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ORIGINAL ARTICLE

High recurrence rate of eczema herpeticum in moderate/severe atopic dermatitis –TREATgermany registry analysis

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Summary

Background: Eczema herpeticum (EH) is a disseminated skin infection caused by herpes simplex virus in atopic dermatitis (AD) patients. The frequency of EH and the clinical features of EH patients have not yet been investigated in a larger cohort.

Methods: We sought to investigate the TREATgermany cohort, a multicenter, non-interventional clinical registry of moderately to severely affected AD patients in Germany. Baseline characteristics of patients included between December 2017 and April 2021 were compared between patients without, single, and multiple EH.

Results: Of the 893 patients, 195 (21.8%) had at least one EH. Of the 195 patients with EH, 107 had multiple EH (54.9%), representing 12.0% of the total study population. While there were no differences in demographic characteristics, previous treatment, and disease scores at enrollment (itch, IGA, oSCORAD, EASI), patients with EH had more frequent atopic comorbidities and sensitizations to house dust mite, food, and mold.
Discussion: TREATgermany registry data suggest a high prevalence and recurrence rate of EH, while there appears to be no specific clinical phenotype, besides an increase in allergies, to identify EH patients in the daily routine.

KEYWORDS
Atopic dermatitis, herpes simplex, registry

INTRODUCTION

Atopic dermatitis (AD) is one of the most prevalent chronic inflammatory skin diseases[1,2] and associated with increased risks of bacterial, fungal, and viral infections.[3,4] The latter is frequently caused by herpes simplex virus (HSV) and shows severe, widespread, and potentially life-threatening courses known as "eczema herpeticum" (EH).[5] In recent years, a number of new treatments have undergone clinical development, directly targeting identified AD-specific Th2 associated cytokines (Interleukin [IL]-4, IL-13 or IL-31) and their respective receptors (dupilumab, tralokinumab, lebrikizumab, nemolizumab) or indirectly interfering signaling pathways, preferentially by inhibiting the Janus kinases (JAK) 1 and 2 (baricitinib, abrocitinib, upadacitinib).[6–8] Most of these drugs have now been approved for the therapy of AD in the EU.[9] While two meta-analyses of clinical trials revealed that IL-4 and IL-13 inhibition may decrease the risk of EH (Fleming et al.[10] odds ratio: 0.34 95% CI, 0.14–0.84; Eichenfield et al.[11] risk ratio: 0.31, 95% CI 0.12–0.82) and has no influence on the rate of systemic infections, JAK inhibition led to increased risk mainly of HSV infections (in baricitinib trials: incidence rate of 2.0).[12–15] Of note, patients at increased risk of severe HSV-1 infections based on their history were excluded from clinical studies in the development programs of JAK inhibitors, but are not excluded by the EU labels for the treatment of AD.[12]

To move closer to a patient-individualized therapy, it would be helpful to identify AD patients at risk for EH. In our previous work, we showed that AD patients with AD and EH exhibit increased frequencies of type 2 polarized virus-specific T cells.[16] Furthermore, different genetic risk factors such as single nucleotide polymorphisms in the interferon pathway, such as interferon releasing factor (IRF) 3 and 7, and the skin barrier have been described (summarized in[5]). However, until now there is no clinical or laboratory marker that can be used in clinical routine to identify AD patients at increased risk for EH. Furthermore, EH patients have only been investigated in specific EH cohorts but never in a large AD registry so far.

Therefore, we analyzed the AD patients in the TREATgermany registry, focusing on the clinical characteristics of patients with EH compared to patients without a history of EH. Our aim was to identify possible clinical characteristics that would allow physicians to identify patients at increased risk for EH and that could, in perspective, assist in the treatment decision process.

METHODS

The TREATgermany registry is an academia-led, prospective, multicenter national registry for moderately to severely affected AD patients. With currently (09/2022) over 1,400 patients included, it is one of the largest non-interventional registries for AD.[17,18] It has been approved by the medical faculty of the Technical University of Dresden, Germany (No. EK 118032016) and by the respective ethics committees of the participating sites. Additionally, it is registered in the clinicatrials.gov database (NCT03057860) and the ENCePP Resource Database (EMA). Patients for the present analysis were recruited at 38 university hospitals, clinics, and dermatological practices. Patients with AD according to the UK working party diagnostic criteria and an oSCORAD > 20 or current systemic therapy or previous anti-inflammatory systemic treatment for AD within past 24 months, meaning a moderate to severe AD, are included in the registry. Detailed visit schedules, assessments, and data management were described previously by Heratizadeh et al.[19] TREATgermany is part of the European TREATeurope family of registries[20] and observes all outcomes recommended by the Harmonising Outcome Measures for Eczema (HOME) initiative.[21–23]

For the present study, all adult patients included in the registry between December 2017 and April 2021 formed the study cohort. Patients were asked about single or multiple occurrences of EH in the past. Since the question concerning EH was introduced in the questionnaire in 2017, only patients who were enrolled in the registry from December 2017 onwards could be considered in the analysis. Patient-reported data on age, height, weight,

marital status, education, employment, smoking status, disease onset, and allergic comorbidity were investigated as potential predictors for EH. Furthermore, patient disease severity and activity scores were included: itch and pain (both measured by a 11-point numeric rating scale), and patient global assessment (PGA). Clinical aspects noted by the physician comprised previous topical and systemic treatment, allergic comorbidity, allergic sensitizations, and disease severity measured by Eczema area and severity index (EASI) and objective Scoring AD (oSCORAD). Additionally, as EH predominantly affects the facial area, we compared the EASI for the head/neck area occurrence of patients with and without EH. The main hypotheses to investigate were that AD patients with a history of EH develop the disease earlier in life, suffer from more severe AD, and more frequently from atopic concomitant diseases.

Statistics

Information collected at the baseline was used for the present study. General characteristics were analyzed using descriptive statistics and compared statistically with Mann-Whitney U test and chi square test, where applicable. Two and three groups, respectively, were used for the analysis: no EH vs EH and no EH vs. single EH vs. multiple EH. For the statistical comparison of the three groups, chi square and Kruskal-Wallis tests were applied.

Answers of patients and physicians were digitalized using REDCap (Research Electronic Data Capture, Vanderbilt University). Stata 15 was used for all analyses and alpha error was set at 0.05. Graphics were generated with Microsoft Excel 2021 (Microsoft Corporation, Redmond, Washington, United States).

RESULTS

Patient characteristics

Of the 1,134 patients enrolled in TREATgermany from beginning of the registry in June 2016 up to April 2021, 893 patients from 38 sites were enrolled in December 2017 or later and therefore were included in the analysis. Of these, 195 (21.8%) patients reported at least one EH in the history (Figure 1) at the baseline visit. Of note, 107 of the 195 EH patients (54.9%) reported more than one episode of EH, which represents 12.0% of the total study population. In 30 of 893 cases (3.4%) the EH history was unclear due to missing answer of the patient. For further analysis, this group was excluded. Patients who never experienced an episode of EH were younger than those who did ($p < 0.01$), no statistically significant differences were seen in sex, education, employment and smoking status (Table 1). Patients with more than one EH in the history showed similar characteristics compared to patients with a single EH (data not shown).

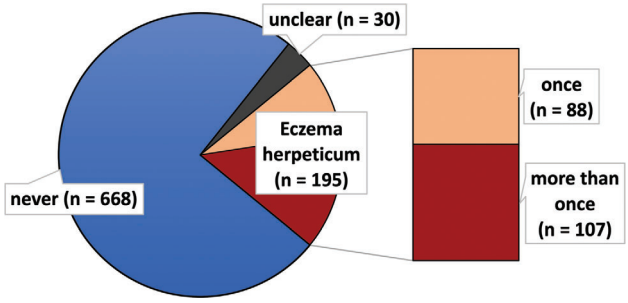

FIGURE 1 Eczema herpeticum (EH) in the TREATgermany registry. 893 patients were included in the analysis. 195 of the 893 patients (21.8%) reported at least one episode of EH, 107 of the 195 patients (54.9%) more than a single episode.

Disease characteristics

No relevant differences were seen in the patient and physician reported age of onset of AD (Table 2). Analyzing the disease severity at inclusion, no differences were detected between the non-EH, single EH episode and multiple EH groups regarding oSCORAD ($p = 0.99$) and EASI ($p = 0.65$) taking the absolute value. Interestingly, differences were seen when analyzing the grouping as clear skin, mildly, moderately, and severely affected for both oSCORAD ($p = 0.03$) and EASI ($p < 0.01$), respectively. More patients suffered from moderate and less from mild AD in the multiple EH group compared to the other groups. There was a trend of a higher EASI score for the head/neck area in patients with EH compared to patients without an EH in the medical history (2.0 ± 1.6 and 2.1 ± 1.7 vs. 1.8 ± 1.5, $p = 0.17$). Evaluation of the patients reported scores pain, pruritus, and PGA revealed no differences that would allow discrimination of patient groups. No body part was more affected by AD in EH patients compared with AD patients without EH (see online supplementary Table S1). Only the feet tended to be less frequently affected in EH patients.

Comorbidity

To determine whether atopic concomitant diseases could present a potential risk factor for EH, we analyzed the physician and patient-reported comorbid diseases. Asthma (59.8% vs. 50.8%, $p = 0.03$) and rhinitis (76.9% vs. 68.9%, $p = 0.03$) were more frequent in patients with EH compared to non-EH patients (see Table 3 and online supplementary Table 2). This was evident from the patient-based information. There was a trend towards higher prevalence rates of asthma and allergic rhinitis in patients with multiple EH compared to patients with a single EH. Whilst total IgE revealed no possible marker to identify EH patients, house dust mite (80.0% vs. 65.9%, $p < 0.01$), mold (49.3% vs. 32.4%, $p < 0.01$), and food sensitization (58.2% vs. 43.2%, $p < 0.01$) were more frequently reported in patients with a history of EH.

TABLE 1 Baseline demographic characteristics of eczema herpeticum (EH) and non-EH patients. Comparison of sex, age, body-mass index (BMI) and other demographical characteristics revealed differences only in age. Eczema herpeticum patients in the registry were older compared to non-EH patients. Patients with missing information of EH are not shown.

Baseline Characteristic	EH (n = 195)	No EH (n = 668)	All (n = 893)
Sex			
Divers	1 (0.5%)	0 (0.0%)	1 (0.1%)
Male	102 (52.3%)	383 (57.3%)	502 (56.2%)
Female	92 (47.2%)	285 (42.7%)	390 (43.7%)
Age, mean ± SD	42.5 ± 13.6	39.7 ± 14.9	40.4 ± 14.6
BMI, mean ± SD	25.3 ± 5.0	25.8 ± 5.4	25.7 ± 5.3
Marital Status			
Partner, not married	49 (25.3%)	187 (28.2%)	242 (27.6%)
Married	88 (45.4%)	234 (35.3%)	328 (37.4%)
Divorced	7 (3.6%)	22 (3.3%)	32 (3.6%)
Widowed	1 (0.5%)	7 (1.1%)	8 (0.9%)
Single	49 (25.3%)	213 (32.1%)	268 (30.5%)
Level of education			
Without graduation	3 (1.5%)	3 (0.4%)	7 (0.8%)
Certificate of secondary education	21 (10.8%)	76 (11.4%)	97 (11.0%)
General certificate of secondary education	70 (35.9%)	236 (35.4%)	318 (36.0%)
General qualification for university entrance	52 (26.7%)	191 (28.6%)	248 (28.1%)
Graduate degree	49 (25.1%)	161 (24.1%)	214 (24.2%)
Employment			
Unemployed	38 (19.5%)	149 (22.3%)	190 (21.5%)
Employed	157 (80.5%)	519 (77.7%)	695 (78.5%)
Smoking Status			
Smoker	45 (23.1%)	160 (24.0%)	214 (24.2%)
Ex-Smoker (< 10 years without smoking)	30 (15.4%)	90 (13.5%)	122 (13.8%)
Ex-Smoker (≥ 10 years without smoking)	16 (8.2%)	78 (11.7%)	96 (10.8%)
Never Smoked	104 (53.3%)	340 (50.9%)	453 (51.2%)

Abbr.: EH, eczema herpeticum; BMI, body-mass index; SD, standard deviation

Therapy

We analyzed topical and phototherapy in the last 12 months before inclusion in the TREATgermany registry as well as the systemic therapy in the medical history of the patients. Whilst patients with multiple EH showed a trend to use more tacrolimus topically, no differences were seen for UV and systemic treatment (Table 4).

DISCUSSION

This is the first study describing the frequency and the clinical phenotype of AD patients with a history of EH in a large AD registry. The aim was to explore potential clinical characteristics that would allow identification of EH patients and, potentially, individuals at risk for these severe infections within the cohort of patients with a moderate to severe AD.

The general characteristics were comparable between EH and non-EH patients. This is consistent with previous studies where no differences regarding the sex distribution was seen.[24–26] A lower proportion of women in the group of EH patients compared with non-EH patients was reported only by Beck et al.[27]

In the past four decades, only a few studies have been published analyzing clinical characteristics such as disease characteristics, severity, and atopic comorbidity of EH patients. The present analysis allows for the first time an estimation of the potential frequency of EH, as previous studies only recruited specifically EH patients. In some stud-

TABLE 2 Disease parameters comparing non, single, and multiple EH group. Significant differences were shown regarding the categorial classification of oSCORAD and EASI, however, no differences regarding any other disease severity characteristics were seen.

Disease parameters	Multiple EH (n = 107)	Single EH (n = 88)	No EH (n = 668)	p value
Age at onset of AD, mean ± SD	10.3 ± 17.7	6.1 ± 11.8	9.0 ± 15.9	0.67**
Age at onset of AD				**0.28***
Since infancy	64 (59.8%)	57 (65.5%)	382 (57.2%)	
Since before school entry	15 (14.0%)	16 (18.4%)	91 (13.6%)	
Since school/adolescence	8 (7.5%)	6 (6.9%)	86 (12.9%)	
Since adulthood	19 (17.8%)	8 (9.2%)	102 (15.3%)	
Do not know	1 (0.9%)	0 (0.0%)	7 (1.0%)	
Pain, mean ± SD	3.9 ± 2.5	3.7 ± 2.9	3.9 ± 2.8	
Itch, mean ± SD	6.2 ± 2.6	5.4 ± 2.7	5.9 ± 2.8	
oSCORAD, mean ± SD	40.6 ± 15.7	41.0 ± 17.6	41.5 ± 16.2	0.99**
oSCORAD – Categories:				**0.03***
Clear (0 to <8)	6 (5.6%)	2 (2.3%)	12 (1.8%)	
Mild (8 to <24)	4 (3.7%)	13 (14.8%)	81 (12.2%)	
Moderate (24 to <38)	37 (34.6%)	24 (27.3%)	184 (27.8%)	
Severe (38 to 83)	60 (56.1%)	49 (55.7%)	386 (58.2%)	
EASI, mean ± SD	16.7 ± 12.2	16.4 ± 13.8	17.1 ± 13.4	0.65**
EASI – Categories:				
Clear (0)	5 (4.7%)	1 (1.1%)	7 (1.1%)	<0.01*
Mild (>0 to <6)	8 (7.5%)	21 (24.1%)	137 (20.8%)	
Moderate (6 to <23)	65 (61.3%)	44 (50.6%)	348 (52.7%)	
Severe (23 to 72)	28 (26.4%)	21 (24.1%)	168 (25.5%)	
EASI Head, mean ± SD	2.0 ± 1.6	2.1 ± 1.7	1.8 ± 1.5	
PGA				**0.40***
Clear	2 (1.9%)	2 (2.3%)	16 (2.4%)	
Almost clear	5 (4.7%)	8 (9.2%)	54 (8.1%)	
Mild	21 (19.6%)	22 (25.3%)	106 (16.0%)	
Moderate	27 (25.2%)	23 (26.4%)	196 (29.5%)	
Severe	41 (38.3%)	23 (26.4%)	202 (30.4%)	
Very severe	11 (10.3%)	9 (10.3%)	90 (13.6%)	

Abbr.: EH, eczema herpeticum; AD, atopic dermatitis; SD, standard deviation; EASI, Eczema area and severity index; oSCORAD, objective Scoring AD; PGA, global assessment
*Chi square test
**Kruskal-Wallis test

ies, AD patients without EH were used as controls without defining specific inclusion criteria. Furthermore, in regard to the current question of viral susceptibility under systemic therapy, the present study is the first to specifically address moderate to severe AD, defined by an oSCORAD of at least 20 or by treatment with systemic therapy. This means that the frequency of EH in the total population of AD patients may be lower than 22% observed in this study. Furthermore, the limitation of self-reported EH history should be taken into account. Importantly, the majority of patients with a history of EH reported more than one episode. The recurrency rate of 54.8% is in line with Beck et al. (50%), but higher than reported by Seegräber et al. (28%).[25,27] Disease severity was similar in all three studies. In the present study, EH patients were significantly older than non-EH patients, which is in contrast to Beck et al. This could support the hypothesis that EH frequency has decreased in the last decades, but prospective studies, especially including children, are important to investigate this.

Wollenberg et al. investigated 100 EH patients and 105 controls revealing increased total IgE levels and earlier onset of AD.[24,26] Of note, no information is provided regarding the AD severity in this study. In the present study, EH patients were characterized by increased frequency of sensitizations, whilst no differences were seen regarding total IgE. In line with Beck et al. they suffered more frequently from asthma and allergic rhinitis.[27] However, significant differences found only in the patient-reported information. Two studies indicated an increased AD severity and sensitization to aeroallergens and Malassezia sympodialis in EH patients.[27,28]

TABLE 3 Atopic concomitant diseases in non and EH patients. EH patients suffered more frequently from asthma and allergic rhinitis as well as house dust mite, mold, and food sensitization. The response categories were combined into "yes" and "no". Missing answers and the answer category "unknown" were excluded. The frequencies of the actual response categories are shown in the supplement Table S1.

	Atopic comorbidity	EH	no EH	p value
Physicians report	Allergic rhinitis	n = 188	n = 634	0.34*
	Yes (Exists, treated/not treated with medication)	126 (67.0%)	401 (63.2%)	
	No	62 (33.0%)	233 (36.8%)	
	Bronchial asthma	n = 192	n = 649	0.16*
	Yes (Exists, treated/not treated with medication)	93 (48.4%)	277 (42.7%)	
	No	99 (51.6%)	372 (57.3%)	
Patients report	Allergic rhinitis	n = 195	n = 666	0.03*
	Yes (Last year/In the past)	150 (76.9%)	459 (68.9%)	
	No	45 (23.1%)	207 (31.1%)	
	Bronchial asthma	n = 194	n = 664	0.03*
	Yes (Last year/In the past)	116 (59.8%)	337 (50.8%)	
	No	78 (40.2%)	327 (49.2%)	
Physician reported sensitizations	Pollen	n = 178	n = 586	0.24*
	Yes	143 (80.3%)	446 (76.1%)	
	No	35 (19.7%)	140 (23.9%)	
	House dust mite	n = 175	n = 574	< 0.01*
	Yes	140 (80.0%)	378 (65.9%)	
	No	35 (20.0%)	196 (34.1%)	
	Mold	n = 140	n = 485	< 0.01*
	Yes	69 (49.3%)	157 (32.4%)	
	No	71 (50.7%)	328 (67.6%)	
	Food allergens	n = 158	n = 511	< 0.01*
	Yes	92 (58.2%)	221 (43.2%)	
	No	66 (41.8%)	290 (56.8%)	

Abbr.: EH, eczema herpeticum
*Chi square test

Regarding disease severity, we detected more patients with moderate AD in the multiple EH group compared to single and non-EH, but the absolute values for oSCORAD and EASI did not differ significantly. It can be hypothesized that we did not detect any differences regarding the severity based on the inclusion criterium of a moderate to severe AD in our cohort. In particular, this may be because the control group (patients without a history of EH) also belonged to the subgroup of AD patients with moderate to severe AD. This is in contrast to all other studies, where the controls were less severely affected. In addition, we cannot confirm that moderately to severely affected patients with a history of EH have an earlier onset of AD, as reported in two studies. It should be noted that in the study of Wollenberg et al. the mean age of onset AD in the EH group was 5.6 years. In the study of Seegräber et al. it was 5.43 ± 12.9 years in the recurrent EH group and 11.1 ± 6.5 years in patients with a single episode of EH.

Lübbe et al. depicted a case of EH in an AD patient using the topical immunomodulatory substance tacrolimus.[29] However, an increased risk of EH was not evident in studies on tacrolimus with larger cohorts.[30] We showed an increased use of tacrolimus ointment in the EH groups by trend, though it should be noted that topical treatment was not studied in direct relation to the manifestation of EH. Due to the cross-sectional nature of our analysis, any associations of EH with AD-treatments have to be interpreted with caution. Topical corticosteroids as a risk factor were not discernible in the cohort study of Wollenberg et al. and significant seasonal differences of the incidence as appearing in AD and herpes simplex were not identified,[24] although a slight accumulation was observed in winter and spring.[26,31]

In conclusion, previous studies and the present study indicate that there is no clear clinical feature that would help physicians in daily routine to identify EH patients in the group of moderately to severely affected AD patients. Especially since there is currently no real-life data regarding the potentially increased risk of viral infections under JAK inhibitor treatment, the patient history of viral infections is the only option to identify susceptible individuals.

TABLE 4 Previous therapy of the three patient groups. Regarding the topical therapy, patients with multiple EH showed increased tacrolimus ointment use by trend. Comparable previous phototherapy and systemic therapy were seen among all three groups.

Previous therapy	Multiple EH (n = 107)	Single EH (n = 88)	No EH (n = 668)
Topical Therapy (last 12 months)			
Glucocorticosteroids	95 (88.8%)	80 (90.9%)	588 (88.3%)
Pimecrolimus	36 (33.6%)	32 (36.4%)	201 (30.2%)
Tacrolimus	49 (45.8%)	35 (39.8%)	233 (35.0%)
UV Therapy (last 12 months)	33 (30.8%)	32 (36.4%)	229 (34.4%)
Systemic Therapy (ever)			
Cyclosporine	32 (29.9%)	25 (28.4%)	167 (25.0%)
Dupilumab	13 (12.1%)	11 (12.5%)	76 (11.4%)
Glucocorticosteroids	65 (60.7%)	52 (59.1%)	377 (56.5%)
Methotrexate (MTX)	4 (3.7%)	2 (2.3%)	21 (3.1%)
Azathioprine	2 (1.9%)	2 (2.3%)	10 (1.5%)
Mycophenolate	0 (0.0%)	2 (2.3%)	8 (1.2%)
Other systemic therapeutics	5 (4.7%)	6 (6.8%)	49 (7.3%)

Abbr.: EH, eczema herpeticum

The molecular changes identified so far cover immune profile abnormalities, type 2 skewing of virus-specific T cells,[16] aberrations in interferon pathway related genes such as IFNG and SNPs in skin barrier proteins such as filaggrin.[32–36] The skin microbiome also contributes to EH due to *S. aureus* toxins, which play a supporting role in viral infection.[37] These aspects cannot currently be used in clinical routine, but large registries like TREATgermany, which include biosampling, can help to identify biomarkers that can be used in daily clinical practice.

Limitations might also result from the fact that the EH history is patient reported. Although the patient questionnaire specifically asks about "extensive herpes infection of the skin (eczema herpeticatum)" the question could be misunderstood due to unfamiliarity with this specific disease and lead to an overestimation of prevalence. However, this may reflect the daily routine, as most often the clinical, physician-based report of the EH is not available. Based on this limitation, only descriptive statistics are provided, leaving out multivariate logistic analyses.

This first study analyzing the frequency and the clinical phenotype of EH patients in a large AD registry cohort demonstrated a high frequency of self-reported EH in the medical history of moderately to severely affected AD patients and a very high recurrence rate of EH in those patients: More than one out of five patients with moderate to severe AD experience EH. More than one out of ten patients even experienced multiple episodes of this severe complication. This highlights the high clinical relevance of EH in the care of patients with moderate-to-severe AD. Demographic data and disease severity were comparable between patients without EH, with a single episode of EH, and with multiple episodes of EH in their history. Atopic concomitant diseases were more frequently in patients with EH regardless of whether a single or multiple EH were reported in the history. Thus, biological markers are needed that can be applied in clinical routine to identify patients at risk for severe HSV infections. This is of particular interest in the context of novel and emerging systemic treatments for moderate to severe AD.

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