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LITERATURE REVIEW: ASSOCIATION BETWEEN BULLOUS PEMPHIGOID AND IMMUNIZATION IN INFANTS

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A B S T R A C T

Background: Bullous pemphigoid (BP), is the most common autoimmune bullous disease and mostly affects the elderly, but is rare in the pediatric population. The etiology is still unknown. In particular, maternal antibodies and foreign antigens such as drugs, infections, and vaccines are thought to trigger BP in childhood. **Purpose:** To review the literature bullous pemphigoid and immunization in infants. **Review:** Approximately 110 reports of BP in childhood, including 21 reports occurred after childhood vaccination. In each case, a short latency period was described from vaccination to clinical manifestation with most cases occurring within a week (range: 5 hours – 4 weeks). This supports the existence of a relationship between vaccination and clinical symptoms of BP, recurrence of BP symptoms along with exposure to vaccination, as well as the high incidence of vaccine-related BP in infants. This is supported by the temporal relationship between vaccination and the onset of lesions as well as the observation of recurrence after administration of a new dose. However, on the other hand, the low incidence of infantile BP in widely vaccinated populations suggests that the association may be only incidental. **Conclusion:** Vaccination clearly has a relationship with the occurrence of bullous pemphigoid in infants. Vaccination may activate the immune system, but the pathogenesis of how vaccines trigger BP is still unknown.

BACKGROUND

Bullous pemphigoid's definition

Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering disease, representing 80% of subepidermal immunobullous cases. The term pemphigoid was first introduced by Lever in 1953 to describe a disease characterized by bullous formation due to subepidermal detachment to differentiate it from pemphigus, an intraepidermal blistering disorder caused by acantholysis.[1]

Bullous pemphigoid is rare in childhood and infancy

Bullous pemphigoid is a blistering autoimmune disorder that most commonly occurs in the elderly with an average age at onset of > 70 years. The average age of patients at diagnosis in Europe is approximately 80 years, with no gender bias. In contrast, the infantile and childhood types of bullous pemphigoid (described as infantile pemphigoid and childhood pemphigoid) are very rare diseases.[2] The first case of bullous pemphigoid in a child was described in 1970 based on direct immunofluorescence diagnosis and the first case of bullous pemphigoid in an infant was described in 1977.[3]

BP can sometimes affect infants and children, with nearly 100 cases reported. Although autoantibodies in younger patients with BP recognize the same epitope in the 16A non-collagen domain of BP180 as in classic BP, differences in clinical course and response to therapy have been described. Two peak events, one at a mean age of 4 months in infantile BP and another at 8 years of age in childhood BP. Infantile BP significantly affects the face (62%), palms, and soles (79%), with an increased frequency of common lesions requiring the use of systemic corticosteroids with good response.[4]

Trigger factors of Bullous pemphigoid

The etiology of BP in infancy and childhood is unclear. Possible causes reported include nonspecific maternal antibody infections, autoimmune diseases of infancy, and certain medications

and vaccines such as diphtheria, tetanus, polio, hepatitis B, and meningococcal C vaccines. Vaccination is considered a potential trigger of BP in this age group because some reported cases occurred hours or days after vaccine administration and even experienced spontaneous remission. However, a known pathogenic relationship between BP and vaccines is difficult considering that children receive many vaccinations in the first few years of life, and BP is very rare in this population. additionally, Possible triggers, such as coronavirus disease 2019 (COVID-19), of BP in infancy should be identified and properly dealt with.[5]

Pathogenesis of Bullous pemphigoid

There are 2 main components of BP pathophysiology: immunological and inflammatory. The immunological element consists of autoantibodies against 2 parts of the basal keratinocyte hemidesmosomal protein BP 230 antigen (BPAG1) and BP 180 antigen (BPAG2 or type XVII collagen). This antigen plays an important role in the adhesion complex that promotes epithelial-stromal adhesion. When autoantibodies bind to their target antigens, inflammatory components follow, activating complement and mast cells. This causes neutrophils and eosinophils to release various inflammatory cells resulting in the release of proteolytic enzymes that damage the dermal-epidermal junction.[6]

The pathogenesis of the disease is related to IgG autoantibodies directed against two structural components of hemidesmosomes, a multiprotein complex at the dermal-epidermal junction that provides structural adhesion between basal keratinocytes and the dermal extracellular matrix, named BP180 (transmembrane glycoprotein) and BP230 (hemidesmosome inner plaque proteins). In addition, IgE autoantibodies are also involved in the pathogenesis of the disease and can be detected in the serum and/or skin of patients using immunoblot/immunoprecipitation analysis, immunofluorescence studies, and enzyme-linked immunoassay (ELISA). Destruction of the epidermal adhesion complexes (desmosomes) of keratinocytes causes autolysis, a phenomenon characterized by loss of cell-cell adhesion, resulting in intra-epidermal blistering and a clinical picture of tender blisters and erosion at the affected site.[7]

REVIEW

Association between Bullous pemphigoid and immunization/vaccine

In the literature, temporal correlation with vaccination was reported in infants under 1 year of age. However, the latency between vaccination and clinical manifestation varies, ranging from 5 hours to 3 weeks; therefore, its triggering role is still debated. According to some authors, trauma caused by vaccination can lead to blister formation through activation of the inflammatory cascade mediated by the Th17/IL-17 pathway in genetically predisposed infants.[8]

Neri et al reported a case of bullous rash triggered by meningococcal and rotavirus vaccines in an infant, and the lesions appeared three weeks after the meningococcal and rotavirus vaccines. However short-term treatment with oral corticosteroids (deflazacort 1 mg/kg/day) led to complete healing within two weeks. Six weeks after remission, their patient repeated the vaccinations without relapse.[9]

Pérez-feal et al reported a healthy 6-month-old infant developed pruritic lesions 3 days after receiving the second dose of meningococcal b vaccine. Histologic examination showed subepidermal blistering with eosinophilic spongiosis and a predominantly lymphohistiocytic dermal inflammatory infiltrate with frequent eosinophils. The boy was diagnosed with infantile bp and started on oral prednisolone at a dosage of 2 mg/kg/day. The boy respond very well to treatment, with complete clearance of lesions within 3 weeks and negativization of anti-bp180 antibody titers.[10]

Borba et al reported a case of a four-month-old female patient who appeared with a new onset pemphigus following HBV vaccination. Interestingly, the initial symptoms characterized by irritability, mild-fever, and a predominant palm-plantar rash started three months after the vaccination. The

meanwhile, the patient received a second dose of the hexavalent INFANRIX™ IPV/Hib vaccine and progressed to the typical BP disease blistering rash over the subsequent days.[7]

A retrospective analysis conducted by Erbagci reported 50 cases of BP after immunization. Of these, 13 patients (10 adults and 3 infants) had received various tetanus toxoid vaccines and boosters. Recently, a retrospective study conducted by SchwiegerBriel et al. refers to more than 80 cases of BP in children in the first year of life, occurring between 1977 and 2014. Of these, 30.8% had received vaccination in the days or weeks before the onset of the disease, with a standard combination of passive vaccines recommended in this age group.[7,11]

Rosińska reported childhood vaccination did not appear to be a trigger for BP in some cases. Because the boy in the case report did not occur immediately before BP occurred. BP occurred due to recurrent upper respiratory tract infections primarily contracted by the boy's older brother from kindergarten. Therefore, COVID-19 remains the most likely trigger for BP, perhaps along with other unexplained chains of mucous membrane infections. It is plausible that BP develops in our babies following an immune response to the pathogen that causes COVID-19 in connection with familial exposure to this infectious agent. Considering this, a study of 414 people concluded that mRNA-based COVID-19 vaccination can cause a spectrum of skin rashes that are generally mild and detrimental.[12]

Pathogenesis immunization may cause Bullous pemphigoid

BP has been suggested to administer various vaccines, such as influenza, swine flu, tetanus toxoid, and herpes zoster virus, although some authors do not support this relationship. Vaccination may activate the immune system, but the pathogenesis of how vaccines trigger BP is still unknown. An association between vaccination and the onset of BP is difficult to prove, given the large use of vaccines and the frequent absence of recurrence of BP after additional vaccination. It can be hypothesized that, in predisposed subjects, vaccination-induced inflammation may cause disruption of the BMZ and reveal hidden epitopes/antigens leading to the production of specific anti-basement membrane antibodies.[5]

COVID-19 vaccination-associated bullous pemphigoid is thought to be regulated by specific pathogenic processes in genetically predisposed individuals. This vaccination will produce the cytokines interleukin (IL)-12 and IL-23 as well as the presence of new antigens which trigger a T-cell-dependent immune response which then triggers the production of autoreactive B cells. B cells then produce IgG and IgE autoantibodies (autoAbs). BP autoantibodies, especially IgG autoantibodies against 2 hemidesmosomal proteins directly: BP180 and BP230 antigens which are components of the dermo-epidermal junction. Autoantibody binding triggers complement activation, and release of inflammatory cells and proteolytic enzymes.[13]

How to diagnosed Bullous pemphigoid

Childhood BP appears to generally have two age peaks: the infancy and late childhood forms. The infantile form occurs in the first year of life and the main symptoms are palmoplantar lesions with or without generalized blistering and rarely accompanied by genital lesions. The childhood form reaches its peak around 8 years of age and has a less uniform lesion appearance with higher involvement of the external genitalia in up to 44% of cases. The two main features that differentiate BP in childhood from BP in adults are acral involvement and mucous membrane involvement.[14]

Nemeth et al. outlined the diagnostic criteria for childhood BP: 1) Age under 18 years; 2) Presence of vesicles/bullae on clinical examination; 3) Evidence of subepidermal blistering with eosinophilia on histology; 4) Linear deposition of IgG or C3 in the basement membrane zone in direct immunofluorescence (DIF) or the presence of anti-basement membrane autoantibodies in indirect immunofluorescence. The histological features of bullous pemphigoid are the same as those in adulthood and vary according to the age of the lesion. Early changes include dermal edema, perivascular lymphohistiocytic inflammation with eosinophils, and eosinophilic spongiosis. A typical

blister shows a subepidermal blister with many inflammatory cells including eosinophils within the blister.[15]

Therapy of Bullous pemphigoid

There are still no clear guidelines for the treatment of BP in childhood. BP in childhood may resolve spontaneously due to its benign clinical quality and frequent recurrence. BP in childhood tends to have a generally good prognosis with appropriate therapy. Mild or localized forms of the disease have historically been treated with topical steroids; however, more severe forms require a more systemic approach. Systemic oral corticosteroids remain the mainstay of treatment, with many studies showing good or complete resolution of symptoms. Examples of treatment regimens include prednisolone starting at 1 mg/kg/day and increasing frequently according to response, methylprednisolone, and betamethasone. Additionally, systemic steroid therapy helps prevent the formation of new lesions and maintains a sustainable remission rate. Topical or oral corticosteroids (prednisolone at a dose of 1-2 mg/kg/day) are the treatment of choice for infantile BP. The prognosis is excellent, with most patients experiencing complete remission without relapse within a few months.[16]

DISCUSSION

Association between BP and immunization/vaccine

The respective vaccines have no known similarity between the structures of the vaccine components and the relevant basement membrane proteins, making it unlikely that an antibody-mediated response will occur from the components themselves. The increased immune response may be triggered by the vaccination process itself which initiates an inflammatory cascade leading to disruption of BMZ integrity with the formation of basement membrane specific antibodies.[17]

Although rare, there are approximately 110 reports of childhood BP in the literature, including 21 reports following childhood vaccination. In each case, a short latency period was described from vaccination to clinical manifestation with most cases occurring within a week (range: 5 hours – 4 weeks). Several aspects of these cases support a plausible association including the narrow interval between vaccination and clinical manifestations, the recurrence of symptoms with vaccination exposure and the high incidence of vaccine-related BP in infants. However, this hypothetical relationship has been challenged.[18]

Baroero et al. the emphasis of the argument against a true association due to the short latency seen in several documented cases including theirs, as evidenced by IgG production starting 10–14 days post-immunization; Therefore, many of the observed cases would be considered too short a time to develop these autoimmune manifestations. Vaccination is a routine practice in developed countries where absolute BP levels remain low, and manifestations are relatively rare in infants despite widespread use of the vaccine.[19]

Vaccination can uncover subclinical BP by reactivating nonspecific immune responses in genetically predisposed individuals. However, whether there is a causal relationship remains to be determined. On the one hand, this association is supported by the temporal relationship between exposure and the onset of lesions as well as the observation of recurrence after administration of a new dose. However, on the other hand, the low incidence of childhood BP in populations where vaccination is widespread suggests that the association may be only incidental.[20]

Conclusions

Vaccination clearly has a relationship with the occurrence of bullous pemphigoid in infants. Vaccination may activate the immune system, but the pathogenesis of how vaccines trigger BP is still unknown.

REFERRENCE

1. Borradori L., Van Beek N., Feliciani C., Tedbirt B., Antiga E., Bergman R., et al.: Updated S2 K guidelines for the management of bullous pemphigoid initiated by the European Academy of Dermatology and Venereology (EADV). J Eur Acad Dermatol Venereol 2022, 36, 1689-1704.
2. Wawrzycki B., Krasowska D., Pietrzak A., Szumilo J., Blazowski L., Pietraszek-Mamcarz J., et al.: Infantile bullous pemphigoid successfully treated with combined pulse corticosteroids and high-dose IVIG. Dermatol Ther 2019, 31, e12635.
3. Jałowska M, Jałowska J, Dmochowski M. Pemphigoid diseases in infancy and childhood. A review of the literature. Przegląd Dermatologiczny. 2023 Jan 1;110(1):12–22.
4. Pemphigoid B, Miyamoto D, Santi C, Aoki V, Maruta C. Continuing mediCAl eduCAtion. 2019; Available from: https://www.scielo.br/pdf/abd/v94n2/0365-0596-abd-94-02-0133.pdf
5. Moro F, Fania L, Sinagra JLM, Salemme A, Zenzo GD. Bullous Pemphigoid: Trigger and Predisposing Factors. Biomolecules [Internet]. 2020 Oct 10;10(10). Available from: https://pubmed.ncbi.nlm.nih.gov/33050407/
6. Baigrie D, Nookala V. Bullous pemphigoid [Internet]. PubMed. Treasure Island (FL): StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK535374/
7. Borba Vieira V, Kanduc D, Shoenfeld Y. Archives of Nutrition and Public Health Research Article Bullous Pemphigoid Following HBV Vaccine: from Case Reports to a Mosaic of Molecular Evidence. 2019 [cited 2024 May 10];1. Available from: https://escientificpublishers.com/assets/data1/images/ANPH-01-0006.pdf
8. Khatereh Anbari, Ghanadi Koruosh, Toulabipour Alireza, Daryuosh Jamebozuorghi, Parastoo Baharvand. Adverse Events Following Immunizations in Infants Under 1 Year of Age in Lorestan Province, Western Iran. Journal of preventive medicine and public health [Internet]. 2023 Mar 31;56(2):172–9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10111094/#sec-a.n.atitle
9. Neri I, Evangelista V, Guglielmo A, Sechi A, Virdi A. A Case of Bullous Rash Apparently Triggered by Meningococcal and Rotavirus Vaccines in an Infant: Focus on Infantile Bullous Pemphigoid. Dermatopathology [Internet]. 2021 Mar 1 [cited 2024 May 10];8(1):33–6. Available from: https://www.mdpi.com/2296-3529/8/1/6
10. Pérez-Feal P, Pita da Veiga G, Sánchez-Aguilar D, Aliste C, Vázquez-Veiga H, Vázquez-Osorio I. Infantile bullous pemphigoid after meningococcal B vaccine. International Journal of Dermatology. 2021 Feb;60(9):1172–3.
11. Díaz MS, Morita L, Ferrari B, Sartori S, Greco MF, Bonells LS. Linear IgA bullous dermatosis: a series of 17 cases. Actas Dermosifiliogr. (2019) 110:673–80. doi: 10.1016/j.ad.2018.06.017
12. Rosińska-Więckowicz A, Jałowska M, Bowszyc-Dmochowska M, Dmochowski M. Case Report: Infantile Bullous Pemphigoid: Triggering by COVID-19 Is Speculative. Frontiers in Medicine. 2021 Nov 22;8.
13. Mulianto N, Hashfi AF. Bullous pemphigoid associated with Covid-19 vaccine in child: A case report. Journal of Pakistan Association of Dermatologists [Internet]. 2023 Jul 2 [cited 2024 May 10];33(2):730–5. Available from: https://jpad.com.pk/index.php/jpad/article/view/2104/1970
14. Faris Oumeish, Hamdi Hamad, Hussain Tukmatchy, Niall Scully and Mohammed Al Abadie (2021). Bullous Pemphigoid Page 2 of 4 in Children: Clinical Presentation, Pathology and Management. Clin Res Dermatol Open Access 8(1): 1-4. DOI: 10.15226/2378-1726/8/1/001130
15. Wuri Puspita Rani, Fitriana Yusiyanti Dewi, Tamimi N, Anggelita Berkah Pratami Turut Yudha. Juvenile Bullous Pemphigoid with Similarity Clinical Features to Chronic Bullous Disease of

Childhood. International journal of medical science and clinical research studies [Internet]. 2023 Nov 20 [cited 2024 May 10];03(11). Available from: http://www.ijmscr.org/index.php/ijmscrs/article/view/1244
16. Schultz, B., Hook, K. Bullous Diseases in Children: A Review of Clinical Features and Treatment Options. *Pediatr Drugs* **21**, 345–356 (2019). https://doi.org/10.1007/s40272-019-00349-3
17. Verheyden M, Bilgic A, Murrell D. A Systematic Review of Drug-Induced Pemphigoid. Acta Dermato Venereologica. 2020;100(15):adv00224.
18. Kasperkiewicz M, Woodley DT. Association between vaccination and autoimmune bullous diseases: A systematic review. Journal of the American Academy of Dermatology. 2022 May;86(5):1160–4.
19. Baroero L, Coppo P, Bertolino L, Maccario S, Savino F. Three case reports of post immunization and post viral Bullous Pemphigoid: looking for the right trigger. BMC Pediatrics. 2019 Feb 23;17(1).
20. Maronese CA, Caproni M, Moltrasio C, Genovese G, Vezzoli P, Sena P, et al. Bullous Pemphigoid Associated With COVID-19 Vaccines: An Italian Multicentre Study. Frontiers in Medicine. 2022 Feb 28;9.