 months (range: 1–4 months). All patients were treated with a minimum of two different systemic agents including methylprednisolone,

colchicine, erythromycin, sulfasalazine, dapsone, azathioprine, methotrexate, mycophenolate mofetil, intravenous immunoglobulin (IVIg), and rituximab. In all patients, clinical remission was obtained after a mean interval of 31.77 ± 27.99 months (range: 2–72 months) following the diagnosis. All systemic therapies could be discontinued in four patients (44.4%) at the time of writing [Table 1].

Two patients with PV were included in the study; both diagnosed during adolescence. One of these patients (case 1) had mucocutaneous disease, with more prominent involvement of the face and trunk [Figure 1a], whereas the another patient (case 2) had only mucosal involvement. In both patients, remission was obtained with the administration of rituximab infusions after multiple treatment attempts with different agents failed.

Our study included two patients diagnosed with BP at a relatively young age (5 months and 2 years). In one of these patients (case 3), who has previously been described in greater detail, a rapid response was obtained using IVIg infusions after treatment failure with methylprednisolone and dapsone.[4] The another patient (case 4) had hyper-immunoglobulin E (IgE) syndrome and was being treated with monthly IVIg infusions and methylprednisolone at the time of onset of vesiculobullous lesions [Figure 1b]. In addition to ongoing treatment for hyper-IgE syndrome, the patient received a long course of oral dapsone to obtain remission after 72 months of treatment.

Five patients (mean age: 7.4 years) were diagnosed with LAD. Only one patient had both mucosal and cutaneous involvement, whereas the other patients had cutaneous disease [Figure 2a-d]. Dapsone was remarkably effective in our cohort: In one patient (case 5), 18 months of dapsone monotherapy resulted in remission off therapy. In three other patients (cases 6–8), who are still in remission on dapsone treatment, combination therapies were necessary to effectively control disease activity. Dapsone was ineffective in case 9, in whom adequate response was achieved using a 9-month-course of methotrexate, leading to remission off treatment.

Systemic agents were well tolerated in all patients, except for the two patients with PV (cases 1 and 2) (22.2%). Adverse effects were mainly due to corticosteroids (osteopenia in both patients, cushingoid side effects in case 1 and cataract in case 2) and azathioprine (slight elevation of transaminases in case 1 and transient and mild lymphopenia in case 2). Dental abscess was noted in case 1 2 weeks after the second rituximab infusion, for which drainage was performed along with systemic antibiotic therapy. In addition, growth retardation was noted in cases 3 and 4.

The demographic and clinical features of the cases are outlined in Table 1.

Discussion

This retrospective study conducted at a tertiary referral center includes nine patients diagnosed with an AIBD before the age of 18 years. In many aspects, this study bears similarities to a more recent single-center retrospective study from Singapore: In both studies, there was a male predominance (female/male: 1/2), and the same number of patients with LAD, PV, and BP were enrolled (5, 2, and 2, respectively).[5] Moreover, no pediatric case of DH was detected in either of the two studies. This is particularly interesting, considering the data from the Western hemisphere indicating that DH is among the most common immunobullous disorders of childhood.[2] This discrepancy may be explained by the geographic differences in the prevalence of DH.[2] Furthermore, this study did not include any patients with epidermolysis bullosa acquisita or bullous lupus erythematosus, as opposed to the studies by Kirtschig *et al*.[3] and Kong *et al*.,[5] respectively.

Both of the patients with PV in this study had an adolescent age of onset, whereas the patients reported by Kong *et al*. had a preadolescent onset.[5] The pediatric patients represented 1.9% of all patients diagnosed with PV at our institution during the study period ($n = 106$), which is similar to the ratio (2.9%) reported by Yazganoglu *et al*. from another large university hospital in Istanbul.[6] However, in the study of Uzun *et al*. conducted at two major university hospitals in the Mediterranean Region of Turkey, none of the 123 PV patients were younger than 18 years, possibly reflecting regional differences of PV demographics.[7]

Along with the potential side effects of prolonged treatment with corticosteroids and immunosuppressive agents, the severe manifestations of PV can have a significant impact on the psychosocial development of adolescents as was obvious in case 1 who was deeply affected by his disfiguring facial lesions and cushingoid side effects of oral methylprednisolone. Of note, most of the patients with juvenile pemphigus reported in the literature had a good prognosis; however, treatment-resistant cases, similar to our patients, have been reported.[5,8] As it is the case with pemphigus in adult age, rituximab represents a valuable treatment option for pediatric patients, as well.[9] In both of our patients, rituximab was required to obtain remission. It was administered as per the "body-weight regimen" (375 mg/m^2 body surface area, twice, 15 days apart) as described by Vinay *et al*.[9] Although no serious infection was documented in our patients, Kong *et al*. noted the development of neutropenic sepsis in their PV patient treated with rituximab,[5] highlighting the importance of clinical vigilance for serious infections.

Both of the patients with BP were treated with IVIg. In the literature, a favorable response was obtained in most of the patients with infantile or juvenile BP using topical or systemic corticosteroids;[2,10] however, IVIg has been utilized with success in refractory cases, such as case 3.[4] Notably, the other patient was being followed up with a genetically confirmed diagnosis of hyper-IgE syndrome and treated with monthly IVIg infusions at the age of 2 years when he developed blisters clinicopathologically compatible with BP. Several monthly courses of systemic corticosteroids, dapsone and methotrexate, were introduced while continuing IVIg and slowly tapering corticosteroids, allowing remission to be achieved 72 months after initial diagnosis. Interestingly, coexistence of BP and hyper-IgE syndrome was previously described in an infant from Turkey.[11] The author postulated that multiple courses of cutaneous and respiratory infections might have triggered the autoantibody production in her patient, akin to the hypothesized mechanism of BP development following vaccinations.[11] Similarly, our patient suffered from numerous episodes of severe skin and respiratory infections before the diagnosis of BP, which seems to support the aforementioned hypothesis.

In many studies focusing on AIBD in childhood, LAD is mentioned as the most common entity.[5,12,13] In the study by Kharfi *et al*.,[13] LAD represented 65.9% of all immunobullous disorders in children, which is slightly higher than the ratio in this study (55.6%). The male predominance in this study (male/female: 1.5) is in accordance with the studies by Nanda *et al*.,[14] Kenani *et al*.,[12] and Kharfi *et al*.[13] (male/female: 1.7, 1.8, and 2.4, respectively). The median age at diagnosis in this study was 5 years, in agreement with the preschool age of onset commonly stated for LAD.[2,12,13,14] The children described herein constituted 50% of all patients diagnosed with LAD within the study period at our institution, which is similar to the proportion of pediatric patients (6/11; %54.5) reported by Zaraa *et al*. from Tunisia.[15]

Infections represent a well-recognized triggering factor for LAD in childhood.[2,12,14] In two of our patients (cases 5 and 9), an upper respiratory tract infection was suspected to be a triggering factor. Nanda *et al*. reported a lack of mucosal involvement in their series of eight patients with LAD,[14] and in the study by Kharfi *et al*., mucosal involvement was noted in 12.9% of patients.[13] In line with these findings, mucosal involvement was not a prominent feature in this series, either, documented in only one of the five patients studied (20%). This study lends further support to the general observation that dapsone is effective in LAD. Although used in all patients with LAD for prolonged periods, dapsone-related serious hematologic adverse effects were not observed.

We recognize the limitations of this study, the most important of which is the retrospective design. Most importantly, the adverse effects of the treatments such as growth retardation or osteopenia might have been evaluated more systematically within the well-designed protocol of a prospective study. Nevertheless, we believe to have ensured strict adherence to the recommendations of the international treatment guidelines during the entire study period, with special emphasis on meticulous screening for adverse effects. Moreover, all of our patients were routinely followed up in cooperation with their attending pediatricians and specific pediatric subspecialty departments, whenever necessary. An important critique could predictably be directed at the prolonged periods of systemic corticosteroid treatment, as outlined in Table 1 (7–48 months). However, for a significant proportion of these rather long intervals, the corticosteroids

were administered at very low dosages (0.1–0.2 mg/kg/day), together with corticosteroid-sparing agents. It was our observation that, in a counterintuitive way, the parents were usually reluctant to completely give up corticosteroids, fearing that the eruption would recur in its initial severity. Thus, we opted to continue the corticosteroids at significantly low dosages, which was somewhat comforting for the parents. The latter might also explain the relatively low incidence of corticosteroid-related side effects despite prolonged treatment. Notably, the time to diagnosis in this study was rather short (1–4 months), probably reflecting our low threshold of suspicion for AIBD as a referral center and the relatively severe, and thus diagnostically less ambiguous initial presentation of our patients.

Conclusion

All in all, this study was aimed at providing demographic and clinical information regarding childhood AIBD in a retrospective fashion over a decade. LAD was identified as the most common AIBD, manifesting in preschool children and responding well to dapsone. Overall, the patients in our study had a good prognosis; however, the two patients with PV and BP required rituximab and IVIg for remission, respectively. Future studies from different geographic regions of the world may help to better delineate the clinicoepidemologic characteristics of this rare group of disorders.

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Conflicts of interest There are no conflicts of interest.

What is new?

- In this study, nine children with autoimmune bullous diseases are presented from a single institution
- In line with the preexisting literature, linear immunoglobulin A disease was the most common entity, presenting in preschool children. However, dermatitis herpetiformis was not identified in our study
- Of note, rituximab was required for remission in both of the patients with pemphigus vulgaris, and intravenous immunoglobulin was used in both of the patients with bullous pemphigoid.

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Figures and Tables

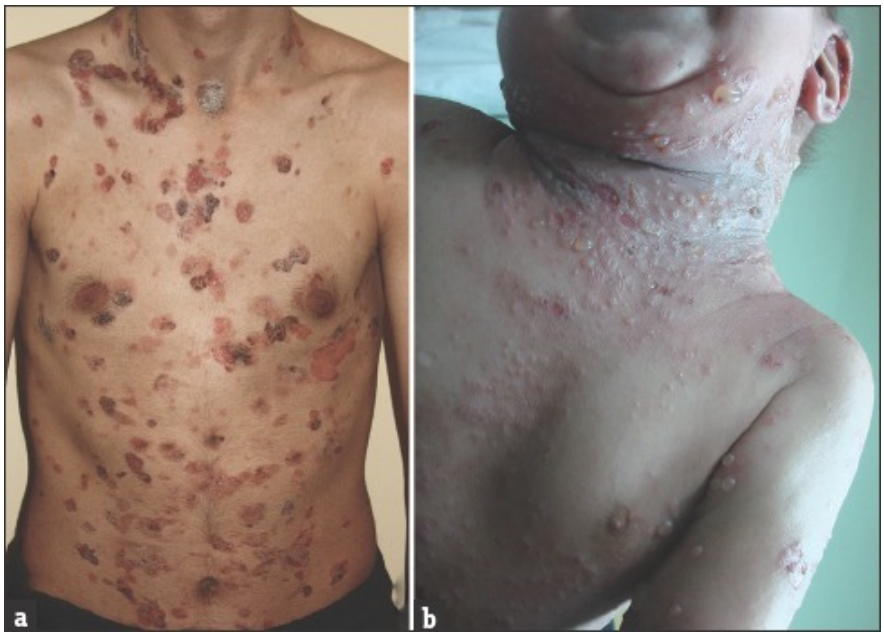
Table 1

Clinical features and treatment outcomes of the patients, in the study

Patient	Sex	Age at diagnosis (years)	Time to diagnosis (months)	Diagnosis	Extent of involvement	Systemic treatment			Final outcome	Time to remission (months)
						Modality	Duration	Adverse effects		
1	Male	14	1	PV	Mucocutaneous	Methylprednisolone	32 months	Osteopenia, cushingoid side effects	Remission on rituximab and low-dose methyl prednisolone	24
						Dapsone	12 months			
						IVIg	13 cycles			
						Azathioprine	14 months	Slight elevation of transaminases		
						Rituximab	4 cycles	Dental abscess		
2	Male	16	2	PV	Oral only	Methylprednisolone	28 months	Cataract, osteopenia	Remission off treatment	44
						Azathioprine	17 months	Lymphopenia		
						IVIg	10 cycles			
						Mycofenolate mofetil	7 months			
						Rituximab	2 cycles			
3	Female	5 months	1	BP	Cutaneous only	Methylprednisolone	7 months	Growth retardation	Remission off treatment	3
						Dapsone	15 months			
						IVIg	4 cycles			
4*	Male	2	1	BP	Cutaneous only	IVIg	Multiple monthly cycles	Growth retardation	Remission on IVIg	72
						Methylprednisolone	28 months			
						Dapsone	56 months			
						Methotrexate	8 months			
5	Male	14	2	LAD	Cutaneous only	Dapsone	18 months		Remission off treatment	18
6	Female	4	1	LAD	Cutaneous only	Colchicine	8 months		Remission on dapsone	72
						Sulfasalazine	6 months			
						Methylprednisolone	7 months			
						Dapsone	66 months			
						Methotrexate	8 months			
7	Male	6	2	LAD	Cutaneous only	Methylprednisolone	10 months		Remission on dapsone	5
						Dapsone	20 months			
8	Female	8	4	LAD	Mucocutaneous	Dapsone	12 months		Remission on dapsone	2
						Methylprednisolone	7 months			
9	Male	5	2	LAD	Cutaneous only	Dapsone	8 months		Remission off treatment	46
						Methylprednisolone	36 months			
						Sulfasalazine	6 months			
						Erythromycin	9 months			

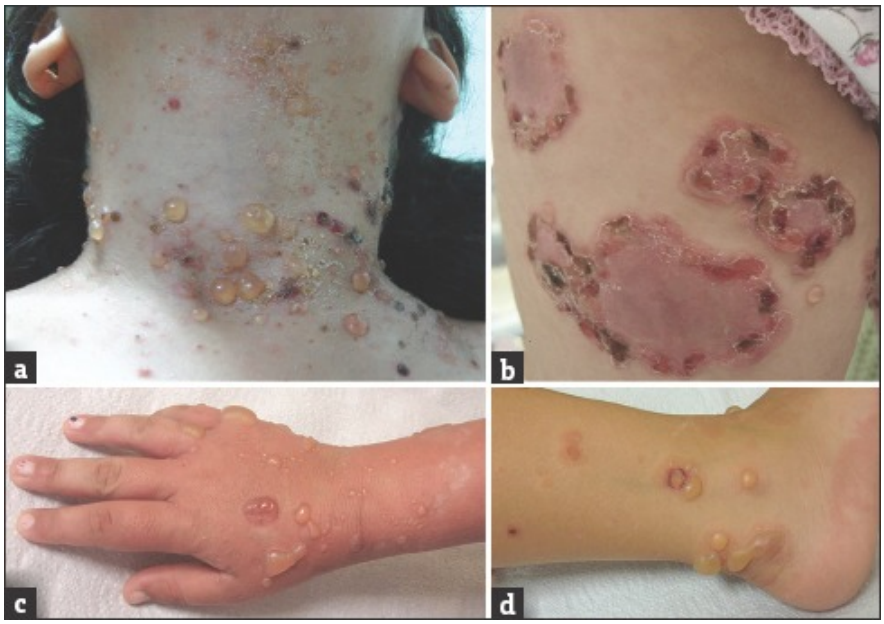
*The patient was being followed up with a diagnosis of hyper IgE syndrome since birth. At the time of diagnosis of BP, the patient was already being treated with IVIg and methylprednisolone for hyper-IgE syndrome. At the final examination, the patient was still on monthly IVIg treatment. BP: Bullous pemphigoid, IVIg: Intravenous immunoglobulin, LAD: Linear immunoglobulin A disease, PV: Pemphigus vulgaris, IgE: Immunoglobulin E

Figure 1



(a) Partially crusted erosions covering a widespread area on the trunk of case 1 with pemphigus vulgaris. He also had involvement of the face and oral mucosa (not shown here). At the time, he was referred to our institution; he had been using 0.5 mg/kg/day of oral methylprednisolone for approximately 2 weeks. (b) Intact and eroded bullae were noted predominantly not only on the neck but also on the face, trunk, and extremities of case 4, who had hyper-immunoglobulin E syndrome and bullous pemphigoid

Figure 2



Cases 6 (a and b) and 8 (c and d) with linear immunoglobulin A disease. The annular/polycyclic configuration of the vesiculobullous lesions with an erythematous background was most prominent on (b) and (d)

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