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ATOPIC DERMO-RESPIRATORY SYNDROME IS A CORRELATE OF ECZEMA HERPETICUM

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Abstract

Background—Factors favouring the emergence of Eczema herpeticum (EH) in patients with atopic dermatitis (AD) remain elusive. The aim of this work was to identify changes in clinical and laboratory parameters in acute EH patients, before and after 6 weeks of treatment, as well as differences between AD patients with and without a history of EH.

Methods—A total of 235 adult subjects were included and subdivided into 6 groups: (i) AD patients with acute EH, (ii) AD patients with history of EH, (iii) AD without EH but with recurrent HSV infections, (iv) AD without EH or recurrent HSV infections and healthy non-AD controls (v) with and (vi) without recurrent HSV infections. Clinical examination of AD, assessment of atopic status and severity were done. Total IgE, allergen-specific IgE and differential blood count were analysed. Clinical diagnosis of acute EH was confirmed by PCR.

Results—More male AD patients are affected by EH than females. Acute episodes of EH are characterized by lower levels of lymphocytes and higher levels of monocytes. AD patients with history of EH display higher total IgE serum levels (ADEH⁺HSV⁺ vs. ADEH[−]HSV⁺, $p < 0.001$) and higher sensitization profiles and stronger severity of AD (EASI and SCORAD; ADEH⁺HSV⁺ vs. ADEH[−]HSV⁺, $p < 0.001$). Concomitant asthma and rhinitis were identified as correlates of EH.

Conclusion—From these data we conclude that AD patients with EH display a distinct clinical and biological phenotype.

Keywords

Atopic dermatitis; Clinical risk factors; Eczema herpeticum; Herpes simplex virus

Atopic dermatitis (AD) is a chronic inflammatory skin disease developing on a complex pathophysiologic background (1,2). Infections of the skin by bacterial and viral organisms are typical complications in patients with AD (3–6). Eczema herpeticum (EH) represents a spreading of herpes simplex virus (HSV) type 1 or 2 infection on eczematous skin lesions. It affects approximately 7–10% of all patients during the course of their AD. Epidemiologic data from large cohorts on the prevalence of EH are scarce. EH mainly starts with a localized HSV infection, followed by development of monomorphic vesicles and crusts, accompanied by lymphadenopathy, malaise, and high fever.

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A significantly lower level of antimicrobial peptides (AMPs), including cathelicidin (LL-37), which plays an important role in defense against bacterial and viral pathogens was found in the skin of AD patients with EH compared to AD patients without EH (7). This might in part result in a more rapid viral replication and growth of HSV (8). A Th2-overbalanced cytokine-milieu in the blood and the skin of AD might abet the reduced number of type I interferon producing plasmacytoid dendritic cells (PDC) (9).

In contrast to AD patients, a disseminated HSV-infection rarely occurs in patients with other skin diseases such as T cell lymphoma, psoriasis, rosacea, allergic contact dermatitis and skin injury after burning (10–14). Therefore, the identification of characteristics of a subgroup of AD patients with EH remains an important issue as it may be informative for other severe viral complications in AD such as eczema vaccinatum. The information currently available about EH is mainly restricted to retrospective studies (15–17) and there is a scarcity of knowledge about clinical and molecular features of AD patients in the acute phase as compared to the remission phase of EH.

This work was performed as a part of a National Institute of Health and National Institute of Allergy and Infectious Diseases (NIAID)-funded multicenter network. The central hypothesis of this study is that AD patients with a history of EH have a unique phenotype that can be recognized by a detailed physical and/or laboratory examination. The aim of this work was to identify changes in clinical and laboratory parameters in acute EH patients, before and after 6 weeks of treatment, as well as differences between AD patients with and without a history of EH.

Methods

Patients

A total of 235 AD patients and healthy controls between 18–60 years of age were recruited from 2006 to 2009 at the Departments of Dermatology and Allergy of the Universities of Bonn and Cologne. AD was diagnosed according to the Hanifin and Rajka criteria. Patients with acute EH were recruited during their episodes while other groups were recruited retrospectively. The mean age ($\pm$ SD) was 32.3 ± 11.1 years. All subjects were Caucasian. Altogether, 115/49% female and 120/51% male patients were consented, eligible and examined. They were subdivided into 6 groups: (i) AD patients with acute EH and recurrent manifestations of HSV infections (at least 2 episodes per year) (Gr.1/ADEH⁺HSV⁺acute; n=21); (ii) AD patients with a history of EH and recurrent manifestations of HSV infections (Gr.2/ADEH⁺HSV⁺history; n=31); (iii) AD patients without EH but with recurrent clinical manifestations of HSV infections (Gr.3/ADEH⁻HSV⁺; n=61); (iv) AD patients without EH or recurrent clinical manifestations of HSV infections (Gr.4/ADEH⁻HSV⁻; n=61); and healthy non-atopic controls (v) with recurrent HSV infections (Gr.5/NA HSV⁺; n=24) and (iv) without recurrent HSV infections (Gr.6/NA HSV⁻; n=37). ADEH⁺ subjects were defined as subjects with AD who had at least 1 EH episode that had a diameter of 5 cm or larger documented by a dermatologist at the study site. The diagnosis of a history of EH was based on the documented records from the patients who were treated in the wards of both dermatological departments. All patients with acute EH were treated according to the guidelines with systemic acyclovir (3×500mg i.v./die) for 5 days and the local antiseptic octenidin. Eleven patients of the Gr.1/ADEH⁺HSV⁺acute returned for a follow-up visit after 6.3 ± 2 weeks while ten patients did not appear for the follow-up visit. The diagnosis of acute EH was confirmed by PCR for viral DNA from blister fluid.

The study was approved by the local ethics committee and conducted according to the ICHG6/GCP guidelines. Written informed consent was obtained from all participants.

Information including personal and family history, prior or current therapies and viral and microbial infections were evaluated with the help of a detailed questionnaire.

Clinical scoring system

Atopy was further ascertained and evaluated using the score developed by Diepgen (18–19). Briefly, the Diepgen score includes features characterizing the atopic status (e.g. allergic asthma, cheilitis sicca, Dennie-Morgan infraorbital fold, white dermographism) (for more details about this scoring see supplemental material in repository). This scoring system provides a validated tool which quantitatively explores the atopic background. The Rajka-Langeland score (20) was used to appreciate the course in severity of AD in each individual patient during the past 3 months. Both SCORAD (21) and EASI (22) have been used to evaluate the acute severity of the disease at the time point of investigation.

Total specific IgE

Total serum IgE and allergen specific IgE against 17 different allergens was quantified in the sera of AD subjects with an Immulite 2000 system (Siemens AG, Eschborn, Germany). These allergens were: *D.pteronyssinus*, *D.farinae*, Timothy, Birch, Cat dander, *Aspergillus fumigatus*, *Candida albicans*, P. Ovale, Egg, Milk protein, Cod fish, Wheat, Hazelnut, green apple, peanut, *S. aureus* enterotoxins A and B.

Blood sample analysis

IgG and IgM HSV antibody titres in the sera were analyzed by enzyme-linked immunosorbent assay (ELISA) (Enzygnost®; Behring GmbH, Marburg, Germany). Differential blood count was determined according to standardized procedures. Flow cytometric analysis of T cells, B cells and monocytes was done using antibodies against CD19⁺, CD14⁺, CD3⁺, CD4⁺/CD3⁺, CD8⁺/CD3⁺, HLA-DR⁺/CD4⁺, HLA-DR⁺/CD8⁺ and CD16⁺/CD56⁺ cells from BD-Pharmingen (Heidelberg, Germany). Data were analyzed with the FACScan (BD-FACScan Flowcytometer, San Jose, USA) using BD-FACSCComp software.

Statistical analysis

Categorical data (i.e. gender) were presented as enumerations and percentages. Chi-square-tests and Fisher's Exact Tests were used for statistical analysis. A p-value <0.05 was considered significant. All results were shown as arithmetic mean±standard deviation (SD) or as arithmetic mean±standard error of the mean (SEM). Analysis of variance techniques were employed to compare diagnostic groups with respect to clinical endpoints, and pair wise comparisons among groups were computed. No adjustments for multiple comparisons were made.

Results

Clinical and biological hallmarks of acute Eczema herpeticum

We first analyzed clinical and laboratory data of patients in acute EH (Gr.1) and during follow-up phase (Gr.1fu) and compared the data to patients with history of EH (Gr.2). More males (71%) than females (29%) presented with acute episodes of EH (Table 1). This was not due to more frequent HSV infections since females had significantly more HSV episodes per year than males (females: 8.00±2.8 versus males: 1.6±0.7; p< 0.001).

Only 1 out of 21 patients with acute EH reported use of a topical steroid to control their disease. None of the patients used topical calcineurin inhibitors. As shown by the SCORAD (and EASI, data not shown) evaluations, patients with acute EH had a higher clinical

severity score than patients with history of EH (Fig. 1). However, this seemed to be mainly due to a greater severity for the head area involved by EH. There was a clear decrease of the clinical severity (SCORAD from 50.6 ± 11.35 to 22.8 ± 5.05 ; -55% , $p < 0.001$) during the 6 week follow-up phase compared to the ADEH+HSV+ acute patients reaching a scoring which was significantly lower than for patients with history of EH (Gr.2: SCORAD: 41.87 ± 10.17 ; $p < 0.001$) (Fig. 1). There was no difference in the degree of improvement between patients with ($n=6$) and without ($n=5$) anti-inflammatory treatment in the follow-up phase (-55% versus -60% respectively; n.s.).

There were no significant differences in the total leucocytes, neutrophils and eosinophils counts during the acute EH episode when compared to patients with history of EH (Table 2). In contrast, a lower level of lymphocytes was observed. This was due to significantly lower numbers of CD3+/CD4+ T-cells while CD19+ B-cells did not vary. Of note, monocytes were significantly higher in patients during acute EH than for patients with history of EH. During the follow up phase, all the above mentioned laboratory findings reached values which did not significantly differ from patients with history of EH.

Severe atopic dermatitis combined with allergic airway diseases (dermo-respiratory syndrome) correlates with the development of EH

We next evaluated whether patients with EH (acute and history; Gr.1+Gr.2/ADEH+HSV+) exhibit distinct clinical features when compared to AD patients without EH (Gr.3/ADEH-HSV+). The presence of EH episodes could not be explained by a tendency to have more HSV episodes since there was no significant difference in the frequency of recurrent HSV infections per year between patients with EH (ADEH+HSV+ acute and history) (mean 2.4 episodes/year) and AD patients with recurrent HSV infections without any episode of EH (ADEH-HSV+) (mean 2.6 episodes/year) nor between patients with AD (ADEH+HSV+ history and ADEH-HSV+) and patients without AD (NA HSV+) suggesting that AD is not associated with an increase in the number of HSV episodes.

There were significantly more males with EH (ADEH+HSV+ history: 77%) than females, and fewer males in the EH- group (ADEH-HSV+: 43%, $p < 0.001$) (Table 1). However, males and females did not differ in terms of severity within groups. The mean age of onset of AD in patients with EH was (non-significantly) lower as compared to the other AD groups (4.89 ± 8.15 vs 7.57 ± 11.70 years).

Higher clinical scores were observed in patients with EH compared to patients of the other groups as appreciated by Rajka-Langeland, SCORAD and EASI scoring systems (Fig. 2). Based on Rajka-Langeland scores, the extent of the skin lesions (2.0 versus 1.5), itch intensity (2.1 versus 1.6) and the prevalence of eczematous skin lesions in the head and neck area (2.6 versus 1.4) was more pronounced in the ADEH+HSV+ group (Gr.1+Gr.2) when compared to Gr.3/ADEH-HSV+ patients (all $p < 0.001$). Interestingly, the Rajka-Langeland score which, in contrast to SCORAD and EASI, more reflects the recent past history of AD in patients, suggested that patients with EH had overall a higher degree of severity in the past 3 months than patients without EH in their history. Similarly, as reflected by the Diepgen score, patients with history of EH exhibit a stronger atopic background than those without history of EH (23.35 ± 6.17 vs 18.93 ± 5.36 ; $p < 0.001$). Fig. 3 shows that distinct clinical items of the Diepgen score were significantly more prevalent in EH patients.

Most importantly, patients with EH had significantly higher frequency of concomitant physician diagnosed asthma (64% versus 27%; $p < 0.001$) and allergic rhinitis (86% versus 58%; $p < 0.001$) than ADEH-HSV+ patients. Of note, patients with history of EH more often had siblings suffering from atopic dermatitis (36% versus 26%; $p < 0.001$) and allergic rhinitis (46% versus 19%; $p < 0.001$). We did not detect any significant difference with regard

to all above mentioned clinical parameters when comparing ADEH⁺HSV⁺ patients to ADEH⁺HSV⁻ patients (data not shown).

Biological phenotype of patients with history of Eczema herpeticum

The total serum IgE level of patients with history of EH (Gr.1+Gr.2/ ADEH⁺HSV⁺) was significantly higher than in patients from Gr.3/ADEH⁺HSV⁺ and Gr.4/ADEH⁺HSV⁻ (Table 3). Among the panel of allergens tested herein, specific IgE against *Pityrosporum ovale* (P. ovale) was significantly higher in AD patients with one or more episodes of EH than in the Gr.3/ADEH⁺HSV⁺ patients among those with positive tests ($p=0.019$) (Table 3) (for more details about the values of the other tested allergens see supplemental material in repository).

We did not find significant differences in total leucocytes, lymphocytes counts and sub-populations between patients with history of EH (Gr.2/ADEH⁺HSV⁺history) and patients without EH (Gr.3/ADEH⁺HSV⁺ and Gr. 4/ ADEH⁺HSV⁻). However, as expected there was a significant eosinophilia in all groups of patients with AD when compared to the control individuals of Gr.5/NA HSV⁺ and Gr.6/NA HSV⁻. However, there were no significant changes in any laboratory findings between the 2 control groups, i.e. Gr.5/NA HSV⁺ and Gr. 6/NA HSV⁻ (table 2).

Discussion

Acute EH

Patients with acute EH showed a more severe form of AD but we cannot conclude whether an acute flare of AD favoured the emergence of EH or inversely, the spreading HSV infection secondarily triggered the underlying disease. The observation that patients treated solely with anti-viral medication and antiseptics experienced a similar dramatic improvement in the follow-up than patients treated with anti-inflammatory compounds suggests that worsening of AD may have been secondary to the spreading of HSV. HSV infections have been reported to be able to trigger other chronic skin diseases such as pemphigus vulgaris (23) or Hailey-Hailey disease (24).

The fact that only one of the 21 patients suffering from acute EH reported anti-inflammatory treatment with topical corticosteroids 7 days before the viral eruption, strongly suggests that untreated AD-lesions may favor the emergence of EH episodes, as already suggested in a previous study (17). These observations are not in line with other studies where a connection between an anti-inflammatory treatment with steroids and the consequential development of EH has been reported (2). Studies of long term treatment with topical calcineurin inhibitors showed no increase in the incidence of viral, bacterial or fungal skin infections (25,26). An enhanced expression of AMPs in response to treatment of human keratinocytes with TLR2/6-ligands combined with vitamin-D3 and pimecrolimus in vitro, implies that this treatment might even exert some protective effects (19). Our data support the concept that anti-inflammatory therapy of AD could prevent the development of EH.

A decreased lymphocyte count is commonly expected in the course of viral infections. In EH this phenomenon is due to a significant decrease in CD4⁺/CD3⁺, CD8⁺/CD3⁺ and CD16⁺/CD56⁺ cells which is restored during the 6 weeks following the acute episode. However, we also observed an increase of the numbers of monocytes during acute EH. This has been reported in some other infections with viruses from the same family such as varicella zoster virus infections (27,28). The mechanism of this increase remains unclear but suggests a role of monocytes and related cells such as myeloid dendritic cells in the putative spreading of such virus locally and systemically. Indeed further phenotypical and functional

analysis of circulating monocytes in patients with EH reveal significant differences between the different groups (Hinz et al., in preparation).

Clinical phenotype of patients with EH

Patients with history of EH exhibit more “atopic signs” as detected by the Diepgen score than patients with only history of HSV. A more pronounced immunological shift toward Th2 response could indicate a higher incidence of atopic diseases among this subgroup of patients. TSLP is an IL-7-like cytokine that triggers dendritic cells to induce differentiation of naive T cells into Th2 cells (29). Polymorphisms of the TSLP gene and its receptors could be important candidates for AD and the development of EH (29). A group of innate immunity genes which are associated with the aberrant response of AD skin to vaccinia virus and could play a crucial role in the pathogenesis of eczema vaccinatum has been identified (30). To what extent this could be conferred to the AD patients with eczema herpeticum has to be further evaluated.

A well-known feature of AD patients predisposing for the development of EH is a high total serum IgE level (2,15,16,21). In line with these observations, a high total serum IgE level which is a criterion in the Diepgen score was also confirmed as a correlate for EH in our study as well as in others (16). Since the total serum IgE is associated with the severity of AD, this might simply indicate greater disease severity, or vice versa, factors related to viral spreading might promote the production of IgE or other immunoglobulins (22,23). However, we cannot exclude an association between asthma bronchiale and EH attributable to higher disease severity.

The age of onset of AD showed no significant differences between the groups, but there was a definite trend for an earlier onset of AD in patients with EH than in patients of the other groups. This confirms previous studies where an early age of onset of AD was identified as a potential risk factor and supposed to favour the development of EH in a subgroup of AD patients (15,16). Since a correlation between an early onset, severity of AD and the presence of mutations in the gene encoding Filaggrin has been shown, one may speculate that AD patients bearing this kind of genetic defect are more prone to develop EH (26). This assumption has recently been confirmed by early genetic studies addressing this issue (27). High incidence of HSV infections causing EH has been reported in previous studies (16). Similarly, we found that 53% of the EH cases in the present study were related to a secondary HSV infection, and this frequency is higher than previously reported in the literature (28,29). Moreover, nearly 50% of our EH patients reported two or more episodes of EH. This high proportion could be explained by our recruitment of patients from 18 to 68 years of age and/or a bias due to hospital based recruitment of more severe cases as compared to a sample of out-patients (2,16).

In conclusion, in the present study we have shown that patients with acute EH develop this complication on the background of an untreated severe AD. The acute phase is associated with a series of biological alterations including monocytosis which normalize within 6 weeks. We have further identified dermo-respiratory syndrome as a correlate of EH. Further detailed phenotypic and functional analyses of cells isolated from these patients should provide new insights into the mechanisms underlying this severe viral complication of AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used

AD	Atopic Dermatitis
AMP	Antimicrobial peptides
EASI	Eczema Area and Severity Index
EH	Eczema herpeticum
FACS	Fluorescence activated cell sorting
HSV	Herpes simplex virus
LL-37	Human cathelicidin
NA	Non-atopic
PDC	Plasmacytoid dendritic cells
SCORAD	Scoring Atopic Dermatitis

REFERENCES

1. Williams HC. Clinical practice. Atopic dermatitis. *N Engl J Med*. 2005; 352:2314–2324. [PubMed: 15930422]
2. Bieber T. Atopic dermatitis. *N Engl J Med*. 2008; 358:1483–1494. [PubMed: 18385500]
3. Bork K, Brauninger W. Increasing incidence of eczema herpeticum: analysis of seventy-five cases. *J Am Acad Dermatol*. 1988; 19:1024–1029. [PubMed: 3204177]
4. Bussmann C, Peng WM, Bieber T, Novak N. Molecular pathogenesis and clinical implications of eczema herpeticum. *Expert Rev Mol Med*. 2008; 10:e21. [PubMed: 18620613]
5. Wollenberg A, Wetzel S, Burgdorf WH, Haas J. Viral infections in atopic dermatitis: pathogenic aspects and clinical management. *J Allergy Clin Immunol*. 2003; 112:667–674. [PubMed: 14564342]
6. Novelli VM, Atherton DJ, Marshall WC. Eczema herpeticum. Clinical and laboratory features. *Clin Pediatr (Phila)*. 1988; 27:231–233. [PubMed: 2835199]
7. Howell MD, Wollenberg A, Gallo RL, Flaig M, Streib JE, Wong C, et al. Cathelicidin deficiency predisposes to eczema herpeticum. *J Allergy Clin Immunol*. 2006; 117:836–841. [PubMed: 16630942]
8. Goodyear HM, Davies JA, McLeish P, Buchan A, Skinner GR, Winther M, et al. Growth of herpes simplex type 1 on skin explants of atopic eczema. *Clin Exp Dermatol*. 1996; 21:185–189. [PubMed: 8914357]
9. Wollenberg A, Wagner M, Gunther S, Towarowski A, Tuma E, Moderer M, et al. Plasmacytoid dendritic cells: a new cutaneous dendritic cell subset with distinct role in inflammatory skin diseases. *J Invest Dermatol*. 2002; 119:1096–1102. [PubMed: 12445198]
10. Brion N, Guillaume JC, Dubertret L, Touraine R. Disseminated cutaneous herpes of the adult and Sezary syndrome (author's transl). *Ann Dermatol Venereol*. 1981; 108:517–521. [PubMed: 7030180]
11. Kucukyilmaz I, Alpsoy E, Yazar S. Kaposi's varicelliform eruption in association with rosacea. *J Am Acad Dermatol*. 2004; 51:S169–S172. [PubMed: 15577762]

12. Nishimura M, Maekawa M, Hino Y, Mihara K, Kohda H. Kaposi's varicelliform eruption. Development in a patient with a healing second-degree burn. *Arch Dermatol.* 1984; 120:799–800. [PubMed: 6721551]
13. Paradisi A, Capizzi R, Guerriero G, Rotoli M, Bussoletti C, Amerio PL. Kaposi's varicelliform eruption complicating allergic contact dermatitis. *J Am Acad Dermatol.* 2006; 54:732–733. [PubMed: 16546605]
14. Santmyire-Rosenberger BR, Nigra TP. Psoriasis herpeticum: three cases of Kaposi's varicelliform eruption in psoriasis. *J Am Acad Dermatol.* 2005; 53:52–56. [PubMed: 15965420]
15. Beck LA, Boguniewicz M, Hata T, Schneider LC, Hanifin J, Gallo R, et al. Phenotype of atopic dermatitis subjects with a history of eczema herpeticum. *J Allergy Clin Immunol.* 2009; 124:260–269. 9 e1-7. [PubMed: 19541356]
16. Peng WM, Jenneck C, Bussmann C, Bogdanow M, Hart J, Leung DY, et al. Risk factors of atopic dermatitis patients for eczema herpeticum. *J Invest Dermatol.* 2007; 127:1261–1263. [PubMed: 17170734]
17. Wollenberg A, Zoch C, Wetzel S, Plewig G, Przybilla B. Predisposing factors and clinical features of eczema herpeticum: a retrospective analysis of 100 cases. *J Am Acad Dermatol.* 2003; 49:198–205. [PubMed: 12894065]
18. Diepgen TL, Fartasch M, Hornstein OP. Evaluation and relevance of atopic basic and minor features in patients with atopic dermatitis and in the general population. *Acta Derm Venereol Suppl (Stockh).* 1989; 144:50–54. [PubMed: 2800907]
19. Diepgen TL, Sauerbrei W, Fartasch M. Development and validation of diagnostic scores for atopic dermatitis incorporating criteria of data quality and practical usefulness. *J Clin Epidemiol.* 1996; 49:1031–1038. [PubMed: 8780613]
20. Rajka G, Langeland T. Grading of the severity of atopic dermatitis. *Acta Derm Venereol Suppl (Stockh).* 1989; 144:13–14. [PubMed: 2800895]
21. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. *Dermatology.* 1993; 186:23–31. [PubMed: 8435513]
22. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. *EASI Evaluator Group. Exp Dermatol.* 2001; 10:11–18. [PubMed: 11168575]
23. Caldarola G, Kneisel A, Hertl M, Feliciani C. Herpes simplex virus infection in pemphigus vulgaris: clinical and immunological considerations. *Eur J Dermatol.* 2008; 18:440–443. [PubMed: 18573719]
24. Peppiatt T, Keefe M, White JE. Hailey-Hailey disease--exacerbation by herpes simplex virus and patch tests. *Clin Exp Dermatol.* 1992; 17:201–202. [PubMed: 1451302]
25. Paul C, Cork M, Rossi AB, Papp KA, Barbier N, de Prost Y. Safety and tolerability of 1% pimecrolimus cream among infants: experience with 1133 patients treated for up to 2 years. *Pediatrics.* 2006; 117:e118–e128. [PubMed: 16361223]
26. Wollenberg A, Reitamo S, Girolomoni G, Lahfa M, Ruzicka T, Healy E, et al. Proactive treatment of atopic dermatitis in adults with 0.1% tacrolimus ointment. *Allergy.* 2008; 63:742–750.
27. Horiuchi Y. Mo2+ HLA-DR- monocytosis in varicella zoster virus infection. *J Dermatol.* 1997; 24:205–207. [PubMed: 9114622]
28. Tsukahara T, Yaguchi A, Horiuchi Y. Significance of monocytosis in varicella and herpes zoster. *J Dermatol.* 1992; 19:94–98. [PubMed: 1619111]
29. Gao PS, Rafaels NM, Mu D, Hand T, Murray T, Boguniewicz M, et al. Genetic variants in thymic stromal lymphopoietin are associated with atopic dermatitis and eczema herpeticum. *J Allergy Clin Immunol.* 2010; 125:1403–1407. [PubMed: 20466416]
30. Grigoryev DN, Howell MD, Watkins TN, Chen YC, Cheadle C, Boguniewicz M, et al. Vaccinia virus-specific molecular signature in atopic dermatitis skin. *J Allergy Clin Immunol.* 2010; 125:153–159. [PubMed: 20109744]

Figure 1.

Comparison of the SCORAD between Eczema herpeticum patients during the acute phase of the disease and during remission of EH, 4–12 weeks after the acute episode. Additionally the mean $\pm$ SD of the SCORAD of the ADEH+HSV+ history group is shown. * $p < 0.001$ = statistically significant [Statistical analysis: the difference in log 10 transformed SCORAD scores (baseline versus follow-up) were compared using paired t-tests, restricting to those subjects who had both baseline and follow-up measurements in the ADEH+HSV+ acute group; follow-up values for group 1 (acute EH) were compared to baseline scores for group 2 (history of EH) using two-sample t-tests]

Figure 2.

Mean values of several scores (SCORAD, Diepgen, EASI and Rajka-Langeland-Score) are shown for the ADEH⁺HSV⁺ acute, ADEH⁺HSV⁺ history and the two other AD⁺ groups (ADEH⁻HSV⁺ and ADEH⁻HSV⁻); SD=standard deviation. *p<0.05 = statistically significant [Statistical analysis: these analyses performed on severity scores using analysis of variance (ANOVA) techniques with pairwise comparisons as needed. All severity scores were log 10 transformed except Rajka-Langeland scores.]

Figure 3. Comparison of several clinical items of the Diepgen score between the ADEH⁺HSV⁺ history and the ADEH⁻HSV⁺ groups. *p<0.05 = statistically significant [Statistical analysis: comparisons of presence or absence of symptom between groups made with Fishers Exact Tests]

Table 1

Demographic characteristics; SD=standard deviation.

Gender	Gr.1/ ADEH ⁺ HSV ⁺ acute n=21	Gr.2/ ADEH ⁺ HSV ⁺ history n=31	Gr. 3/ ADEH ⁻ HSV ⁺ n=61	Gr.4/ ADEH ⁻ HSV ⁻ n=61	Gr.5/ NA HSV ⁺ n=24	Gr.6/ NA HSV ⁻ n=37	Total n=235
Female							
No. of HSV episodes/ year [mean ± SD]	6 (29%) 8.0 ±2.8	7 (23%) 1.5 ±0.6	35 (57%) 2.8 ±2.1	30 (49%) -	15 (62%) 3.1 ±2.3	22 (59%) -	115 (49%) 2.6 ±2.4
HSV1/2 IgG (Absolute Value) [mean ± SD]	1: 13,300 (± 7,281.9)	1: 18,600 (± 5,319.8)	1: 18,573.5 (± 7,007.8)	-	1: 20,892.3 (± 7,424.1)	-	1: 18,737 (± 6,973.3)
Male							
No. of HSV episodes/ year [mean ± SD]	15 (71%) 1.6 ±0.7	24 (77%) 2.3 ±2.5	26 (43%) 2.7 ±1.6	31 (51%) -	9 (38%) 1.7 ±1.0	15 (41%) -	120 (51%) 1.9 ±1.9
HSV1/2 IgG (Absolute Value) [mean ± SD]	1: 21,105.9 (± 11,591.7)	1: 19,204.7 (± 10,501.6)	1: 18,662.5 (± 7,009.2)	-	1: 20,642.9 (± 11,453.1)	-	1: 19,567 (± 9,728.9)
Age [mean ± SD]	30.8 ± 9.8	35.2 ± 11.3	33.7 ± 11.2	30.3 ± 10.2	32.4 ± 13.1	31.5 ± 11.2	32.3 ± 11.1

[Statistical analysis: performed on untransformed values for number of episodes per year using analysis of variance (ANOVA) techniques with pairwise comparisons]

Table 2

Comparison of the differential blood counts and the FACS-analysis between the several groups (ADEH⁺HSV⁺ during the acute phase and during remission (fu=follow-up examination; 4 – 12 weeks after the acute episode), ADEH⁺HSV⁺ history; ADEH⁺HSV⁺, ADEH⁺HSV⁻ and the two NA groups.

	Gr.1/ ADEH ⁺ HSV ⁺ acute (n= 21)	Gr.1fu/ ADEH ⁺ HSV ⁺ acute fu (n=11)	Gr.2/ ADEH ⁺ HSV ⁺ history (n=31)	Gr. 3/ ADEH ⁻ HSV ⁺ (n=61)	Gr.4/ ADEH ⁻ HSV ⁻ (n=61)	Gr.5/ NA HSV ⁺ (n=24)	Gr.6/ NA HSV ⁻ (n=37)
Leucocytes (Cells/cmm) Normal range: 4000 – 10000 cells/cmm	6,697.78 ±2,619.75	7,045.00 ±2,251.68	6,713.93 ±2,040.14	6,846.44 ±2,102.13	6,864.96 ±1,849.62	6,642.92 ±2,874.98	6,093.51 ±1,559.74
Eosinophils (Cells/cmm) Normal range: 70 – 700 cells/cmm	424.61 ±325.56	624.70 ±405.73	392.82 ±297.61	395.65 ±385.80	399.27 ±372.48	150.42 ⁺ ±95.52 *	163.54 ⁺ ±114.50
Monocytes (Cells/cmm) Normal range: 80 – 600 cells/cmm	423.83 ±233.01	418.10 ±234.26	357.14 ±129.68	347.81 ±142.76	321.78 ⁺ ±159.35	326.33 ⁺ ±122.71	312.49 ⁺ ±121.53
Lymphocytes (Cells/cmm) Normal range: 800– 4000 cells/cmm	1,192.72 [*] ±458	1,491 ±507.74	1,441.82 ⁺ ±420.05	1,700.82 ⁺ ±625.69	1,691.33 ⁺ ±523.23	1,852.17 ⁺ ±695.57	1,784.43 ⁺ ±588.03
CD3⁺/CD4⁺ (Cells/cmm) Normal range: 400 – 1800 cells/cmm	471.17 [*] ±231.42	618.20 ±256.85	628.43 ⁺ ±185.95	718.63 ⁺ ±304.21	700.39 ⁺ ±237.33	743.29 ⁺ ±230.93	758.89 ⁺ ±282.96
CD3⁺/CD8⁺ (Cells/cmm) Normal range: 200 – 1000 cells/cmm	284.50 ±142.44	374.50 ±203.91	313.82 ±235.04	389.20 ⁺ ±195.92	389.31 ⁺ ±179.21	379.00 ⁺ ±142.41	408.14 ⁺ ±204.06

⁺ p<0.05 = statistically significant vs. ADEH+HSV+ acute Gr.1;

^{*} p<0.05 = statistically significant vs. ADEH⁺HSV⁺ history group Gr.2.

[Statistical analysis: performed on log transformed values and using analysis of variance (ANOVA) techniques with pairwise comparisons]

Table 3

Comparison of the total serum IgE level and the specific IgE (*Pityrosporum ovale*) between the ADEH⁺HSV⁺ (acute & history) and the two other AD⁺ groups (ADEH⁻HSV⁺ and ADEH⁻HSV⁻).

	Gr.1 + Gr.2 ADEH ⁺ HSV ⁺ (acute & history) mean±SD n=52	Gr. 3 ADEH ⁻ HSV ⁺ mean±SD n=61	Gr. 4 ADEH ⁻ HSV ⁻ mean±SD n=61
Total serum IgE (kU/l)	6,787.80 ± 14,038.00	2,128.05 ± 4,231.74 *	2,593.34 ± 6,552.43 *
Specific IgE <i>Pityrosporum ovale</i> (kU/l)	53.07 ± 38.73	28.74 ± 34.09 *	51.29 ± 39.86

* p<0.05 = statistically significant vs. Gr.1+Gr.2/ADEH⁺HSV⁺ (acute+history group).

[Statistical analysis: differences with respect to antigen-specific and total IgE between groups were assessed by first categorizing subjects as positive or negative (detectable, ≥ 0.35 IU/l versus not detectable < 0.35 IU/l levels) and making comparisons between groups with respect to this binary variable first (with Fisher's Exact Test). Then restricting attention to those with detectable levels (≥ 0.35 IU/l), we log 10 transformed these values and compared between groups using two-sample t-tests]