Clinical Features of Eczema Herpeticum in Comparison with Localized Herpes Simplex Virus Infection

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Background: The pathogenesis of eczema herpeticum (EH) still remains unclear. Atopic dermatitis (AD) and use of corticosteroids are thought to be associated with EH. Some serologic tests like eosinophil counts, IgE, and erythrocyte sedimentation rate (ESR) are considered as the predictors for the development of EH.

Objectives: The purpose of this study is to understand clinical and laboratory characteristics of EH and localized herpes simplex virus (HSV) infection in terms of age, sites of involvement, use of topical corticosteroids, the past and/or present AD, and some laboratory findings.

Method: Patients (n=25) who had EH were compared with patients (n=25) who had localized HSV infection.

Results: There was an age preponderance whereby children and young adults less than 30 years of age were more likely to have EH. EH was definitely more likely to occur in facial herpes than genital herpes. The sites of involvement of EH tended to be the face, the neck, and the trunk, in order of frequency. Use of topical corticosteroids did not appear to be associated with EH. Patients with EH were more likely to have past and/or present AD than control patients. Neither serum eosinophil counts nor IgE level was likely to be higher, otherwise, ESR was significantly higher in EH than in control patients.

Conclusions: The results suggested EH was more likely to occur at a younger age, on the face, in association with AD and with an increased ESR, compared to localized HSV infection. (Ann Dermatol 17(1) 1~6, 2005)

Key Words: Eczema herpeticum, Herpes simplex virus infection

INTRODUCTION

Eczema herpeticum (EH) is defined as a disseminated cutaneous herpes simplex virus (HSV) infection, accompanied by constitutional symptoms in patients with eczematous skin diseases, or in immunosuppressed conditions[1]. HSV-1 is the main etiology, though HSV-2 is also causative[2-4]. EH usually results from direct transfer of HSV, but indirect inoculation via manual scratching or contaminated towels or underwear is possible[5]. Patients with EH present with rapidly spreading vesicular eruptions. They may be confined to abnormal skin but often disseminated, and evolve into erosions and ulcers, and generally heal in 2-6 weeks with little scarring. However, some hosts may potentially become threatened with viremia, giving rise to multiple organ involvement[6]. The predilection sites are the face and neck, and the vesicles extend progressively to other parts of the body. EH can be diagnosed by several methods, such as the Tzanck smear, serology, cultures and polymerase chain reaction for HSV infection. Fortunately, systemic administration of acyclovir, or its derivatives, was definitely proved to be valuable for the treatment of EH[7,8].

Although pathogenesis of EH is still not largely understood, some reports[8-10] have demonstrated that the

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majority of EH occurs in patients with atopic dermatitis (AD), arguing a role for serum eosinophil counts and IgE level[8,11-17], and use of topical corticosteroids[8,14,15] or tacrolimus[16,17] in the development of EH. This study aimed to understand the characteristics of EH by retrospectively comparing the clinical and laboratory findings of EH and localized HSV infection.

MATERIALS AND METHODS

Patients

From 1998 to 2002, 25 patients diagnosed with EH were assembled. The patients consisted of 17 males and 8 females, with an age range of between 3 and 53 years. The diagnosis of EH was determined by two techniques: A Tzanck smear test and the serologic HSV antibody test. Two cases with a positive Tzanck smear and no serologic test were included. They could be differentiated from herpes zoster by the absence of characteristic pain and dermatomal invasion. A control group of 25 patients suffering from a localized HSV infection was randomly selected. The control group had a sex ratio and age range similar to the EH group (14 males and 11 females, 8 to 56 years old).

Method

The ages were divided into subgroups by decade, and the condition and age of patients were examined by comparing the EH group with the control group. The sites and the extent of widespread herpetic lesions were estimated. In all patients, the use of topical corticosteroids before (within 1 week) and/or at the onset of the herpetic infection, the history of prior (earlier than 16 weeks) and/or current (within 16 weeks) AD on the basis of regular treatment, and the primary or secondary HSV infection in the records were investigated. HSV-IgM positive and HSV-IgG negative cases were classified as primary infections, while HSV-IgM negative and HSV-IgG positive cases were classified as secondary infections. All patients, except two cases, took HSV-IgM and HSV-IgG tests at the same time. Eosinophil counts, erythrocyte sedimentation rate (ESR), and IgE level were also checked on the first visit.

Statistics

The data of EH and control groups were calculated and analyzed by SPSS 11.0 for Windows (SPSS, Inc: 2001, Chicago). The Pearson chi-square test and Mann-Whitney *U* test were performed to compare the two groups, with a P value of less than 0.05 being considered statistically significant.

RESULTS

The ratio of female to male patients with EH was about 2:1. Ten cases (40%) out of 25 patients with EH were in the 20-29 year-old age range, and this was found to be the most vulnerable age group. Furthermore, 21 cases (84%) were found to be under 30 years of age (P=0.007) (Table 1).

The sites of involvement in patients with EH were found to be on the face in 24 cases (96%), on the neck in 16 cases (64%), and on the trunk in 7 cases (28%), which was indicative of downward extension

Table 1. Age Distribution of Patients with EH and the Control Patients

Age(y)	EH No.(%)	Control No.(%)
≥ 50	1 (4)	3 (12)
40 - 49	1 (4)	5 (20)
30 - 39	2 (8)	5 (20)
20 - 29	10 (40)*	6 (24)
10 - 19	7 (28)*	4 (16)
≤ 9	4 (16)*	2 (8)
Total	25 (100)	25 (100)

EH, eczema herpeticum; Control, localized HSV infection.
*Patients with EH were likely to be younger than the control patients (P=0.007).

Table 2. Characteristics of Patients with Eczema Herpeticum and Control Patients with Localized HSV Infection

	Eczema herpeticum		Localized HSV infection		*P* value*
	No.(%) of patients		No.(%) of patients		
Sites†, face	n=25	24 (96)	n=25	14 (56)	0.001
neck	n=25	16 (64)	n=25	1 (4)	0.000
trunk	n=25	7 (28)	n=25	1 (4)	0.021
genitals	n=25	1 (4)	n=25	9 (36)	0.005
Use of steroids	n=21	14 (67)	n=21	9 (43)	0.121
AD‡, past	n=20	11 (55)	n=22	5 (23)	0.031
present	n=20	9 (45)	n=22	4 (18)	0.060
past and/or present	n=20	13 (65)	n=22	7 (32)	0.032
HSV, primary:secondary	n=23	10 (43):13 (57)	n=22	7 (32):15 (68)	0.420
	Range	M±SD	Range	M±SD	*P* value**
Age (y)	n=25 3 - 53	22.4±11.9	n=25 8 - 56	24.8±9.5	0.020
Eosinophil (%)	n=20 1.0 - 12.1	5.0±3.5	n=18 1.2 - 6.6	3.8±1.9	0.203
ESR (mm/hr)	n=22 5 - 37	17.7±9.6	n=17 1 - 33	9.9±8.6	0.008
IgE (IU/mL)	n=21 6 - 1211	347.0±411.6	n=20 12 - 1092	320.2±385.5	0.814

HSV, herpes simplex virus; AD, atopic dermatitis; †face only (n=8), face+neck (n=10), face+neck+trunk (n=6) in EH. ‡past (n=4), present (n=2), past+presnt (n=7) in EH; past (n=3), present (n=2), past+present (n=2) in control. M±SD, mean±standard deviation; *Pearson *chi* - square test; **Mann - Whitney U test.

from the face to the trunk. The face, neck and trunk were significantly more probable areas for EH (*P*=0.001, 0.000, 0.021, respectively), whereas, the genitals (4%) were the least probable area for EH (*P*=0.005).

The use of topical corticosteroids before or at the onset of HSV infection was found in 14 cases (36%) of patients with EH and 9 cases (24%) of patients in the control group. There was no significant difference (*P*=0.121).

The rate of past AD in patients with EH versus the control patients was 55% (11/20) vs 23% (5/22), with a significant difference (P=0.031). The rate of present AD in EH patients versus the control group was 45% (9/20) vs 18% (4/22), with no significant difference (*P*=0.060). The rate of past and/or present AD in EH patients versus the control group was 65% (13/20) vs 32% (7/22), with a significant difference (*P*=0.032).

The rate of primary versus secondary HSV infection was 43% (10/23) vs 57% (13/23) in patients with EH and 32% (7/22) vs 68% (15/22) in control patients, with no significant difference found (P=0.420).

The mean eosinophil count in patients with EH (5.0%) was not significantly different in control patients (3.8%) (*P*=0.781). The mean ESR in patients with EH (17.7 mm/hr) was significantly higher than in control patients (9.9 mm/hr) (*P*=0.008). The mean IgE levels in patients with EH (347.0 IU/mL) were not significantly different in control patients (320.2 IU/mL) (*P*=0.814) (Table 2).

DISCUSSION

According to Bork and Brauninger[8], the incidence of EH increased during the 1980's. On the other hand, Wollenberg et al.[15] reported that they did not notice an increase of EH during the 1990's. Some researchers have described the mean age of patients with EH as 22.7 years (56% between 15 and 24 years)[8], and 22.3±11.3 years (vastly between 20 and 29 years)[15]. Similarly, the figure was 22.4±11.9 years of age (40% between 20 and 29 years and 28% between 10 and 19 years) in this study. Thus, EH was found to be more likely to occur in children and young adults less than 30 years old (*P*=0.007)

(Table 1).

Based on the findings of this study, the face was the most frequent site of infection, and the lesions extended to adjacent areas including the neck and the trunk as EH progressed. In comparison, EH concomitant with genital herpes was found in only one case of 25 patients (Table 2). Herr et al.[18] indicated that HSV-1 might be more prevalent than HSV-2 in people under 30 years of age, and that HSV-1 was much more frequently isolated from the lesions above the waist than below it. It can therefore be postulated that HSV-1 is much more likely to cause EH than HSV-2, though the mechanism in which EH tends to develop on the face, neck and trunk is not known. To verify the speculation, HSV typing by polymerase chain reaction, in connection with the occurring sites of EH, will be required in further studies. Interestingly, it was reported that the F35 genotype of HSV-1 seemed to be closely associated with EH[19].

Systemic or topical corticosteroid therapy is known to facilitate HSV infection. Furthermore, use of corticosteroids[8,14] or tacrolimus[16,17] has sometimes been blamed for the development of EH. Use of topical corticosteroids was reported to precede an episode of herpes in only three of 21 cases with AD[14]. Another article[8] revealed 11% of patients with EH had received corticosteroid. But, the correlation had been inconsistently assessed, since it needed to judge whether heavy corticosteroid use simply reflected the severity of the underlying eczema. The majority of patients with EH had not been treated with corticosteroids in the 4 weeks before admission, which argued against a causative role for corticosteroid pretreatment in the pathogenesis of EH[15]. The findings demonstrated the rate of precedent and/or current use of topical corticosteroids seemed to be insignificantly different between EH and the control group (Table 2), which could be contradictory to the theory that the use of corticosteroids may influence the development of EH.

Together with various dermatoses, AD is believed to be the most common pre-existing skin disorder leading to EH. It can be explained by the fact that disruption of the skin barrier makes the skin vulnerable to viral infection and extension[3]. Besides, immunologic aberration in some skin conditions accounts for the pathogenesis of EH[9]. It is likely that reduced numbers of circulating natural killer cells and a decrease in interleukin-2 (IL-2) receptors during early EH contribute to the susceptibility of HSV infection[20]. Increased activity in IL-4 and IL-10, as in AD, can play a role in the development of EH[21,22]. A lower number of type 1 interferon-producing plasmacytoid dendritic cells in AD may be responsible for EH[22]. Also, severe EH is associated with prolonged depression of cell-mediated immunity (CMI) that may be due to abnormal suppressor T (CD8+) cell function[23].

HSV infection concurrent with AD may be usually severe or widespread[8,9]. Patients with EH had a significantly longer history of AD and 58% of the patients with EH had AD develop within the first decade of life, suggesting an early onset of AD is a risk factor for EH[15]. To differentiate the past AD from the present AD, the period of 16 weeks was set as a maintenance phase of inactivity during which no relapse of AD was observed[23]. The rate of the past and/or present AD was significantly higher in EH patients than in the control group (Table 2). From the result, it is inferred that AD may play a role in the development of EH. Separately, the rate of the past AD was also higher in EH, which means the history of AD may be important for predicting the outcome of HSV infection. Unfortunately, this study lacked the data on the whole span or the severity of AD which could be related to pathogenesis of EH, and the number of cases did not seem to be sufficient to endorse a full credibility to the theory.

EH is caused by both primary and secondary infection with HSV. Twenty percent of 75 cases followed endogenous recurrent herpes labialis[8]. Another report[15] noted the ratio of primary vs secondary HSV infection in patients with EH to be 20 vs 26, with the same ratio (10 vs 13) as in this study (Table 2), revealing a higher incidence of secondary infection than previously reviewed. This study suggests that there is no difference in the development of EH due to either a primary or secondary HSV infection.

Some laboratory tests, including eosinophil counts, IgE, and ESR, have been referred to as indicators to the development of EH[8,11-17,19]. Reversely, Wollenberg et al.[15] stated there was no significant difference in eosinophil counts between patients with EH and patients with AD. And, in neither EH nor AD patients was a higher percentage involvement of the skin lesions associated with a significantly higher total serum IgE level[15]. Although notable

fluctuations in serum IgE levels and in extent of AD were seen in more than half of the cases, no relationship was found between the two factors[11]. No association between the absence of CMI to HSV and serum IgE level or activity of the eczema was apparent in atopic patients[22]. Eight AD cases in children with EH[13] showed IgE: 39 to 474, mean 197 IU/ml; eosinophil count 139 to 560, mean 314/mm^3, which were slightly lower than the findings. Insignificantly increased eosinophil counts and IgE level in patients with EH (Table 2) might be associated with a relatively higher incidence of AD, rather than HSV infection itself. Consequently, it turned out that eosinophil counts and IgE level could not be associated with the pathogenesis of EH.

A recent article[15] proposed that patients with EH had a significantly higher ESR on admission than at discharge, and increased ESR might be linked to either EH or heavy bacterial colonization. In this study, ESR measured on the first visit was significantly higher in EH patients than in the control group (Table 2). Since bacterial infection generally follows HSV infection and we could not necessarily observe superimposed bacterial infection at the time of EH diagnosis and ESR measurement, it is reasonable to presume that increased ESR is associated with EH rather than bacterial infection. From another point of view, however, ESR should be carefully evaluated because it can be widely related to nonspecific inflammatory reactions. In this context, ESR should be consecutively checked in patients who start with a localized HSV infection which proceeds to EH. A further prospectively-designed study is mandatory to ensure the reliability of ESR as the predictor to EH.

REFERENCES

1. Crumpacker CS: Herpes simplex. In: Freedberg IM, Eisen AZ, Austen KF, Goldsmith LA, Katz SI, Fitzpatrick TB, eds. Dematology in general medicine. 5th ed. New York, McGraw Hill, 1999, pp2413-2426.
2. Nasemann T: Herpes simplex. Padiatr Padol 1976; 11(4):621-627.
3. Goodyear HM, Davies JA, McLeish P, Buchan A, Skinner GR, Winther M, Harper JI: Growth of herpes simplex type 1 on skin explants of atopic eczema. Clin Exp Dermatol 1996;21(3):185-189.
4. Hazen PG, Eppes RB: Eczema herpeticum caused by herpesvirus type 2. A case in a patient with Darier disease. Arch Dermatol 1997;113:1085-1086.
5. Amatsu A, Yoshida M: Detection of herpes simplex virus DNA in non-herpetic areas of patients with eczema herpeticum. Dermatology 2000;200: 104-107.
6. Sanderson IR, Brueton LA, Savage MO, Harper JI: Eczema herpeticum: a potentially fatal disease. Br Med J (Clin Res Ed) 1987;294(6573):693-694.
7. Muelleman PJ, Doyle JA, House RF Jr: Eczema herpeticum treated with oral acyclovir. J Am Acad Dermatol 1986;15:716-717.
8. Bork K, Brauninger W: Increasing incidence of eczema herpeticum: analysis of seventy-five cases. J Am Acad Dermatol 1988;19(6):1024-1029.
9. Rystedt I, Strannegard IL, Strannegard O: Recurrent viral infections in patients with past or present atopic dermatitis. Br J Dermatol 1986;114(5):575-582.
10. Atherton DJ, Harper JI: Management of eczema herpeticum. J Am Acad Dermatol 1988;18:757-758.
11. Stone SP, Gleich GJ, Muller SA: Atopic dermatitis and IgE. Relationship between changes in IgE levels and severity of disease. Arch Dermatol 1976; 112(9):1254-1255.
12. Korting GW, Krautheim H, Wieland W: Eczema herpeticatum. Med Welt 1983;34(21):611-631.
13. Lai YC, Shyur SD, Fu JL: Eczema herpeticum in children with atopic dermatitis. Acta Paediatr Taiwan 1999;40(5):325-329.
14. David TJ, Longson M: Herpes simplex infections in atopic eczema. Arch Dis Child 1985;60(4):338-343.
15. 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(2):198-205.
16. Lubbe J, Pournaras CC, Saurat JH: Eczema herpeticum during treatment of atopic dermatitis with 0.1% tacrolimus ointment. Dermatology 2000; 201(3):249-251.
17. Fleischer AB Jr, Ling M, Eichenfield L, Satoi Y, Jaracz E, Rico MJ, Maher RM: Tacrolimus Ointment Study Group. Tacrolimus ointment for the treatment of atopic dermatitis is not associated with an increase in cutaneous infections. J Am

Acad Dermatol 2002;47(4):562-570.
18. Herr H, Kim YT, Choi TY: Determination of herpes simplex virus isotypes by nested polymerase chain reaction. Korean J Dermatol 1998;36(4):643-651.
19. Yoshida M, Umene K: Close association of predominant genotype of herpes simplex virus type 1 with eczema herpeticum analyzed using restriction fragment length polymorphism of polymerase chain reaction. J Virol Methods 2003;109(1):11-16.
20. Goodyear HM, McLeish P, Randall S, Buchan A, Skinner GR, Winther M, Rolland J, Morgan G, Harper JI: Immunological studies of herpes simplex virus infection in children with atopic eczema. Br J Dermatol 1996;134(1):85-93.
21. Raychaudhuri SP, Raychaudhuri SK: Revisit to Kaposi's varicelliform eruption: role of IL-4. Int J Dermatol 1995;34(12):854-856.
21. Wollenberg A, Wagner M, Gunther S, Towarowski A, Tuma E, Moderer M, Rothenfusser S, Wetzel S, Endres S, Hartmann G: Plasmacytoid dendritic cells: a new cutaneous dendritic cell subset with distinct role in inflammatory skin diseases. J Invest Dermatol 2002;119(5):1096-1102.
22. Vestey JP, Howie SE, Norval M, Maingay JP, Neill WA: Immune responses to herpes simplex virus in patients with facial herpes simplex and those with eczema herpeticum. Br J Dermatol 1988;118(6):775-782.
23. Berth-Jones J, Damstra RJ, Golsch S, Livden JK, Van Hooteghem O, Allegra F, Parker CA: Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomized, double blind, parallel group study. BMJ 2003;21:326(7403):1367-1373.