

Agammaglobulinemia and lack of immunization protection in exudative atopic dermatitis

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Abstract Atopic dermatitis is very frequent in the first 6 months of life, and the severe exudative form of this skin disorder is by no means rare. Failure to achieve immunization protection is a potentially life-threatening complication of exudative atopic dermatitis that may go unrecognized. We report the case of a 6-month-old infant with severe exudative atopic dermatitis in whom hypoproteinemia and agammaglobulinemia were attributed to the massive exudation after exclusion of other possible causes. The patient failed to respond to standard immunization, and adequate protection with a good antibody response could be achieved only after exudation from the skin lesions had been treated by intensive topical skin therapy and multiple intravenous immunoglobulin substitution. Two otherwise similar earlier case reports did not investigate the immune status. Therefore, to the best of our knowledge, this is the first report to draw attention to absence of immunization protection in exudative atopic dermatitis. **Conclusion:** We hope that our case report will motivate pediatricians to check the immunization status of patients with exudative atopic dermatitis and take the necessary steps to improve their care.

Keywords Exudative atopic dermatitis · Immunization · Immune status · Agammaglobulinemia · Complication

Abbreviations

AD	Atopic dermatitis
α 1-AT	Alpha-1-antitrypsin
Hib	<i>Haemophilus</i> polyribosylribitol phosphate
THI	Transient hypogammaglobulinemia of infancy

Atopic dermatitis (AD) is a common chronic, relapsing, inflammatory skin disorder that presents by 1 year of age in 60 % of children, usually within the first 6 months of life [1]. In children with AD, however, the immune response may be diminished and delayed compared with non-atopic infants, thus decreasing the success of vaccination [2]. In other words, AD occurs at a time when numerous infectious diseases, some of them still fatal today, are warded off by vaccinations. We report the case of a 6-month-old infant with severe exudative AD and put forward a new explanation for the lack of immunization protection in this disease.

The mother's pregnancy and delivery were uneventful. She had herself suffered from AD, with improvement during puberty, and she and the father were consanguineous (first cousins). Otherwise, the family history was uneventful. The female infant was diagnosed with AD at the age of 3 months. On examination at admission, her physical development was normal: weight, height, and head circumference were within the normal range. Treatment consisted of bath emollients, topical steroids, triclosan, and glycerin, with intermittent intravenous administration of systemic antibiotics to treat relapsing secondary skin infections.

We observed marked erythroderma and eczema associated with exudative lesions and facial AD with scaly and weepy plaques on the cheeks and scalp with desquamation (Fig. 1). Erythematous lesions and plaques were seen predominantly on the legs and the back. Other physical findings, including psychomotor development, remained normal.

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Fig. 1 Marked erythroderma and eczema associated with exudative lesions and facial AD with scaly and weepy plaques on the cheeks and scalp with desquamation

The principal laboratory findings (normal values in square brackets) were mild hypoproteinemia (serum protein 4.6 g/dl [6–7.6 g/dl]; serum albumin 2.8 g/dl [3.6–5 g/dl]) and agammaglobulinemia (serum IgG <50 mg/dl [232–1,411 mg/dl]). The serum IgA level was 7.2 mg/dl [<83 mg/dl], serum IgM level was 8.8 [<145 mg/dl], and serum IgE was significantly elevated to 983 mg/dl [<15 IU/ml]. Alpha-1-antitrypsin (α 1-AT) was normal and protein was absent in urine. Serum-specific IgE testing for food (ImmunoCAP®) revealed allergy to egg but no milk allergy. After two doses of diphtheria, tetanus, pertussis, polio, hepatitis B, hemophilus influenza, and pneumococcal vaccination, there was an inadequate antibody response of anti-diphtheria toxoid antibody level 0.05 IU/ml [>0.1 IU/ml]. Anti-tetanus toxoid antibody level 0.1 IU/ml [>0.1 IU/ml] and Hib (*Haemophilus polyribosylribitol phosphate*) 0.16 mg/l [normal value for the age of the patient 0.9–93 mg/l; minimum protective level 0.15 mg/l] were low, but still within normal values. In summary, anti-tetanus toxoid antibody level and Hib antibody level were at the lower limit of normal and anti-diphtheria toxoid antibody level was abnormal. Analysis of T and B cell subsets using flow cytometry showed values within normal limits. Skin biopsy revealed nonspecific spongiotic dermatitis.

Given the normal α 1-AT and absence of proteinuria and no clinical signs of diarrhea for enteric protein loss were observed, the hypoproteinemia and agammaglobulinemia could have resulted from the massive exudative AD. Rare congenital immunodeficiency disorders such as hyper-IgE- and Omenn syndrome could be excluded. Severe congenital skin diseases were ruled out by the nonspecific skin biopsy findings. One possible differential diagnosis was transient hypogammaglobulinemia of infancy (THI); in this disease, however, serum IgG is diminished, but not entirely absent as in our patient. Moreover, children with THI have immune antibodies [4].

After 2 months of intensive topical skin treatment and multiple intravenous immunoglobulin substitution (1.2 g/kg body weight) because of rapid decline of IgG levels after administration, the skin lesions were no longer exudative (Fig. 2), and immunoglobulin levels gradually became normal by the age of 18 months. The exact course of immunoglobulin substitution and further immunoglobulin levels is shown in Table 1.

All recommended vaccinations were administered at the usual age with good antibody response. After the first applications of immunoglobulin substitution, skin infections never occurred again.

Only two previous case reports similar to ours have been described. Shinagawa et al. [5] reported on an infant with hyperaldosteronemia and hypogammaglobulinemia. In contrast to our child, however, their patient showed severe failure to thrive, so an intestinal loss of IgG can be presumed. In a group of eight patients with AD and hypogammaglobulinemia, one child had agammaglobulinemia, but it was not reported whether there was protein loss via the gut or whether the child failed to thrive. Moreover, the immune response in this child was not quantified [7]. Wang et al. [7] reported also on four patients with hypogammaglobulinemia who possibly lost protein via skin lesions, but only one had mildly low serum albumin levels, which suggests that the hypogammaglobulinemia in these patients was probably not related to loss of serum protein. However in these cases, protective antibody response was observed after tetanus and Hib vaccination [7].



Fig. 2 After 2 months of intensive topical skin treatment and multiple intravenous immunoglobulin substitution, the skin lesions were no longer exudative

Table 1 Laboratory results, before and after immunoglobulin substitution

Time point	IgG (mg/dl) ^a	IgG substitution (g/kg)	Anti-diphtheria toxoid antibody level [>0.1 IU/ml]	Anti-tetanus toxoid antibody level [>0.1 IU/ml]
01 Feb 2011	<50	1 g/kg (04 Feb 2011)	<0.1	0.1
11 Feb 2011	746			
22 Feb 2011	207			
01 March 2011	85	1.2 g/kg		
03 March 2011	1,436			
29 March 2011	56	1.1 g/kg		
20 April 2011	129			
05 May 2011	136			
18 May 2011	161			
15 June 2011	220			
11 July 2011	212			
25 Oct 2011	544			
03 May 2012	554		0.7	1.7

^aAbnormal values are presented in bold

Yasuno et al. described five infants with AD and THI. A protein loss through the gastrointestinal tract or skin was in these cases unlikely. Thus, they hypothesized that THI may play a role in AD severity due to the maturational delay in IgG production [9].

The association of AD and transient hypogammaglobulinemia is described before [4, 6]. In contrast to our patient, patients with THI usually have normal response to immunization. To our knowledge, complete agammaglobulinemia as a feature of THI is very rare. Probably in our patient, there was a combination of THI and transdermal IgG loss.

It is known that patients with AD show an impaired innate and distorted adaptive immune response. Several innate immune mechanisms are relevant for AD pathophysiology as these are impaired in AD patients and may contribute to the increased susceptibility of AD patients to skin infections. These mechanisms may aggravate a hereditary skin barrier defect [3, 8].

Our case, possibly supported by other authors [2, 7], demonstrates that the IgG level and, if indicated, the immune status should be determined in children with severe exudative AD to detect any severe lack of immunization protection.

Therefore, intensive dermatological treatment should be initiated in these cases. Intravenous administration of immunoglobulins should be considered if no sufficient response to immunization is achieved. In this way, patients with severe AD can be reliably protected against potentially fatal infectious diseases.

Conflict of interest The authors have no conflicts of interest to disclose.

References

1. Akdis CA, Akdis M, Bieber T, Bindsley-Jensen C, Boguniewicz M, Eigenmann P, Hamid Q, Kapp A, Leung DY, Lipozencic J, Luger TA, Muraro A, Novak N, Platts-Mills TA, Rosenwasser L, Scheynius A, Simons FE, Spergel J, Turjanmaa K, Wahn U, Weidinger S, Werfel T, Zuberbier T (2006) Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. *J Allergy Clin Immunol* 118:152–169
2. Arkwright PD, Patel L, Moran A, Haeney MR, Ewing CI, David TJ (2000) Atopic eczema is associated with delayed maturation of the antibody response to pneumococcal vaccine. *Clin Exp Immunol* 122:16–19
3. Boguniewicz M, Leung DY (2011) Atopic dermatitis: a disease of altered skin barrier and immune dysregulation. *Immunol Rev* 242:233–246
4. Keles S, Artac H, Kara R, Gokturk B, Ozen A, Reisli I (2010) Transient hypogammaglobulinemia and unclassified hypogammaglobulinemia: ‘similarities and differences’. *Pediatr Allergy Immunol* 21:843–851
5. Shinagawa T, Matsuda S, Ishiguro H, Shikada M, Takakura I, Morimoto T, Niimura F, Oh Y (2007) Hyperaldosteronemia and hypogammaglobulinemia secondary to atopic dermatitis-induced exudation in an infant presenting with growth failure. *Tokai J Exp Clin Med* 32:18–22
6. Walker AM, Kemp AS, Hill DJ, Shelton MJ (1994) Features of transient hypogammaglobulinaemia infants screened for immunological abnormalities. *Arch Dis Child* 70:183–186
7. Wang AS, Liang MG, Schneider LC (2012) Severe atopic dermatitis and transient hypogammaglobulinemia in children. *Pediatr Dermatol* 29:73–78
8. Wollenberg A, R  wer HC, Schaubert J (2011) Innate immunity in atopic dermatitis. *Clin Rev Allergy Immunol* 41:272–281
9. Yasuno T, Yamasaki A, Maeda Y, Fujiki A, Yagyu S (2007) Atopic dermatitis and transient hypogammaglobulinemia of infancy improved simultaneously. *Pediatr Int* 49:406–408