

Acute follicular conjunctivitis and keratoconjunctivitis due to herpes simplex virus in London

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SUMMARY During the 18 months January 1975 to June 1976, 25 cases of acute herpetic follicular conjunctivitis and keratoconjunctivitis resembling adenovirus ocular infection presented in the External Eye Disease Clinic, Moorfields Eye Hospital, City Road, London. Herpes simplex virus was isolated in HEp2 cells in 22 patients, and the remaining 3 patients were identified by a minimum 4-fold rise in the level of antiherpes simplex virus antibody in their blood. No adenovirus was isolated from these patients, but complement fixation test for adenovirus was positive in 1 patient with cultural test positive for herpes simplex virus. Most patients were between 20 and 35 years old and the ratio of males to females was 12 to 13. At the initial visit the clinical features of disease were moderate to severe conjunctival papillary and follicular reactions with epithelial and subepithelial punctate keratitis but little systemic disease. In the absence of typical herpetic lesions of face, lids, or cornea the disease resembled adenovirus types 8 or 19 keratoconjunctivitis. Of these 25 patients 5 subsequently developed typical herpetic lesions of lids or cornea. In the remaining 20 cases the correct diagnosis could be made only by cultural or serological tests. Virological diagnosis provides a rational basis for antiherpetic chemotherapy, which appears to shorten the course of infection.

Acute primary herpetic blepharokeratoconjunctivitis and chronic recurrent keratitis are common manifestations of herpes simplex virus (HSV) infection. Less well recognised is acute follicular conjunctivitis without characteristic lid or corneal lesions.

This report presents the findings in 25 cases of acute herpetic follicular conjunctivitis which presented without characteristic lid, face, or corneal signs of herpetic infections. In most of them, the correct diagnosis could be made only by cultural or serological tests for HSV infection.

Methods and patients

Patients with acute follicular conjunctivitis or keratoconjunctivitis without facial, lid, or corneal lesions typical of HSV infection at the first visit, but with positive cultural or serological tests for HSV, were included.

The patients were examined with a Haag-Streit

slit lamp and symptoms were graded on a 0 to 3 scale (mild, moderate, severe) as described previously (Darougar *et al.*, 1977b). Conjunctival swabbings were placed in plastic capsules containing 2 SP transport medium (Gordon *et al.*, 1969) with 3% fetal bovine serum and stored in a refrigerator at -70°C. Each clinical specimen was inoculated into 2 tubes containing HEp2 cells. Cultures were maintained for 21 days and examined frequently for the presence of cytopathic effect (CPE) (McSwiggan *et al.*, 1975). Isolates were identified by the fluorescent antibody test.

Sera collected by venepuncture at intervals of 2 to 3 weeks were tested by a complement fixation test (CFT) for herpes simplex virus and adenovirus group antibodies. Conjunctival impressions taken from some patients by specially-designed plastic spatulae were fixed, stained, and examined by the method described by Thatcher *et al.* (1977).

Results

During the 18 months January 1975 to June 1976 25 patients with acute follicular conjunctivitis and

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no herpetic lesions of the lids, face, or cornea at the time of their first visit to the clinic, but with positive cultural or serological tests for herpes simplex virus, were identified. Of these 25 patients 5 subsequently developed palpebral vesicles or dendritic ulcers.

The patients' ages ranged from 8 to 50 years, the majority being between 20 and 35 years. The ratio of males to females was 12 to 13. Of these 25 cases 18 were diagnosed in 1975 and 7 in the first 6 months of 1976. No seasonal pattern of incidence was observed.

PREVIOUS HISTORY

Five patients gave a history of previous infection suggestive of herpes simplex: 3 had recurrent cold sores on nose or lips, 1 had lid disease (possibly herpetic) 5 years previously, and 1 had a history of a possible corneal ulcer 5 years previously. In no case was there a clear history of previous ocular herpetic infection.

Of the 25 patients 2 had been in contact with patients with cold sores, 3 in contact with other persons suffering from conjunctivitis, and a further 3 had been in swimming pools 9 to 21 days before the onset of their ocular infection. In 1 of this latter group some fellow swimmers had also developed conjunctivitis at the same time. In the other 17 cases there was no history of contact with other patients nor had they attended hospitals, clinics, or a swimming pool.

In 5 cases there was a history of pharyngitis and rhinitis during the week preceding the conjunctivitis. Another patient had a cold 3 weeks before developing eye disease. One patient had Hodgkin's disease and was on systemic treatment with prednisolone 5 mg daily.

SYMPTOMS AND SIGNS

Fifteen of the 25 patients had enlarged preauricular lymph nodes, which in 12 cases were tender. In 8 cases in which the disease affected both eyes the lymphadenopathy was bilateral.

The commonest symptoms were moderate hyperaemia associated with lacrimation, discharge, grittiness, and swelling of the lids (Table 1 and Fig. 1).

In 8 cases the second eye became inflamed in less than 1 week from the onset of the infection. In the other 17 the infection remained unilateral. The average duration of conjunctival inflammation was 4 weeks (range 2 to 12 weeks). In 17 cases lids showed diffuse oedema and mild to moderate erythema. No vesicle or ulceration was observed in these cases at the initial examination. However, in 4 cases vesicles or ulcers developed on the lid 2 to 3 days after the first examination.

The bulbar conjunctiva showed mild to moderate hyperaemia in 23 cases. Limbal follicles were noted in 2 and a moderate ecchymosis in 1 (Fig. 2). The palpebral conjunctiva showed moderate to severe hyperaemia and papillary hypertrophy in 21 cases

Table 1 *Prevalence and severity of symptoms at first visit in 25 cases of herpetic follicular conjunctivitis*

Symptoms	Severity		
	Mild	Moderate	Severe
Swelling of lids	7	5	1
Hyperaemia	11	13	0
Lacrimation	7	9	2
Discharge	15	6	0
Grittiness	11	5	0
Itching	6	2	0
Photophobia	4	2	1
Pain	4	1	0
Blurred vision	6	1	0

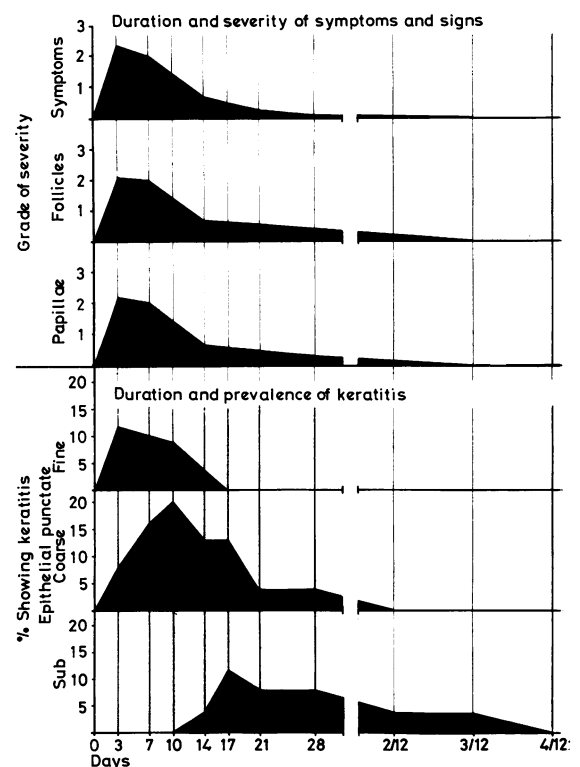


Fig. 1 *Duration and severity of symptoms and signs of disease in 25 cases of acute herpetic follicular conjunctivitis and keratoconjunctivitis*



Fig. 2 Moderate ecchymosis in a case of acute herpetic follicular conjunctivitis

and moderate to severe follicular reaction in 19 (Table 2). Papillary hypertrophy was most severe in the upper tarsus as well as the lower lid (Figs. 3, 4, 5) and lasted for 2 to 12 weeks (Fig. 1). Follicular reaction was present in all cases. Moderate to severe follicular hypertrophy was present mainly in the lower and upper fornices (Figs. 6, 7, 8). The follicles were small, discrete, and lasted 2 to 8 weeks (Fig. 1).

Nine of the 25 cases developed moderate coarse epithelial punctate keratitis (Jones, 1962). This was generally preceded by fine punctate keratitis (Jones, 1962). In 5 cases mild to moderate sub-

epithelial punctate keratitis (Fig. 9) resembling that of epidemic keratoconjunctivitis (Jones, 1962) developed. The opacities were coarse, fewer than 15 in number, and mainly located in the interpalpebral fissure. The average time from the onset of symptoms to the occurrence of subepithelial lesions was 17 days (Fig. 1). The subepithelial punctate keratitis persisted between 1 and 4 months.

In 2 cases small dendritic ulcers developed on days 4 and 9 respectively. They both responded well to therapy with idoxuridine 0.5% eye ointment. Of the cases with keratitis 2 developed a mild uveitis which responded quickly to therapy with trifluorothymidine 1% eye drops.

PATHOLOGY

In all, 38 conjunctival specimens were collected from 25 patients. In 22 of 25 cases herpes simplex virus was isolated in HEp2 cells.

Of the 24 specimens collected during the first week of infection 21 (88%) were positive for herpes

Table 2 Prevalence and severity of signs in the palpebral conjunctiva at first visit in 25 cases of acute herpetic follicular conjunctivitis

Sign	Severity		
	Mild	Moderate	Severe
Hyperaemia	8	13	4
Papillary hypertrophy	4	12	9
Follicular hypertrophy	6	15	4

Fig. 3 Severe papillary reaction in upper tarsal conjunctiva in the first week of acute herpetic follicular conjunctivitis





Fig. 4 Severe papillary reaction in lower lid conjunctiva in the first week of acute herpetic follicular conjunctivitis

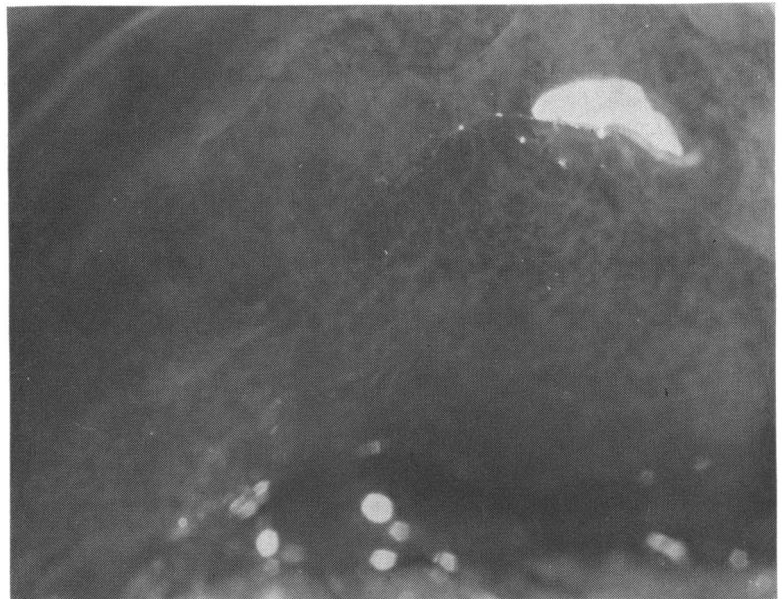


Fig. 5 Severe papillary reaction in upper fornix conjunctiva in the first week of acute herpetic follicular conjunctivitis

virus but only 4 out of 10 specimens collected during the second week gave positive results. No virus was isolated after the 11th day of infection. Adenovirus was not isolated from these patients.

Paired or triplicate sera were tested in 14 cases. A 4-fold or greater rise in the level of herpes simplex virus antibody was observed in 4 cases. In 3 of these no herpes virus was isolated. In 1 case in which the conjunctival swab was positive for herpes virus a 4-fold rise in adenovirus antibody titre was obtained.

Conjunctival impressions taken from 7 patients during the course of their disease showed a mixed population of inflammatory cells in which polymorphonuclear cells and monocytes were evenly distributed. No multinucleated epithelial cells were observed in these impressions.

TREATMENT

With a preliminary diagnosis of an adenovirus infection all patients were initially treated with eye drops or eye ointment of chloramphenicol, genta-

Fig. 6 *Follicular reaction in upper tarsal conjunctiva in the second week of acute herpetic follicular conjunctivitis*

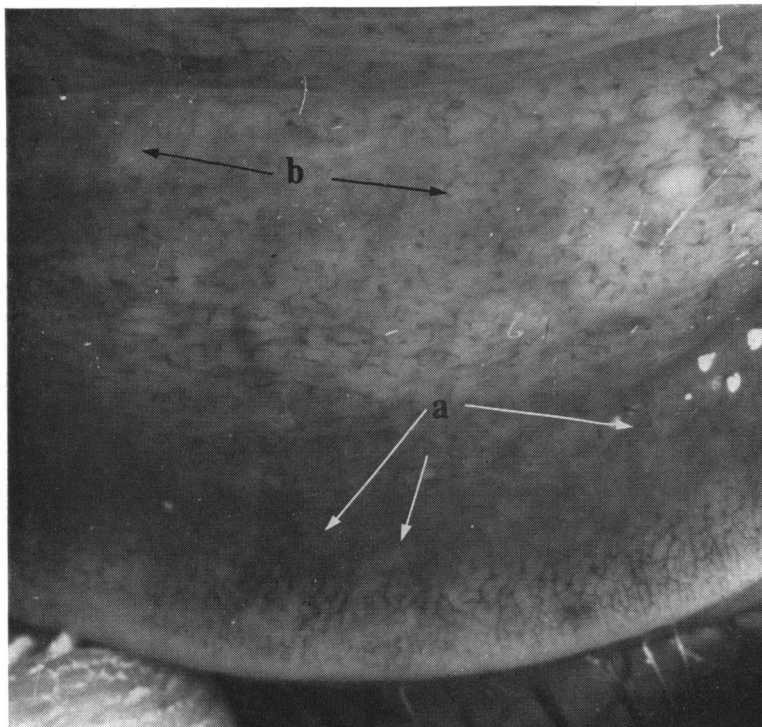
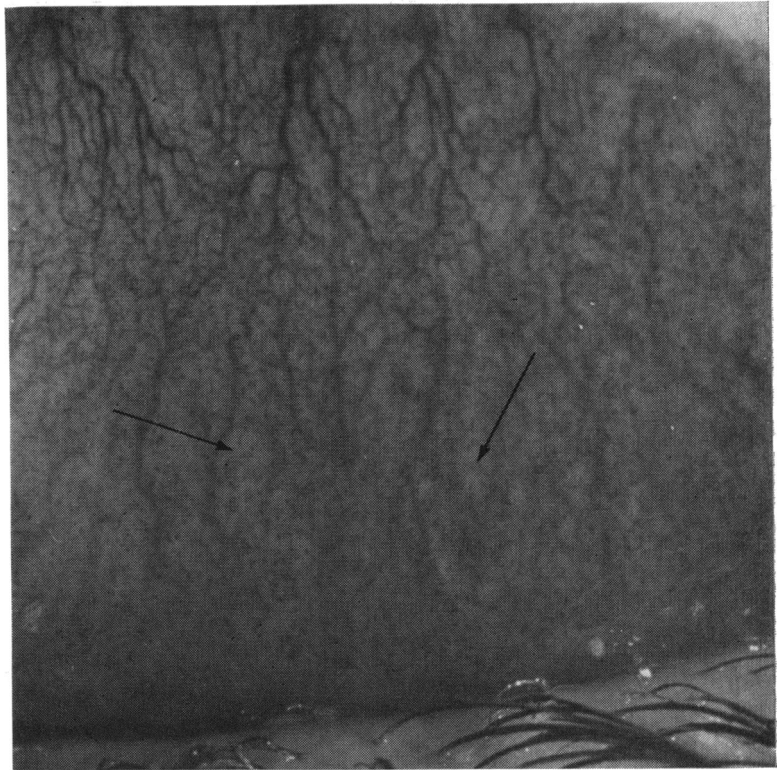


Fig. 7 *Follicular reaction in (a) tarsal and (b) fornix area of the lower lid conjunctiva in the second week of acute herpetic follicular conjunctivitis*

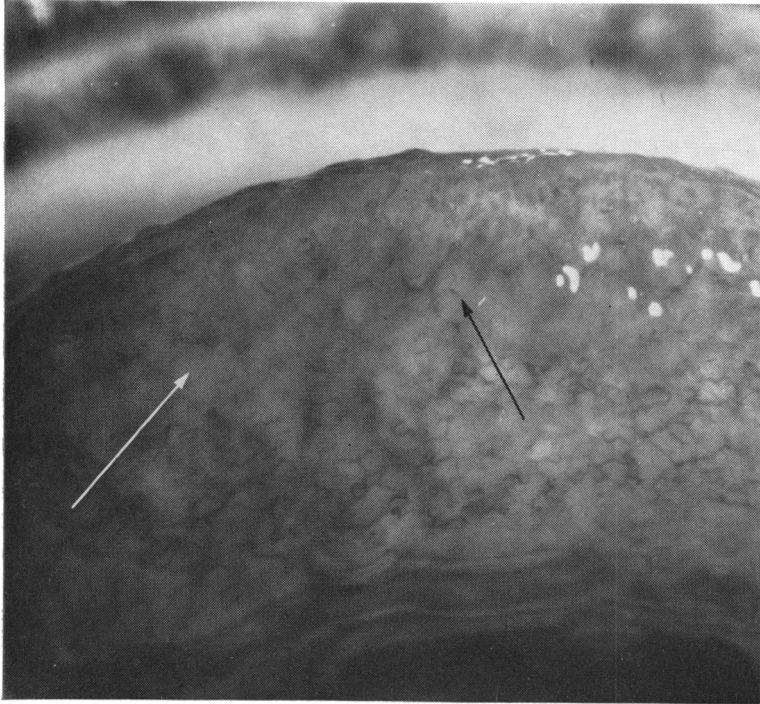


Fig. 8 Follicular reaction in upper fornix conjunctiva in the second week of acute herpetic follicular conjunctivitis

micin, or neomycin to prevent bacterial infection. In 12 patients with mild to moderate follicular conjunctivitis treatment with antibiotics was continued. The symptoms and signs in these patients disappeared in 2 to 4 weeks.

In 6 patients who subsequently developed lid lesions or corneal ulcer suggestive of herpetic infection the treatment was changed to idoxuridine eye ointment 5 times daily.

In the other 7 patients with moderate to severe keratoconjunctivitis who had not benefited from the antibiotics the treatment was changed to a 7-day course of trifluorothymidine 1% eye drops (TFT) hourly for the first day, 2-hourly for the second day, and 5 times daily for the next 5 days. In this group the symptoms declined in 2 to 3 days and had completely disappeared in 4 to 5 days. The duration of keratoconjunctivitis in this group was 3 to 4 weeks.

Discussion

Primary herpes simplex ocular infection is a common entity and may constitute one-quarter of all cases of acute follicular conjunctivitis attending ophthalmic outpatient clinics (Jones, 1959) when other causes are not epidemic. The infection occurs predominantly in early life and is generally associated with herpetic lesions on the face, lids, or the cornea.

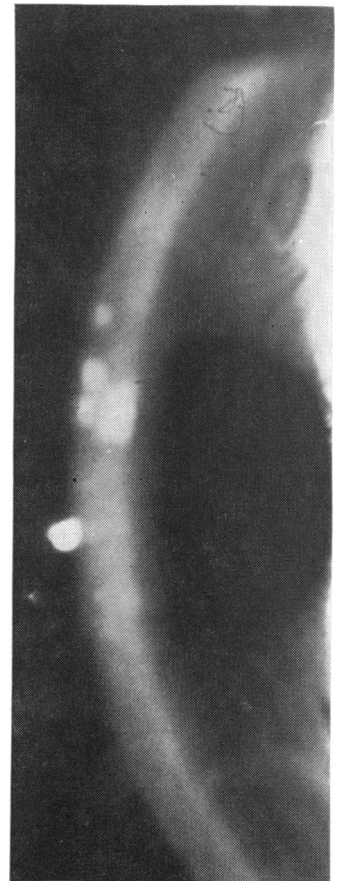


Fig. 9 Macro-photograph ($\times 20$) of coarse sub-epithelial punctate corneal opacities in the broad slit-lamp beam

Herpes simplex virus has occasionally been isolated from cases of acute follicular conjunctivitis with punctate keratitis resembling adenovirus keratoconjunctivitis. Maumenee *et al.* (1945) reported isolation of herpes simplex virus from a patient with bilateral keratoconjunctivitis with no evidence of dendritic ulcers or facial herpetic lesions. Jawetz *et al.* (1955) isolated herpes simplex virus in 2 patients with acute keratoconjunctivitis. Both these patients, however, were also shown to have a rising titre against adenovirus type 8. Jones (1962) found 3 cases of primary herpetic conjunctivitis without lid disease. More recently Knopf and Hierholzer (1975) found evidence of herpes simplex infection in 2 cases which were initially diagnosed as epidemic keratoconjunctivitis. In 1 of these there was serological evidence of concurrent infection with adenovirus type 7.

Concomitant ocular infections with adenovirus and herpes virus may suggest that adenovirus infection may reactivate the latent herpes virus (Nesburn *et al.*, 1967) or chronic infection with low-grade multiplication of herpes virus (Kauffman *et al.*, 1968). However, in the present series of patients the cultural and serological tests for the diagnosis of adenovirus infection were all negative except in 1 patient, indicating that in 24 out of 25 patients the herpes simplex virus was responsible for the ocular disease.

The clinical and epidemiological features of acute herpetic conjunctivitis—moderate to severe papillary and follicular reactions with epithelial and sub-epithelial punctate keratitis but with little systemic disease—are, in the absence of typical facial and corneal lesions of herpes virus, closely similar to adenovirus infections, including types 8 and 19 keratoconjunctivitis (Jones, 1962; Darougar *et al.*, 1977a). It is therefore important in cases of acute follicular conjunctivitis to consider herpes simplex virus as a possible cause of the disease and to determine the diagnosis with laboratory tests. This is especially important if corticosteroids are at risk of being administered.

In this study HEP2 cells were used for isolation of herpes virus and adenovirus. Studies by McSwiggan *et al.* (1975) have shown that the sensitivity of this cell line is similar to that of HEK cells for the isolation of herpes virus and adenovirus from the eye, though the development of CPE is markedly slower in HEP2 cells. The high isolation rate of 88% obtained in specimens collected during the first week of infection in the present series indicates the importance of early collection of specimens for the diagnosis of ocular herpetic infection.

In contrast to adenovirus, herpes simplex virus

is sensitive to various antiviral compounds, including idoxuridine, trifluorothymidine, and adenine arabinoside. It is therefore essential for correct management of this infection to establish an early virological diagnosis to provide a rational approach to therapy.

The authors are indebted to their colleagues at Moorfields Eye Hospital for referring the patients and to the Audio-Visual Department of the Institute of Ophthalmology for help in preparation of photographs.

This work was supported by a Locally Organised Clinical Research Grant, Moorfields Eye Hospital, City Road, London EC1V 2PD.

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