

Risk Factors of Atopic Dermatitis Patients for Eczema Herpeticum

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TO THE EDITOR

Atopic dermatitis (AD) is a pruritic chronically relapsing skin disease in which T helper type 2 cells play a crucial role in cutaneous and extracutaneous immune responses (Leung and Bieber, 2003). A subgroup of AD patients develops one or more episodes of a severe viral superinfection caused by herpes simplex virus (HSV) on eczematous skin lesions. This condition is termed AD complicated by eczema herpeticum (ADEH) (Mackley *et al.*, 2002; Wollenberg *et al.*, 2003). The exact factors favoring the emergence of ADEH in this subgroup of patients with AD, which occurs most frequently within the second and third decade of life, are still unclear (Bork and Brauning, 1988; Wollenberg *et al.*, 2003). It is known that primary and secondary infections with HSV type 1 or 2 can induce ADEH. In most cases ADEH starts with a simple labial infection with

HSV type 1 developing rapidly from small vesicles into pustules and punched-out crusts, which might in severe cases spread from the facial area over the entire body and is accompanied by fever, malaise, lymphadenopathy, and rapid impairment of the general condition (Wollenberg *et al.*, 2003).

This study investigated the clinical and immunological properties of AD patients with history for ADEH in comparison to AD patients without ADEH, in order to identify risk factors predisposing a subgroup of AD patients to severe viral infections. The Declaration of Helsinki Principles was followed, the protocol was approved by the local ethical committee and informed consent was obtained from each individual participating in the study.

AD patients investigated were 40% male and 60% female subjects between

13 and 78 years of age. About 20% ($n=51$) of the patients had one or more episodes of ADEH. There was no gender-specific predominance of ADEH but a slightly higher severity or the extent of skin lesions (SCORAD) in ADEH+HSV+ patients (Table 1). However, patients of the ADEH group (ADEH+HSV+) had significantly higher prevalence of eczematous skin lesions located primarily in the head and neck area (Table 1). We found that patients of the ADEH+HSV+ group had a higher prevalence of early age of onset of AD in combination with a chronic-recurrent course of AD until adulthood (Table 1).

Total serum IgE levels were significantly higher in the ADEH subgroup than in the other groups. Sensitization against aeroallergens was more pronounced in the ADEH+HSV+ subgroup of patients (Table S1). Sensitization against the lipophilic

Table 1. Clinical features of the different AD subgroups

	ADEH+HSV+($n=51$)	ADEH-HSV+($n=75$)	ADEH-HSV-($n=112$)
Early age of onset (<6 years) [§]	76.5%**	54.7%	50.9%
Predilection in the head and neck area [§]	64.7%*	37.3%	27.7%
Objektive SCORAD [‡]	39.6±14.8*	30.5±17.1	31.0±16.1
Episodes of HSV infections per year [‡]	3.1±4.4	3.3±3.2*	0
	ADEH+HSV+($n=31$)	ADEH-HSV+($n=33$)	ADEH-HSV-($n=18$)
HSV IgG level in the sera (reciprocal titer) [‡]	19,219.0±15,492.4	15,790.9±13,618.7	13,289.4±12,023.9
Level of neutralizing antibodies against HSV in the sera (reciprocal titer) [‡]	20.3±21.2	13.9±13.8	11.4±9.2

AD, atopic dermatitis; ADEH, AD complicated by eczema herpeticum; HSV, herpes simplex virus.

Clinical parameters of AD patients without any episode of ADEH or recurrent HSV infections (ADEH-HSV-), AD patients without any episode of ADEH but recurrent HSV infections (ADEH-HSV+) and AD patients with one or more episodes of ADEH and recurrent HSV infections (ADEH+HSV+) are shown in this table. For the evaluation of statistical significance, the χ^2 test (indicated with §) and the Kruskal-Wallis test (indicated with ‡) were performed.

* $P<0.05$; ** $P<0.01$.

Abbreviations: AD, atopic dermatitis; ADEH, AD complicated by eczema herpeticum; FCS, fetal calf serum; HSV, herpes simplex virus; MOI, multiplicity of infection; PBMC, peripheral blood mononuclear cells

yeast *Malassezia sympodialis* was significantly higher in AD patients with ADEH + HSV + (Table S1). This finding is of specific clinical importance as elevated levels of allergen specific IgE against *M. sympodialis* have been reported to be associated with the head and neck form of AD (Devos and van der Valk, 2000).

Using logistic regression analysis to evaluate the relative importance of the different parameters, we could show that an early age of onset of AD ($P=0.041$) a predilection of the skin lesions in the head and neck area ($P=0.001$); high allergen-specific IgE against *Aspergillus fumigatus* ($P=0.004$); allergen specific IgE against *M. sympodialis* ($P<0.001$) and allergen specific IgE against Birch pollen ($P=0.002$) were of significant importance for the development of ADEH.

IFN- β serum levels were significantly reduced in AD patients of the ADEH + HSV + subgroup (Figure 1a), whereas serum levels of IFN- γ were significantly reduced in all three AD

subgroups studied compared to non-AD controls (Figure 1b), whereas no differences in IFN- α serum levels could be found (data not shown).

Further on, we observed a slight reverse correlation between total IgE

serum levels and serum IFN- γ levels using the Spearman correlation coefficient (non-parametric) $r=-0.334$ ($P=0.035$) for analysis. Patients of all AD subgroups displayed enhanced serum levels of T helper type 2 cytokines

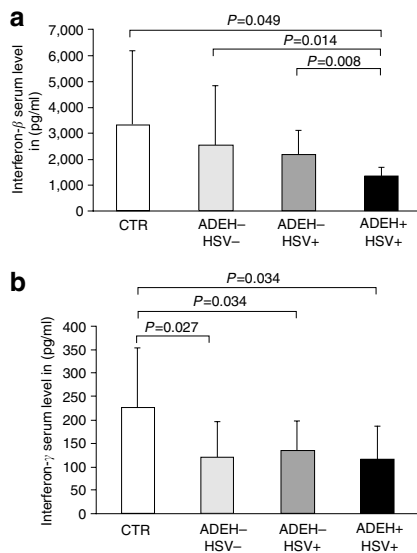


Figure 1. ADEH patients display lower IFN- β and IFN- γ serum levels. (a) Serum levels of IFN- β and (b) IFN- γ of AD patients without ADEH or recurrent HSV infections (ADEH-HSV-), AD patients without ADEH but recurrent HSV infections (ADEH-HSV+), and AD patients with one or more episodes of ADEH and recurrent HSV infections (ADEH+ HSV+) in comparison to healthy control donors without atopy (CTR) are depicted in (pg/ml) on the y axis. The data of 10 patients randomly selected from each group have been analyzed.

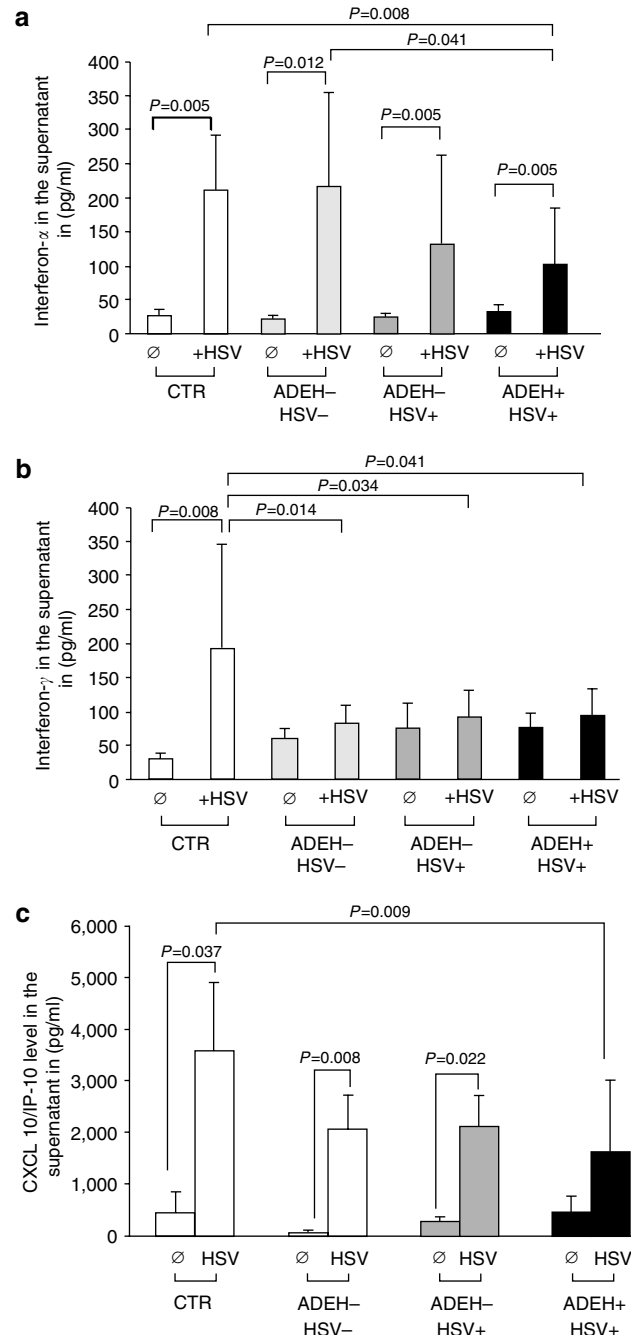


Figure 2. Lower capacity to produce IFN- α , - γ , and CXCL10/IP-10 of PBMC from ADEH + HSV + patients in response to HSV stimulation. (a) The amount of IFN- α , (b) IFN- γ , and (c) CXCL10/IP-10 in the cell culture supernatants of PBMC stimulated for 18 hours with UV-inactivated HSV or left unstimulated of ADEH-HSV-, ADEH-HSV+, ADEH+ HSV+ and healthy controls (CTR) is depicted in (pg/ml) on the y axis. Data of 10 patients randomly selected from each group have been analyzed.

in comparison to the healthy control group without significant differences between the different AD subgroups concerning these cytokines.

To study the ability of peripheral blood mononuclear cell (PBMC) isolated from AD patients of the different subgroups *versus* healthy controls to produce type I and II IFNs after stimulation with HSV, culture supernatants of PBMC of ADEH–HSV–, ADEH–HSV+, and ADEH+HSV+ patients and non-AD controls (CTR) with or without UV-HSV stimulation for 18 hours were collected and the results were analyzed by ELISA using and statistical analysis with the help of the Wilcoxon test. Stimulation of PBMC with HSV induced the production of IFN- α in all subgroups of AD and healthy controls. However, the lowest induction of IFN- α production was in ADEH patients (Figure 2a). In contrast to PBMC of healthy controls, which produced enhanced levels of IFN- γ after HSV stimulation, no significant increase of IFN- γ production of PBMC could be achieved in any of the AD subgroups after stimulation with HSV (Figure 2b).

PBMC of ADEH patients showed a significantly reduced production of CXCL10/IFN- γ -inducible protein 10 after stimulation with HSV in comparison to healthy controls (Figure 2c). These observations are interesting because CXCL10/IFN- γ -inducible protein 10 plays an important role in host defense against HSV infections by activated T cells after stimulation with HSV (Lundberg and Cantin, 2003).

Indeed, our current data show that the systemic T helper type 2 predominance on one hand and T helper type 1 deficiency on the other hand is much more pronounced in the subgroup of AD patients at risk for ADEH. At present, it is not known whether this T helper type 1/T helper type 2 imbalance is a direct cause for the increased

susceptibility for viral infections or just mirrors a higher state of “atopy” and much more severe course of AD (La *et al.*, 2005) in the subgroup of patients at risk for ADEH.

The reason why especially HSV in comparison to other virus types frequently causes viral complications in AD might be that the most striking feature of HSV is its capability to establish lifelong latency after primary infection. In this way, HSV persists in the host and reactivates periodically with HSV lesions on mucosal or skin surfaces in consequence of neuroimmunogenic factors such as stress or UV light. Further on, specific genotypic strains of HSV have been shown to lead to ADEH more often than others (Umene *et al.*, 1996; Yoshida and Umene, 2003).

In the future, early identification of patients at risk for viral complications would be important to develop effective prevention strategies and to evolve novel therapeutic options targeting components of the immune systems, which sustain effective viral host defense. Together with a clear-cut definition of patients with a high susceptibility for serious adverse events after viral challenges knowledge gained in this work would enable us to perform reliable risk-benefit analyses to standardize the procedure for the large subgroup of AD patients which currently represent over 10% of the industrial population.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

Table S1. Total and allergen specific IgE levels in AD subgroups.

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