

## **A large outbreak of keratoconjunctivitis due to adenovirus type 8**

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### SUMMARY

A large nosocomial outbreak of keratoconjunctivitis due to adenovirus type 8 is described. Two hundred cases were identified, 123 by isolation of the virus and 77 by detecting HI antibodies in convalescent sera. Infection usually presented as a severe keratoconjunctivitis, and 107 (54%) of infected patients developed sub-epithelial corneal opacities. The majority (66%) of infections were acquired at the accident and emergency department attached to a large urban eye hospital when patients attended for other reasons; trauma to the eye, especially corneal foreign bodies, was the most frequent cause for the initial attendance. Transmission of virus within the family occurred in 13% of cases, but there was little spread outside family or hospital environments. The outbreak lasted from May to September, 1982, but it was not confirmed by isolation of the virus until the end of June when control measures were instituted. Delay in applying control measures was probably the major factor accounting for this large, prolonged outbreak of epidemic keratoconjunctivitis.

### INTRODUCTION

Infection of the external eye with adenovirus type 8 (AV 8) causes a severe, usually bilateral, keratoconjunctivitis which often leaves residual corneal opacities. These opacities take months or occasionally years to resolve (Dawson *et al.* 1970), so prolonged blurring of vision may occur. Outbreaks of AV 8 keratoconjunctivitis are particularly liable to occur when the virus is unwittingly introduced into busy eye hospital clinics, since these environments provide maximum opportunities for transmission of virus to a susceptible population, unless hygienic working practices are scrupulously maintained.

This report describes a particularly large epidemic of 200 virologically proven cases that occurred in association with a busy urban eye hospital, which, once it was recognised, took three months to bring under control.

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## SUBJECTS AND METHODS

*Study group*

This consisted of all patients who presented with follicular conjunctivitis at the Accident and Emergency (A and E) Department of the Manchester Royal Eye Hospital (MREH) between 1st May and 30th September, 1982, on whom virological investigations were carried out.

*Clinical and epidemiological data*

This information was obtained by retrospective examination of each patient's notes. Patients, who were all subjected to slit lamp examination, were graded according to clinical severity as follows: grade 1, patients with follicular conjunctivitis but no corneal involvement; grade 2, patients with superficial corneal changes (punctate epithelial erosions) in addition to follicular conjunctivitis, and grade 3, patients with keratoconjunctivitis who developed the sub-epithelial corneal opacities which are particularly associated with AV 8 and its allied serotypes (types 10 and 19) (Tullo, 1980).

Epidemiologically patients were divided into four categories: those in whom AV 8 infection was either epidemiologically likely (category 1), possible (category 2), or unlikely (category 3), or those in whom this information was not available (category 4). Category 1 consisted of patients who had either themselves attended the A and E department at the MREH within one month of onset of follicular conjunctivitis (hospital-acquired infection) or who had been in close contact (domestic or social) with a person who had recently attended the MREH with conjunctivitis. Category 2 consisted of patients who had been in contact with another person or people said to have conjunctivitis, but in whom there was no definite history of attendance at the MREH. Category 3 consisted of patients who had not attended the MREH before onset of conjunctivitis, and who denied any contact with another conjunctivitis sufferer.

*Virological investigations*

Virus isolation from conjunctival swabs was attempted in human embryo fibroblasts, HEp 2, Vero and monkey kidney cells. Human embryo kidney (HEK) cells, which are recognised as the most sensitive cells for isolation of AV 8 (Bell, Martin & Ross, 1969), were not routinely available throughout the study, but were used retrospectively to attempt isolation of virus from 62 conjunctival swabs which had not yielded virus in the routine cell lines, but which were obtained from patients in whom AV 8 infection was likely on epidemiological grounds. Adenovirus isolates were identified with neutralising antisera kindly supplied by Dr P. Gardner, Division of Microbiological Reagents and Quality Control, Central Public Health Laboratory, Colindale, London.

Paired (acute and convalescent) sera, or single convalescent sera (obtained 14 days or more after onset of symptoms) were tested for AV 8-specific haemagglutination-inhibiting (HI) antibodies (Bell *et al.* 1969). Antigen was grown in HEp 2 cells inoculated with an AV 8 isolate obtained from one of the patients identified early in the outbreak, and stored at  $-20^{\circ}\text{C}$ . On the day of the test it was held at  $60^{\circ}\text{C}$  for one min to reduce infectivity, titrated and used at a concentration of four haemagglutinating units.

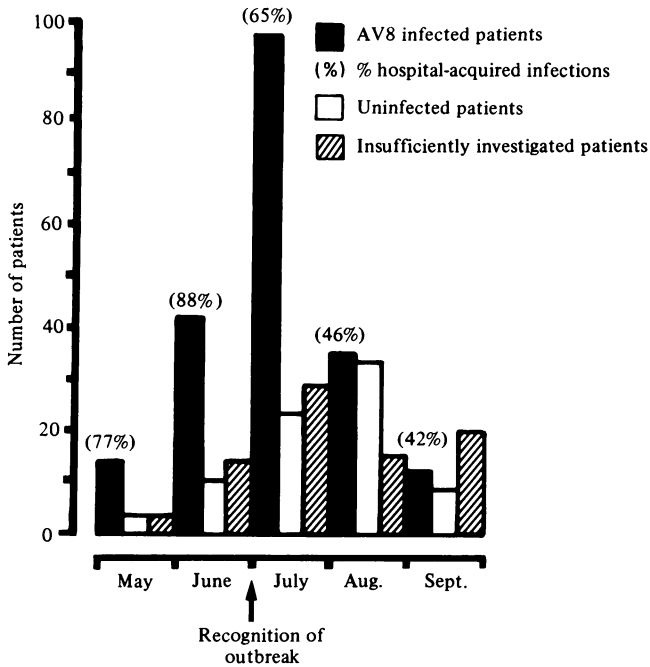


Fig 1. Temporal analysis of the adenovirus type 8 (AV 8) outbreak, May – September, 1982.

## RESULTS

### *The outbreak*

This lasted for five months, from May to September (fig. 1), but it was only recognised at the end of June, when adenovirus isolates recovered from conjunctival swabs obtained from several patients in late May were identified as AV 8. These identifications coincided with a sharp increase in the number of patients attending the MREH with keratoconjunctivitis. It is probable that the outbreak actually started before May, since the first identified infection (diagnosed retrospectively) occurred in a patient whose initial attendance at the MREH was on April 29, and who re-attended with keratoconjunctivitis on May 5th. It was, however, impossible to identify the patient who first introduced the virus into the hospital, probably because at that stage not all patients who attended the MREH with keratoconjunctivitis were being investigated virologically. The number of identified infections in this outbreak is undoubtedly an underestimate of the actual number of cases that occurred.

Despite the fact that control measures were adopted once the outbreak was recognised, the number of identified infections rose dramatically in July to 98. The increase in the number of patients who were either not infected or insufficiently investigated rose also at the same time, reflecting the more thorough virological investigations which were undertaken on all patients with possible viral conjunctivitis once the outbreak was recognised. Up to the end of June at least 80% of the AV 8 infections were hospital-acquired; from then on, the proportion of hospital-acquired infections fell. The last patient with definite infection presented on September 20th.

*Virological findings*

AV 8 was isolated from 123 patients. Of these, 93 isolates were obtained in one or more of the four routine cell lines, and 30 were recovered in HEK cells only. Serological data was obtained on 71 of these isolation-positive patients; 45 of 53 (85%) seroconverted or showed a significant ( $\geq 4$ -fold) increase in HI antibody, and 16 of 18 patients (89%), from whom a convalescent serum only was available, had an HAI antibody titre of  $\geq 8$ . Convalescent titres ranged from 8 to  $\geq 256$ . On the basis of these findings, a patient was regarded as definitely infected if AV 8 was recovered from the conjunctiva and/or if the patient seroconverted to a titre of 8 or more or showed a significant rise of HI antibodies; 153 such definite infections were identified. Isolation-negative patients or those from whom no conjunctival swabs were obtained, but who had a single convalescent serum titre  $\geq 8$  were defined as probably infected and 47 such patients were recognised. Definitely and probably infected patients together are subsequently referred to as infected patients.

Seventy-five patients were defined as serologically negative; 74 of these had no antibodies (titre  $< 8$ ) in their convalescent sera, and one (1.3%) had a low level of antibody in the acute serum (titre of 8), which was the same in the convalescent serum, and which presumably indicated previous AV 8 infection. These patients, and the four patients in whom other virus or chlamydial infections were identified (viz two herpes simplex virus infections, one adenovirus type 3 and one chlamydial infection) were defined as not infected with AV 8. Isolation-negative patients from whom convalescent sera were not obtained were defined as insufficiently investigated. Classified in this way, 153 definite and 47 probable AV 8 infections were identified during the course of this outbreak, 79 patients were not infected and 80 were insufficiently investigated.

*Clinical findings*

Clinical findings related to the microbiological diagnosis are shown in Table 1. Definite or probable AV 8 infection was associated with keratoconjunctivitis in 184 (92%) of infected patients, and residual subepithelial opacities were seen in 107 (54%). In contrast, 39 (49%) of the 79 uninfected patients had corneal involvement, and only 14 (18%) of these had residual corneal opacities ( $P < 0.001$ ).

*Epidemiological findings*

In those patients where information was available, AV 8 infection was epidemiologically likely in 161 of 186 (87%) of infected patients, compared with only 13 of 57 (24%) of uninfected patients (Table 2;  $P < 0.001$ ). Transmission of virus occurred most frequently in the MREH, since 132 of 161 (82%) of the epidemiologically likely, AV 8 infections were hospital-acquired (Table 3). The mean incubation period of the hospital-acquired infections was 10 days (range 4–18 days). Outside the hospital, spread within the family and to other close contacts also occurred, but there was little evidence of spread of the community at large.

In the 132 patients with hospital-acquired AV 8 infections initial attendance at the MREH was most frequently for removal of foreign body (46 patients) or because of other trauma to the eye (30 patients). Although inadequately sterilised

Table 1. *Microbiological diagnosis in 359 patients with follicular conjunctivitis related to clinical findings*

Microbiological diagnosis	Total patients	Clinical grade*		
		1	2	3
Definite AV 8†	153	13	65	75
Probable AV 8	47	3	12	32
Not infected with AV 8	79	40	25	14
Insufficiently investigated	80	42	31	7

\* See 'Subjects and Methods' for definition of clinical grades.

† Adenovirus type 8.

Table 2. *Microbiological diagnosis in 359 patients with follicular conjunctivitis related to epidemiological findings*

Microbiological diagnosis	Total patients	Epidemiological category*			
		Likely	Possible	Unlikely	Not known
Definite AV 8†	153	125	11	6	11
Probable AV 8	47	36	6	2	3
Not infected with AV 8	79	13	9	35	22
Insufficiently investigated	80	21	5	17	37

\* See 'Subjects and Methods' for definition of these categories.

† Adenovirus type 8.

Table 3. *Probable source of infection in patients likely on epidemiological grounds\* to have adenovirus type 8 (AV 8) infection*

Microbiological diagnosis	Total patients	Source of infection		
		Hospital	Family	Other
Definite AV 8	125	102	21	2
Probable AV 8	36	30	5	1

\* See 'Subjects and Methods' for definition of this category.

tonometer prisms have been identified in the past as major vehicles of infection in iatrogenic outbreak of keratoconjunctivitis (Wegman, Guinee & Millian, 1970; Barnard *et al.* 1973), there was little evidence in this outbreak that the virus was spread in this way, since only seven infected patients had tonometry within the range of the incubation period, before the onset of their symptoms. The most likely mode of transmission of virus in this outbreak was via the examining doctors' fingers.

#### DISCUSSION

The clinical, microbiological and epidemiological information obtained during this outbreak confirmed much of what is already known about AV 8 infection (Jawetz, 1959; Dawson & Darrell, 1963; Barnard *et al.* 1973; Sprague *et al.* 1973;

Tullo, 1980; Di Angelo *et al.* 1981). Clinically, the majority of infected patients presented with a severe keratoconjunctivitis with associated pre-auricular lymphadenopathy. However, since other agents may cause a similar clinical picture, it is impossible, particularly during the early stages of infection, to distinguish AV 8 infection from other causes of keratoconjunctivitis on purely clinical grounds. Virological studies are needed to establish the diagnosis definitively, but this diagnosis is retrospective.

The major questions raised by this outbreak are why it was so large and why it took so long to control. Probably the single most important factor was the late recognition of the outbreak; by the time the virus was first identified, the outbreak had been underway for at least two months. By then, three senior house officers (not included in the present analysis) who worked regularly in the department had become infected, and a large number of patients who had visited the A and E department in June were already incubating the infection. Thus although control measures were instituted promptly in July, large numbers of infected patients had already been generated. They, and their domestic contacts who subsequently became infected, then attended the MREH in July and August. This considerably increased the workload of an already busy clinic, and made immediate containment difficult. Nevertheless, once the outbreak was recognised, the proportion of hospital-acquired infections started to decline.

Control measures relied on minimising all possible opportunities for further iatrogenic spread of virus by already well-defined procedures (Editorial, 1983), of which thorough hand-washing after examination of each patient (Hendley, 1973), segregation of infected patients from other patients attending the A and E department (Barnard *et al.* 1973) and restriction of follow-up examinations during the acute stage of the infection were probably the most important. Awareness by the staff involved of the existence of an outbreak by itself plays an important part in control (Barnard *et al.* 1973), and it must be appreciated that the most likely way in which virus is transferred from patient to patient is by the examining doctors' fingers (Dawson *et al.* 1970). Members of staff who become infected are particularly liable to spread infection, and it is most important that they should remain away from work for at least two weeks.

Prevention of such outbreaks depends on maintenance of strict hygienic working practices at all times. This is not easy in exceedingly busy clinics manned by rotating junior medical staff, who probably have no previous experience of this particular virus infection. AV 8 is usually much less frequently encountered in eye hospitals in the UK than the endemic, community-spread adenoviruses which cause eye disease. Sporadic, imported AV 8 infections are seen in patient who acquire infection in other parts of the world where the virus is endemic, but epidemic AV 8 keratoconjunctivitis is only likely to occur if the virus is allowed to spread within an eye hospital. If hospital transmission does occur, prompt recognition of this is essential to limit further spread, and all staff must be alerted to the significance of keratoconjunctivitis in a patient who has previously attended the hospital with an unrelated complaint.

Virological investigations are essential both for accurate diagnosis in individual patients, and for epidemiological monitoring of adenovirus infections encountered in ophthalmology, but because diagnosis is retrospective, they have little role in

prevention, and are no substitute for adequate precautions to prevent virus transmission within eye hospital clinics before the diagnosis is established.

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