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ORIGINAL ARTICLE

Recurrent eczema herpeticum – a retrospective European multicenter study evaluating the clinical characteristics of eczema herpeticum cases in atopic dermatitis patients

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Abstract

Background Eczema herpeticum (EH) is a disseminated viral infection of eczematous skin disease with the herpes simplex virus. Knowledge on clinical characteristics, risk factors and recurrent disease is limited. Our aim was to better define clinical characteristics and risk factors for EH and especially for recurrent EH.

Methods A retrospective analysis of EH cases assessed the history, clinical signs, prior treatment and laboratory results using a predefined questionnaire.

Results A total of 224 EH cases from eight European centres were included. Extrinsic AD was identified as risk factor for EH, and only one patient suffered from intrinsic AD. Early onset of AD was identified as risk factor for recurrent EH. Pretreatment with topical steroids, systemic steroids, topical calcineurin inhibitors or plain emollients reflected standard therapy. Many patients showed AD lesions without EH, but skin without AD lesions was never affected by herpetic lesions.

Conclusion Patients with clinically active, extrinsic AD are at risk of EH. Recurrent EH is associated with confounders of severe atopic distortion and requires active AD lesions for clinical manifestation. Recurrent eczema herpeticum mainly affects patients with early onset of AD.

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Conflicts of interest

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Introduction

Eczema herpeticum is an acute, severe skin condition found in subjects with atopic dermatitis (AD). It presents with disseminated, monomorphic vesicles and can be accompanied by lymphadenopathy or fever.[1] Before the invention of acyclovir, the disease led to fatal outcomes with a mortality rate of up to 70%.[2] If EH is suspected in a patient, acyclovir or valcyclovir should be initiated immediately, since a delay can increase the length of hospitalization.[3,4]

Whilst AD is the most common chronic inflammatory skin disease, EH is a rare condition with an occurrence of 3% amongst a subset of AD patients.[5] This suggests that certain risk factors influence the likelihood of developing EH. Multiple disadvantages of eczematous skin of AD subjects were associated with the uncontrolled replication of HSV in affected lesions. The disruption of cell junctions unmasks nectin-1, enabling the virus to enter the cell.[6,7] The antiviral immune response in AD is deficient due to the lack of plasmacytoid dendritic cells, thus

resulting in an insufficient IFN-γ production.[8] Defects in IFN-γ response are associated with a higher risk of viral skin infections.[9] Furthermore, the AD-associated cathelicidin deficiency is a predisposing factor for EH.[10] Recent data indicated an elevated type 2 response by virus-specific T cells may contribute to the higher susceptibility to viral infections.[11] The majority of EH cases is caused by HSV-1 with F1 and F35 being the predominant genotypes according to a Japanese study.[12]

Very few studies addressing the susceptibility of AD patients for EH have been performed on a larger number of EH cases.[13–15] A high rate of skin infections with other microbes, a high total serum IgE and an early onset of AD were associated with the occurrence of EH.[14,15] Several case reports indicate that multiple episodes of EH may occur in one patient.[16–19]

We performed a retrospective analysis of 224 cases of EH, to identify novel clinical characteristics of EH, as well as risk factors of recurrent EH.

Methods

Study design and clinical data

This study is a retrospective analysis of 224 cases of EH seen over the course of 10 years by dermatological units at eight European university hospitals. The diagnosis was made by a dermatologist, and the data were then collected using a predefined questionnaire, which included the date of first EH symptoms, the date of EH diagnosis, concomitant diseases, list of medication, history of atopy, family history of atopy, date of diagnosis of AD, history of previous HSV infections, history of previous EH, history of recent exposition to HSV and meningeal or ocular involvement.

Topical and systemic therapies of patients were assessed for up to 4 weeks before onset of EH to evaluate possible effects of AD treatment on EH.

Extrinsic vs. intrinsic AD subtypes

To differentiate between extrinsic and intrinsic AD, the patient's history of atopy and the results of skin prick tests, total serum IgE levels, SX-1-CAP-FEIA and FX-5-CAP-FEIA were checked. AD was categorized according to Wüthrich as extrinsic if the patient presented one or several of the following features: elevated total serum IgE levels (≥100 kU/L), positive results in standard skin prick tests, positive SX-1- or FX-5-CAP-FEIA, a history of allergic rhinoconjunctivitis (RCA) or allergic bronchial asthma.[20]

Scoring of AD severity

Severity of AD was assessed by SCOring of Atopic Dermatitis (SCORAD) and Rajka–Langeland severity grading. The Rajka–Langeland score allows to distinguish between mild, moderate and severe AD by grading extent, course and intensity of the disease.[21] The highest possible score is 9. The SCORAD permits to evaluate extent, severity and subjective symptoms.[22] To assess the intensity, erythema, oedema/papulation, oozing/crusts, excoriations, lichenification and dryness are evaluated as separate subcategories. The highest possible score in this scoring system is 103. The areas affected by AD, as well as the areas affected by EH, were estimated by hatching of predefined human body drawings.

Determination of primary vs. secondary HSV infection

Primary or secondary HSV infections were determined according to a predefined algorithm utilizing the patient's history and serum levels of anti-HSV-IgM and -IgG antibodies, which were available in 69 cases.

Statistical analysis

Mean values, minimum and maximum values, standard deviation and *P*-values were calculated using SPSS statistics software (IBM SPSS Statistics).

Results

Demographics of study population

A total of 224 cases of EH were included in the study, which had occurred in 214 patients. Gender distribution was almost equal with 122 male and 102 female patients. Patient's mean age at onset of EH was 27.3 ± 11.9 years. The mean age of onset of the underlying AD was 9.5 ± 10.1 years (n = 104). Patients with recurrent EH were slightly but insignificantly older (median value 26 years) than those experiencing their first episode of EH (median value 24 years). There was no significant age difference between patients with primary and patients with secondary HSV infection (19.83 ± 12.1 years vs. 26.57 ± 9.75 years).

Long diagnostic period

It took on average 4.2 ± 3.4 days until patients were diagnosed with EH after realizing their first symptoms (min 0 days and max 21 days). Recurrent EH was diagnosed earlier (4.0 ± 2.69 days) compared with first episodes of EH

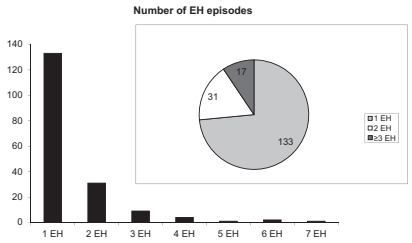

Figure 1 A total of 133 patients suffered from a single episode of EH, 31 patients sustained the disease twice, and 17 patients endured more than two episodes. The recurrence rate was 26.5%.

(4.4 ± 3.74 days), but the difference was not significant ($P = 0.595$).

Primary and secondary HSV infections may cause EH

Out of the 224 cases, 19 were clearly identified as primary HSV infection. In 112 cases, EH was caused by a secondary HSV infection. Naturally, recurrent episodes of EH were assessed as secondary HSV infection. In 93 cases, conclusive data were missing.

26.5% EH recurrence rate

A total of 133 patients ($n = 181$) suffered from their first episode of EH, 31 patients endured the disease twice, and 17 patients suffered from more than two episodes (Fig. 1). One patient endured seven episodes, which was the highest number of EH episodes in this study. The numbers add up to a recurrence rate of 26.5% (Fig. 1).

Recurrent EH is associated with early onset of AD

High disease severity of the underlying AD and an early age of AD onset have been identified as predisposing factors for EH in previous studies.[14,15] To check whether those factors can be associated with recurrent EH, our study compared disease severity assessed by Rajka–Langeland scores, SCORAD index, affected body surface area and the age of AD onset in patients with one episode of EH to patients with multiple episodes of EH. EH patients in the study presented with a mean score of 6.34 ± 1.77 in Rajka–Langeland score and 44.21 ± 18.17 in SCORAD ($n = 89$). Patients with a single episode of EH presented with a mean SCORAD of 42.28 and a mean affected body surface area of 34.4%. Patients with multiple episodes of EH showed mean SCORAD levels of 46.12 and 44.6% affected body surface area. Both parameters were slightly, but insignificantly higher in patients with recurrent AD.

The comparison of age of onset showed that patients with recurrent EH were significantly younger at onset of the underlying AD (5.43 ± 12.9 years of age) opposed to patients with just a single EH episode (11.1 ± 6.5 years of age) ($P = 0.016$, $n = 104$) (Fig 2 and Fig. 3).

Allergological characteristics of EH patients

In our patient cohort, 66.1% reported a history of RCA, and 37.5% reported a history of asthma. The average serum total IgE level was 976.64 kU/L, with a minimum of 17 kU/L and a maximum of 37 940 kU/L ($n = 102$). There was no significant difference in serum IgE levels of patients with one episode of EH opposed to patients with multiple episodes (Fig. 4).

Extrinsic AD is a risk factor for EH

According to the criteria named above, 184 cases of EH occurred in patients with extrinsic AD. Only one patient in the study presented with an intrinsic form of AD. The difference was statistically highly significant ($P < 0.001$, $n = 185$). Conclusive data regarding the extrinsic/intrinsic status were missing in 39 cases.

Prior treatment has no influence on EH development

Both topical treatment and systemic treatment used up to 4 weeks prior to onset of EH were analysed. A total of 76 patients had used at least once topical steroids, 15 at least once tacrolimus ointment and 5 pimecrolimus cream at least once in the last 4 weeks before onset of EH. However, 23 patient had exclusively used emollients and 32 patients had not received any topical treatment at all ($n = 151$) (Fig. 5a). This adds up to 55 patients, who did not receive any topical anti-inflammatory treatment prior to the EH.

A total of 118 patients did not receive any systemic treatment prior to their EH, 10 patients received systemic corticosteroids, 2 received cyclosporine A, and 1 patient received both corticosteroids and cyclosporine A in the last 4 weeks prior to onset of their EH ($n = 131$) (Fig. 5b).

Herpetic lesions are restricted to body areas affected by visible AD lesions

The distribution of EH lesions and AD lesions was assessed by two different methods: shading of body drawings and explicit

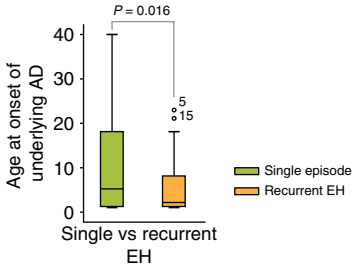

Figure 2 Patients with recurrent EH were significantly younger at onset of AD.

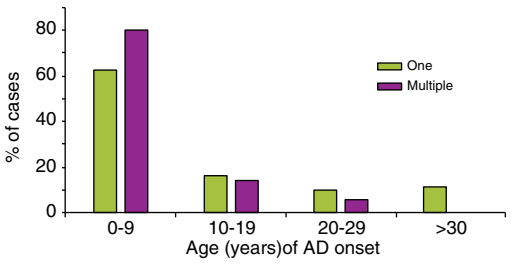

Figure 3 Younger age at onset of the underlying AD is a predisposing factor for EH recurrence

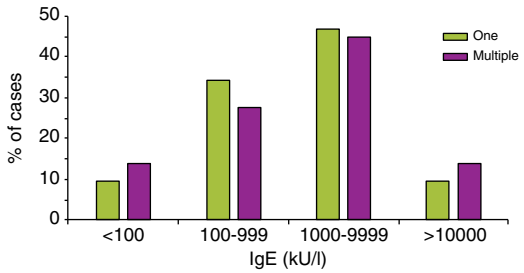

Figure 4 Serum IgE levels of patients with singular and multiple EH episodes, differences were insignificant.

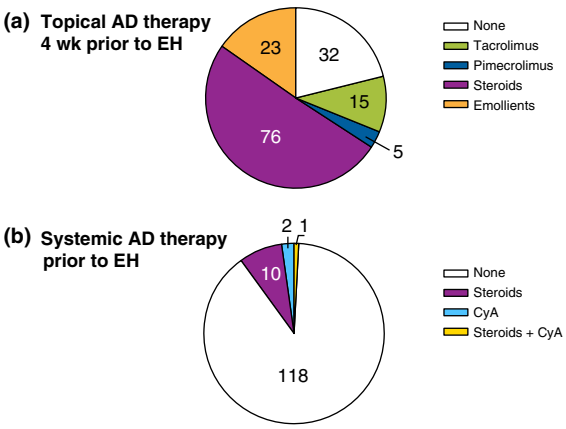

Figure 5 (a) A total of 76 patients had used topical steroids, 15 tacrolimus, 5 pimecrolimus and 23 emollients, and 32 patients had not received topical treatment (n = 151). (b) A total of 118 patients did not receive a systemic treatment prior to EH, 10 received systemic corticosteroids, 2 cyclosporine A, 1 corticosteroids and cyclosporine A (n = 131).

questions for the presence of AD areas without herpetic lesions, as well as herpetic lesions outside of the areas of AD. EH lesions were only found in areas previously affected by the underlying AD. EH lesions did not appear in non-lesional skin regions (n = 126). The information was not available to us in all of the 224 cases.

Discussion

This multicenter study was performed to reveal further information about the clinical characteristics and risk factors for EH in general and especially of recurrent EH. Extrinsic AD displayed the main risk factor for EH. Early onset of AD was identified as risk factor for recurrent EH. Pretreatment with topical steroids, systemic steroids, topical calcineurin inhibitors or emollients reflected standard therapy.[23] Skin without AD lesions was never affected by herpetic lesions. Four larger retrospective studies on EH have been published so far, and our study represents the largest number of cases and is the only study that highlights risk factors for EH recurrence.[13–15,24]

The recurrence rate of EH was 26.5% in our study. The rate seems to vary drastically between studies. Previous studies noted rates of recurrence between 12% and 50%.[13–15,24]

A Canadian study including 79 patients indicated that hospitalized patients have an increased risk of EH recurrence.[24] Since EH is a rare disease, there are no distinct and validated criteria as to when a patient should be hospitalized. Therefore, hospitalization is usually a discretionary decision of the treating physician. It is common sense that hospital admissions are more likely to occur in severe cases. Thus, defining further risk factors besides hospitalization seems crucial.

An early onset of the underlying AD is associated with more severe disease and a known risk factor for EH.[15] In our study, patients with recurrent EH were significantly younger at AD onset than patients with just a single episode of EH. This is a novel finding, as it has never been assessed in larger studies. Our results implicate that an early age of AD onset not only predisposes to EH manifestation, but also to EH recurrences.

A remarkable finding was the significantly higher number (n = 189) of patients with extrinsic AD opposed to only one patient with intrinsic AD. This suggests a correlation between the atopic distortion of the patient and the disposition to EH occurrence. The rate of patients with intrinsic AD is usually about 10–40% according to larger studies.[20,25–27] A previous study showed that patients with extrinsic AD tend to have a more severe, refractory type of AD opposed to patients without signs of atopy.[28] It has been reported that AD patients with a positive history for food allergies or asthma are more likely to develop EH, which further supports this hypothesis.[14]

The mean total IgE level in our patients was 976.64 U/mL, the majority ranging between 1000 and 9999 U/mL (Fig. 4). High IgE levels have been associated with EH previously.[15,29] However, our study did not see a correlation between high IgE levels and EH recurrence. A greater TH2 polarity may explain the higher IgE levels in extrinsic AD. In addition, extrinsic and intrinsic AD patients show different cytokine activation patterns.[30] Cytokines secreted by TH2 cells can induce apoptosis of plasmacytoid dendritic cells.[30] A lack of these cells leads to a deficient IFN-γ production and results in a higher susceptibility to viral infections.[8] This idea is endorsed by a study, which demonstrated high IgE levels, but low IFN-γ levels in patients with EH.[29] The importance of TH2 cells in EH development is also reflected in our finding, that an early onset of AD is a risk factor for EH. Patients with early onset of AD present very low TH1 cell activation, but excessive production of TH2 cells.[30] Recent data support the theory that the TH2 response largely contributes to the pathology of EH.[11] An elevated type 2 cell response to HSV was found in AD patients.

With a mean SCORAD of 44.2 and a mean Rajka–Langeland score of 6.34, our study supports the hypothesis that patients with moderate-to-severe AD are more likely to develop EH.[14] However, there was no significant difference in disease severity between patients with one episode of EH and patients with recurrent EH. To further evaluate the role of disease severity in recurrence of EH, long-term follow-ups of patients with EH would be needed. Currently, we cannot clearly state whether patients were spared from recurrence due to improvement of skin lesions or for other reasons.

Besides the missing data on long-term follow-ups of the patients, the data set was not complete for all readouts. This was due to the retrospective design of the study. Because of the large number of cases, we were still able to detect valuable information on EH and its risk factors.

Some authors discussed an association of EH with the use of topical steroids or topical calcineurin inhibitors.[13,18] Other authors assumed that the use of corticosteroids does not seem to impact EH manifestation.[15,31] Our results support the assumption that there is no correlation between EH occurrence and the previously used AD treatment, as most patients had not received any systemic treatment prior to the event, and 55 patients had not received a topical anti-inflammatory treatment. Untreated AD lesions may actually be more prone to EH, considering that severe AD has been identified as risk factor for EH.[14] Topical steroids or calcineurin inhibitors may even be used to treat the underlying AD in patients with EH. A study showed that the use of such treatments is not associated with a poorer outcome of EH.[32] To the contrary, the discontinuation of topical corticosteroids may actually contribute to the outbreak of EH. This was associated with elevation of regulatory T cells and proinflammatory monocytes after the withdrawal of corticosteroids.[33]

The number of male patients was slightly higher in our study than that of female patients. Male predominance has been described for EH in a study including 50 Korean children and was therefore defined as risk factor for EH.[34] Other large-scale studies showed an insignificant female predominance.[14,15,35] Taken together, gender is most probably not a risk factor for EH.

It took an average of 4 days until the patients in our study were diagnosed with EH. This delay of diagnosis and treatment has not been addressed in any larger study before. The time frame seems unacceptably long, considering the high mortality of untreated disseminated HSV infections.[2] Delayed initiation of acyclovir is associated with an increased length of stay of hospitalized EH patients, and just recently, a lethal case of EH has been reported.[3,36] Therefore, immediate diagnosis and treatment initiation are crucial.

Our patients with recurrent EH were diagnosed a little sooner, but not significantly. It could be expected that patients having ever experienced an episode of EH would seek medical help and treatment sooner because they know what to expect in the next days, but this was not the case.

The morphology of the vesicles in EH has been described multiple times, but information about the distribution pattern was lacking.[14,15,37] This study was able to demonstrate that EH lesions will only affect lesional AD skin. Areas of the skin that do not show signs of eczema will be spared from the characteristic vesicular eruption. This was true in all 126 cases of EH in this study, where distribution was documented. Conclusively, the spread of EH lesions is limited by the distribution pattern of the underlying AD. This information can help to differentiate EH from other skin conditions and will hopefully lead to a faster diagnosis of affected patients.

Clinical implications

Eczema herpeticum occurs almost exclusively in extrinsic AD patients. An early onset of AD is associated with the development of EH, and in addition a predisposing factor of recurrent EH. The spread of EH lesions is limited by the distribution of the underlying AD.

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