

# Herpes simplex infections in atopic eczema

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**SUMMARY** One hundred and seventy nine children with atopic eczema were studied prospectively for two and three quarter years; the mean period of observation being 18 months. Ten children had initial infections with herpes simplex. Four children, very ill with a persistently high fever despite intravenous antibiotics and rectal aspirin, continued to produce vesicles and were given intravenous acyclovir. There were 11 recurrences among five patients. In two patients the recurrences were as severe as the initial lesions, and one of these children had IgG2 deficiency. Use of topical corticosteroids preceded the episode of herpes in only three of the 21 episodes. Symptomatic herpes simplex infections are common in children with atopic eczema, and are suggested by the presence of vesicles or by infected eczema which does not respond to antibiotic treatment. Virological investigations are simple and rapid: electron microscopy takes minutes, and cultures are often positive within 24 hours.

Patients with atopic eczema are susceptible to particularly severe infections with herpes simplex virus. Most cases are probably due to type 1,<sup>1</sup> but eczema herpeticum due to the type 2 virus has been described,<sup>2</sup> and the incidence of type 2 infections may be underestimated because typing is not usually performed. The source of the virus is assumed to be a close relative or friend with herpes labialis,<sup>3</sup> but spread in hospital by nurses may occur.<sup>4</sup> Cases of eczema herpeticum mostly represent an initial infection,<sup>3</sup> though the documentation of this is scanty.<sup>5,6</sup> Patients with eczema herpeticum may become seriously ill with a high fever, and death can occur.<sup>3</sup> The cause of death, though not always clear from published reports, may be due to some undetected immune deficiency state such as the Wiskott-Aldrich syndrome<sup>4,7</sup> or to secondary bacterial infection, usually with a combination of group A  $\beta$  haemolytic streptococci and *Staphylococcus aureus*.<sup>5</sup>

Severe herpes simplex infections are known to be a complication of other dermatological disorders including autosomal dominant ichthyosis vulgaris,<sup>8</sup> Darier's disease,<sup>9</sup> familial benign pemphigus,<sup>10</sup> pemphigus foliaceus,<sup>11</sup> and congenital ichthyosiform erythroderma.<sup>12</sup> It is not known whether the susceptibility of patients with certain skin diseases to severe herpes simplex infections is due to an underlying immunological abnormality or is merely attributable to the abnormal skin.

We report the incidence, clinical and laboratory

features, and treatment of herpes simplex infections in a group of 179 children with atopic eczema.

## Patients and methods

Between January 1982 and September 1984 all children referred to the department of child health with atopic eczema were studied prospectively for evidence of infection. Patients who had been followed for less than six months were excluded. One hundred and seventy nine patients were observed for 3199 patient months, with a mean of 18 months.

Patients were seen routinely at least three monthly as outpatients, but the parents were asked to attend with their child in the event of sudden or unexpected deterioration of the eczema, or if there was new evidence of infection such as crusting, discharge, or the appearance of vesicles or pustules. The finding of intact vesicles or pustules with a small central depression ('umbilicated pustules') led to the suspicion of herpes simplex infection. Where what had been thought to be simple bacterially infected eczema failed to respond to treatment with appropriate oral or parenteral antibiotics within 48 hours, infection with herpes simplex was suspected.

Specimens for virology were only collected in patients where the above criteria led to the suspicion of herpes infection. No specimens were obtained from patients who were well or where only bacterial infection was suspected. Swabs for virology in transport medium (balanced salt solution, bovine

serum albumen, antibiotics) were taken directly to the regional virus laboratory. Where vesicles were present, collection of material for electron microscopy was attempted. A clean dry microscope slide was placed in contact with a vesicle that had been punctured with a small sterile needle. The wet slide was allowed to dry in air. In the laboratory the dried material on the slide was suspended in a drop of distilled water before negative staining and electron microscopy. Herpes virus antibodies were sought with a standard complement fixation test and a locally produced antigen.

An initial infection was defined as the first recognisable clinical lesion suggestive of the presence of herpes simplex virus, combined with isolation of the virus in tissue culture. Seroconversion was defined as an initial specimen of blood with undetectable antibody, with a titre of at least 1/20 in a convalescent specimen, using the complement fixation test.

## Results

**Initial infections.** During the study period initial infections with herpes simplex virus were documented in 10 of the 179 patients. Tables 1 and 2

summarise the clinical and laboratory features. Ichthyosis was present in nine of the 10 patients and a prominent feature in three. Only three children had had topical corticosteroids in the previous six months. In five there was a history of a relative or friend with herpes labialis.

### Clinical features

In one patient the lesions were confined to both cheeks, and management at home simply comprised a topical antiseptic. Seven children required admission to hospital, in one case as a precautionary measure because of poor home circumstances, and in the rest because of the severity of the lesions. One patient also had gingivo-stomatitis. Vesicular lesions were seen where there was no associated bacterial infection, but in the presence of bacterial infection vesicles had the appearance of pustules, were sometimes umbilicated, and contained purulent fluid (Fig. 1). In areas where vesicles were confluent, raw areas of skin were seen after vesicle rupture (Fig. 2). The vesicles were usually fragile and burst easily with gentle rubbing. Once the vesicles had ruptured, and where the vesicles had not been confluent, the resulting lesions could be difficult to distinguish from simple septic spots that

Table 1 *Initial herpes simplex infections: clinical features*

Case no	Age (months)	Sex	Surface area affected by eczema (%)	Site of herpetic lesions	Maximum temperature (°C)
1	20	M	70	Legs, arms, neck, face, trunk	40.2
2	71	F	1	Both cheeks	Not measured*
3	21	M	80	Legs, arms, trunk, eye	40.0
4	32	M	80	Legs, left middle finger (whitlow)	40.0
5	94	F	1	Face	36.6
6	40	M	3	Legs	38.7
7	104	F	90	Face, neck, hands, stomatitis	37.5
8	5	M	15	Face, ear, eye	39.5
9	56	M	20	Hands, arms, heel, behind ear, face	Not measured*
10	54	M	5	Arm	Not measured*

\*Temperature not taken because seen in the clinic without history of fever.

Table 2 *Initial herpes simplex infections: laboratory features*

Case no	Serum IgE (IU/l)	Electron microscopy	Herpes simplex isolation in culture	Seroconversion*
1	468 (normal <29)	Positive	Positive	Yes
2	892 (normal <63)	Not done	Positive	Not tested
3	11 700 (normal <29)	Not done	Positive	Yes
4	11 150 (normal <42)	Positive	Positive	Yes
5	129 (normal <63)	Not done	Positive	Yes
6	810 (normal <42)	Not done	Positive	Yes
7	35 (normal <80)	Not done	Positive	Yes
8	18 (normal <11)	Positive	Positive	Yes
9	1010 (normal <52)	Negative	Positive	Yes
10	5645 (normal <52)	Positive	Positive	Yes

\*Defined as initial specimen with undetectable antibody, with a titre of at least 1/20 in a convalescent specimen, using the complement fixation test.



Fig. 1 Case 3. Most vesicles have become pustular, and there are some satellite lesions on the chest wall.



Fig. 2 Case 4. Left ankle. A raw area is visible centrally where the vesicles had been confluent. Some typical umbilicated pustules are seen above the raw area.



Fig. 3 Case 10. Right arm. Typical vesicles are only seen in the palm. The remaining vesicles have been broken, and the appearance of the wrist or ante-cubital fossa is indistinguishable from that of simple non-herpetic infected eczema.

had been scratched (Fig. 3). The clinical distinction between bacterial and herpetic infection of the fingertip was especially difficult. One child (case 4) had a paronychia which was thought to contain pus due to bacterial infection, but surgical exploration combined with avulsion of the nail showed no pus.

In three children, only failure of infected eczema to respond to parenteral benzylpenicillin and flucloxacillin gave rise to the suspicion of herpes. In two of these pustules were present on admission, and with hindsight the correct diagnosis should have been suspected earlier. In the third, neither we nor the mother had seen vesicles or pustules, and it was the failure of crusted infected eczema to improve with oral antibiotics that led to the collection of specimens for virology.

In four children, continued production of vesicles, the persistence of high fever (greater than 39.5°C) despite parenteral benzylpenicillin and flucloxacillin in high dosage and rectal aspirin, accompanied by prostration and general debility, led to the administration of intravenous acyclovir (5 mg/kg three times a day) for five days. In each case this was followed by a cessation of vesicle production and rapid resolution of fever. Five children were only treated with oral phenoxymethylpenicillin and flucloxacil-

lin, combined with a topical antiseptic ointment containing povidone-iodine.

#### Bacteriological results

No bacteria were recovered from the lesions of cases 1 and 2. *Staph aureus* was recovered from the lesions of the other eight, accompanied by  $\beta$  haemolytic streptococci in seven (Lancefield group A in six, group B in one).

#### Virological results

Electron microscopy was not attempted in five patients, but out of the other five patients, virus particles of the herpes group were seen in four. Herpes simplex virus was grown in tissue culture in all 10 patients. Seroconversion was found in all nine patients from whom appropriate acute phase and convalescent specimens had been obtained.

#### Immunological results

Serum concentrations of the immunoglobulins A, G, and M were normal in nine patients. One patient had normal serum concentrations of IgA, IgG, and IgM, but had a deficiency of the IgG subclass IgG2. She is described in detail elsewhere.<sup>13</sup> The serum IgE values are given in Table 2.

**Recurrent herpetic lesions.** Recurrence of herpetic lesions occurred in five children. Clinical and laboratory data are given in Table 3. In four (cases 1, 4, 7, and 8) the initial infection had occurred during the study period. In one (case 11) the initial infection had occurred several years before the patient was referred to us.

#### Clinical features

In cases 1 and 4 the recurrences were trivial compared with the initial lesions. In case 11 the initial and recurrent episodes were identical. In case 8, the recurrence comprised herpetic keratitis. In case 7 the recurrences were only slightly less extensive than the initial lesions, although recovery was more rapid with the second and subsequent episodes. In each case (apart from case 8, where the relapse was ocular) all recurrences comprised a crop of vesicles easily identified by the parents as herpetic. In none had topical corticosteroids been given before the recurrence. Apart from the third recurrence of case 1, which coincided with a respiratory infection, the recurrences did not coincide with intercurrent illnesses.

The distribution of the recurrent lesions was most odd. In cases 7, 8, and 11, the recurrences were all at the precise site of the initial lesions. In case 4, the first recurrence affected the same single digit that had been affected originally. The second recurrence affected the back of the same hand, though this had not been involved in the initial infection. In case 1 the first recurrence comprised herpetic whitlows (paronychia) of both middle fingers. The second recurrence comprised a crop of vesicles over the dorsum of the inter-phalangeal joint of both thumbs, accompanied by an herpetic whitlow (sub-ungual collection of pus from which the virus was recovered) of the right middle finger. This patient's fingers had not been affected in the initial infection. He was not in the habit of sucking his thumbs or fingers. His third recurrence was again striking for the symmetry of the lesions in both axillae, an area

Table 3 Recurrent herpetic lesions: clinical and laboratory findings

Case No	Age at initial infection (months)	Age at recurrence and site			Electron microscopy	Herpes simplex isolation in culture
		First recurrence	Second recurrence	Third recurrence		
1	20	26 months Both middle fingers (whitlows)	27 months Both thumbs, right middle finger (whitlow)	30 months Axillae, elbows, back, thigh	Pos;pos;pos	Pos;pos;pos
4	32	34 months Left middle finger	50 months Back of left hand	—	Pos;pos	Pos;pos
7	104	105 months Face, neck, hands	107 months Face, neck, hands	109 months Face, neck, hands	Neg;neg;neg	Pos;pos;pos
8	5	7 months Eye	—	—	Not done	Pos
11*	96	166 months Left pinna, left cheek	172 months Left pinna, left cheek	—	Neg;neg	Pos;pos

\*Boy. First attack at 96 months on left pinna and left cheek. Eczema affecting 8% of skin surface area, with mild ichthyosis. IgE 603 IU/l (normal <70). The history suggested that there had been approximately 10 recurrences between the initial infection and his first being seen by us at the age of 140 months.

Pos=positive; neg=negative.

that had not been affected in the initial infection. The other areas affected in the third recurrence, the elbows, back, and thigh, had all been affected in the initial infection.

No patient was systemically ill during a herpetic recurrence except for the respiratory infection associated with the third recurrence in case 1. Topical antiviral treatment (idoxuridine 0.1% eye drops) was given for the ophthalmic relapse. Oral acyclovir (5 mg/kg three times a day for five days) was given to case 11, with topical povidone-iodine ointment and oral phenoxymethylpenicillin and flucloxacillin, in the hope that it might prevent further recurrences; it did not. Recurrences in the other three patients were treated with a topical antiseptic and oral antibiotics.

#### *Bacteriological results*

There were 10 recurrences of skin lesions; *Staph aureus* was recovered in eight, accompanied by  $\beta$  haemolytic streptococci (Lancefield group A) in five (with group B streptococci in one).

#### **Discussion**

In this study of 179 children with atopic eczema, there were 21 symptomatic episodes of herpes simplex infection in a two and three quarter year period. This may be an underestimate, for no attempt was made to look for viral infection in those with lesions suggestive of uncomplicated bacterial infection or in those with no evidence of infection. Initial infections with herpes simplex are common in normal children, and there is no evidence from this study or any other that the incidence is any higher in children with atopic eczema. Our patients were a selected group, with an excess of severe or intractable cases, and it could be that the incidence or severity of herpes infections is not as high in children with less severe eczema. The fact that seven of the 10 children with initial herpes infections had only localised eczema suggests, however, that the occurrence of eczema herpeticum is unrelated to the extent of the eczematous lesions.

Why unusually severe herpes simplex infections are associated with specific skin diseases is obscure. Presumably the explanation lies either in the abnormal skin itself, or in some common underlying immunological explanation. The fact that neutralising antibodies fail to protect from recurrences suggests that the postulated immunological defect is not one of antibody production but of cellular immunity. Whether the virus spreads locally in the skin or whether haematogenous spread occurs has not been established. Topical corticosteroids are

well known to potentiate bacterial or fungal infection in the skin, but there is disagreement about whether they predispose to or potentiate viral infections.<sup>14</sup> In only three of the 21 episodes had there been recent use of topical corticosteroids. This unusual under usage of corticosteroids partly reflected local treatment policy and partly parental fear (often disproportionate) of adverse effects. Clearly, in our series of patients corticosteroids were not an important predisposing factor. A further unexplained problem is the curious distribution of recurrent lesions. While some of these were at the site of the initial infection, as one might expect with a virus that can remain dormant, others were at distant sites and were sometimes striking in their bilateral symmetry. Why only some patients should experience recurrent lesions is also obscure.

Sudden deterioration of atopic eczema is commonly due to infection. Where vesicles are seen the presence of herpes simplex should be sought. Failure of infected eczema to respond to appropriate oral antibiotics within 48 hours suggests herpes. Electron microscopy can be completed in minutes, and herpes simplex grows rapidly in sensitive cell culture, for example human embryo fibroblasts which are commonly used in most virology laboratories in Europe and the United States, so that positive results can often be obtained within 24 hours. Clinical diagnosis alone is not adequate, because similar appearances may be caused by Coxsackie virus infection.<sup>15 16</sup> Electron microscopy alone is not adequate, for it merely confirms the presence of a virus from the herpes group.

Claims that antiviral treatment is lifesaving in eczema herpeticum are probably exaggerated, for it is doubtful whether the disease is life threatening when appropriate antibiotics are given. In most cases eczema herpeticum is likely to be a highly unpleasant disease that recovers on its own. It would seem unreasonable, however, to withhold a fairly safe and effective drug such as acyclovir in severe cases, particularly those with fever and systemic illness, where antiviral treatment so dramatically shortens the illness. Whether acyclovir is best given intravenously<sup>17</sup> or orally<sup>18</sup> is unclear. Acyclovir is, however, rather insoluble and not well absorbed when given orally, so for ill patients we have preferred the intravenous route. The decision to treat for five days was arbitrary—it is possible that 48 hours treatment would have sufficed for the clinical response was so rapid.

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