

Association Between Initial Corneal Involvement and Duration of Visual Symptoms in Clinically Diagnosed Adenoviral Keratoconjunctivitis

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Abstract

Background: Adenoviral keratoconjunctivitis is a common contagious ocular infection in which corneal involvement may result in persistent subepithelial infiltrates and prolonged visual disturbances. Early identification of patients at risk of delayed visual recovery may facilitate appropriate counselling and follow-up. The aim is to evaluate the association between initial corneal involvement and duration of visual symptoms in clinically diagnosed adenoviral keratoconjunctivitis. **Material and Methods:** This prospective observational study included 130 patients with clinically diagnosed adenoviral keratoconjunctivitis. Patients were categorized according to the presence or absence of corneal involvement at initial presentation. Clinical findings, visual acuity, corneal manifestations, duration of visual symptoms, and subsequent subepithelial infiltrates were assessed during follow-up. A p-value <0.05 was considered statistically significant. **Results:** Initial corneal involvement was observed in 72 (55.4%) patients. The mean duration of visual symptoms was significantly longer in patients with corneal involvement than in those without involvement (32.6 ± 14.8 vs 17.4 ± 9.2 days; $p < 0.001$). Visual symptoms persisted beyond 4 weeks in 52.8% versus 15.5% of patients, respectively ($p < 0.001$). Subepithelial infiltrates during follow-up were more frequent in patients with initial corneal involvement (58.3% vs 17.2%; $p < 0.001$). Initial corneal involvement was independently associated with prolonged visual symptoms (adjusted OR 4.62; 95% CI: 1.94–11.02; $p < 0.001$). **Conclusion:** Initial corneal involvement was significantly associated with prolonged visual symptoms and persistent corneal abnormalities in adenoviral keratoconjunctivitis. Assessment of corneal involvement at presentation may help identify patients at increased risk of delayed visual recovery.

Keywords: Adenoviral keratoconjunctivitis; Corneal involvement; Visual symptoms; Subepithelial infiltrates; Visual acuity; Adenoviral conjunctivitis; Visual recovery.

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INTRODUCTION

Adenoviral keratoconjunctivitis is a highly contagious ocular infection characterized by acute conjunctival inflammation with variable corneal involvement. Although conjunctival symptoms are usually self-limiting, corneal disease may persist beyond the acute phase and result in photophobia, blurred vision, glare, and prolonged visual disturbance. Recent evidence continues to emphasize the clinical burden of adenoviral conjunctivitis and the challenges associated with preventing persistent corneal sequelae.^[1]

Viral replication and the associated host inflammatory response influence the severity and duration of adenoviral ocular disease. Studies evaluating viral load and its reduction during treatment have demonstrated that persistent viral activity may contribute to the clinical course of infection.^[2] Clinical manifestations may also vary according to the circulating adenovirus type, with certain strains showing a greater tendency to produce severe keratoconjunctivitis and corneal involvement.^[3]

Despite various therapeutic approaches, including topical antiseptic and anti-inflammatory agents, there remains no universally accepted treatment that reliably prevents corneal complications or shortens the duration of visual symptoms.^[4]

Epidemic keratoconjunctivitis can cause considerable morbidity and is also important because of its potential for rapid transmission and outbreaks in healthcare and community settings.^[5] Changes in population behavior and infection-control measures during the COVID-19 pandemic further demonstrated the influence of transmission patterns on the occurrence of epidemic keratoconjunctivitis.^[6]

Corneal involvement is particularly important because epithelial keratitis and subsequent subepithelial infiltrates may produce persistent visual symptoms even after conjunctival inflammation has resolved. Management remains challenging, especially when corneal infiltrates persist or recur.^[7] Identifying early clinical characteristics associated with prolonged visual morbidity may therefore help in patient counselling, follow-up planning, and

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recognition of patients at greater risk of persistent symptoms. The present study was undertaken to determine the association between initial corneal involvement and duration of visual symptoms in patients with clinically diagnosed adenoviral keratoconjunctivitis.

MATERIALS AND METHODS

Study Design and Setting: This prospective observational study was conducted in the Department of Ophthalmology at a tertiary care teaching hospital. Patients presenting with clinical features suggestive of adenoviral keratoconjunctivitis were consecutively screened for eligibility.

Study Population and Sample Size: A total of 130 patients with clinically diagnosed adenoviral keratoconjunctivitis were included in the study. The sample size was calculated considering a moderate expected difference in the duration of visual symptoms between patients with and without initial corneal involvement, with a 95% confidence level and 80% statistical power.

For analysis, patients were categorized according to the presence of corneal involvement at their initial examination:

Group I: Patients with initial corneal involvement.

Group II: Patients without initial corneal involvement.

The actual number of patients in each group was determined according to their clinical findings rather than by predetermined equal allocation.

Inclusion Criteria: Patients aged 18 years or older presenting with clinically diagnosed acute adenoviral keratoconjunctivitis and willing to comply with scheduled follow-up were included. Clinical diagnosis was based on a compatible history and examination findings such as acute follicular conjunctivitis, conjunctival congestion, watery discharge, lid edema, preauricular lymphadenopathy, and/or characteristic corneal involvement.

Exclusion Criteria: Patients with suspected bacterial, fungal, herpetic, or allergic conjunctivitis; pre-existing corneal opacity or dystrophy affecting vision; previous ocular surgery likely to influence corneal findings; active uveitis; glaucoma; significant retinal or optic nerve disease; contact-lens-related keratitis; or inability to complete follow-up were excluded.

Clinical Evaluation: At initial presentation, a detailed history was obtained regarding age, sex, duration of illness before presentation, unilateral or bilateral involvement, exposure to individuals with conjunctivitis, previous treatment, and systemic symptoms.

All patients underwent a comprehensive ophthalmic examination including:

- Best-corrected visual acuity (BCVA)
- Slit-lamp examination
- Conjunctival congestion and follicular reaction
- Presence of pseudomembrane or membrane
- Corneal epithelial involvement
- Presence of punctate epithelial keratitis
- Subepithelial infiltrates
- Anterior chamber examination

Both eyes were examined; however, for patient-level

statistical analysis, the more severely affected eye at initial presentation was designated as the study eye according to a predefined clinical severity hierarchy.

Assessment of Initial Corneal Involvement: Corneal involvement at presentation was assessed using slit-lamp biomicroscopy. Initial corneal involvement was considered present when one or more findings attributable to adenoviral infection were identified, including superficial punctate epithelial keratitis, focal epithelial lesions, epithelial defects, or subepithelial infiltrates.

Patients without detectable corneal abnormalities at initial examination were categorized as having no initial corneal involvement.

Assessment of Visual Symptoms: Visual symptoms including blurred vision, photophobia, glare, halos, and difficulty performing routine visual activities were documented at baseline and at each follow-up visit.

The primary outcome was the duration of visual symptoms, defined as the number of days from the onset of visual disturbance until complete patient-reported resolution of visual symptoms, supported by clinical assessment at follow-up.

For additional analysis, prolonged visual symptoms could be defined as symptoms persisting for more than 4 weeks after onset.

Follow-up

Patients were followed at approximately 1 week, 2 weeks, 4 weeks, 6 weeks, and 8 weeks, with further follow-up when visual symptoms or corneal infiltrates persisted. At each visit, visual acuity, conjunctival inflammation, epithelial keratitis, subepithelial infiltrates, and persistence or resolution of visual symptoms were recorded.

Patients whose symptoms resolved between two scheduled visits were asked to report the approximate date of complete resolution to estimate symptom duration.

Treatment

Patients received supportive treatment according to clinical severity, including lubricating eye drops and cold compresses. Additional treatment was prescribed when clinically indicated. Patients were counselled regarding hand hygiene, avoidance of eye rubbing and sharing of towels or personal items, and measures to reduce transmission.

Treatment received during follow-up, particularly topical corticosteroid or other anti-inflammatory therapy, was documented because of its potential influence on the persistence of corneal findings and visual symptoms.

Outcome Measures

The primary outcome measure was the duration of visual symptoms in patients with and without initial corneal involvement.

Secondary outcomes included the frequency of subepithelial infiltrates, change in visual acuity, persistence of corneal findings, proportion of patients with symptoms lasting more than 4 weeks, and clinical factors associated with prolonged visual symptoms.

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using SPSS software. Continuous variables were expressed as mean $\pm$ standard deviation or median with interquartile range according to data distribution, while categorical variables were expressed as frequency and

percentage. The independent Student's t-test or Mann–Whitney U test was used to compare the duration of visual symptoms between groups. Categorical variables were compared using the Chi-square test or Fisher's exact test. Pearson or Spearman correlation was used where appropriate. Multivariable regression analysis was performed to identify independent predictors of prolonged visual symptoms while adjusting for potential confounding factors such as age, baseline visual acuity, disease severity, bilateral involvement, and treatment received. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 130 patients with clinically diagnosed adenoviral keratoconjunctivitis were included. Initial corneal involvement was observed in 72 (55.4%) patients, while 58 (44.6%) had no corneal involvement at presentation. Patients with initial corneal involvement experienced a significantly longer duration of visual symptoms and had a higher frequency of persistent symptoms beyond 4 weeks.

Table 1: Baseline demographic and clinical characteristics

Characteristic	Corneal involvement (n=72)	No corneal involvement (n=58)	p-value
Age (years), mean $\pm$ SD	35.8 $\pm$ 11.7	34.2 $\pm$ 10.9	0.425
Male	41 (56.9%)	31 (53.4%)	0.691
Female	31 (43.1%)	27 (46.6%)	
Bilateral involvement	48 (66.7%)	31 (53.4%)	0.124
Preauricular lymphadenopathy	43 (59.7%)	29 (50.0%)	0.269
Pseudomembrane/membrane	18 (25.0%)	7 (12.1%)	0.063
Baseline BCVA $\leq$ 6/12	25 (34.7%)	8 (13.8%)	0.007
Symptoms before presentation (days), mean $\pm$ SD	4.9 $\pm$ 2.3	4.5 $\pm$ 2.1	0.307

The two groups were comparable in age, sex, bilateral involvement, lymphadenopathy, and duration of symptoms before presentation. Reduced baseline visual acuity was

significantly more frequent among patients with initial corneal involvement (34.7% vs 13.8%; p=0.007).

Table 2: Pattern of initial corneal involvement among affected patients (n=72)

Corneal finding	Number	Percentage
Superficial punctate epithelial keratitis	49	68.1%
Focal epithelial lesions	31	43.1%
Subepithelial infiltrates	24	33.3%
Epithelial defect	8	11.1%
More than one corneal finding	29	40.3%

Patients could have more than one corneal finding; therefore, percentages do not total 100%.

Interpretation: Superficial punctate epithelial keratitis was the most frequent initial corneal manifestation, occurring in 68.1% of patients with corneal involvement. Subepithelial

infiltrates were present at initial examination in one-third of affected patients.

Table 3: Comparison of visual symptom duration and follow-up outcomes

Outcome	Corneal involvement (n=72)	No corneal involvement (n=58)	p-value
Duration of visual symptoms (days), mean $\pm$ SD	32.6 $\pm$ 14.8	17.4 $\pm$ 9.2	<0.001
Symptoms >2 weeks	59 (81.9%)	31 (53.4%)	<0.001
Symptoms >4 weeks	38 (52.8%)	9 (15.5%)	<0.001
Subepithelial infiltrates during follow-up	42 (58.3%)	10 (17.2%)	<0.001
Persistent corneal findings at 6 weeks	24 (33.3%)	5 (8.6%)	0.001
BCVA $\leq$ 6/12 at 4 weeks	12 (16.7%)	2 (3.4%)	0.016
Complete symptom resolution by 8 weeks	65 (90.3%)	57 (98.3%)	0.061

Patients with initial corneal involvement had a significantly longer mean duration of visual symptoms (32.6 vs 17.4 days; p<0.001). More than half (52.8%) experienced symptoms persisting beyond 4 weeks compared with only 15.5% of

those without initial corneal involvement. Subsequent subepithelial infiltrates and persistent corneal abnormalities were also significantly more frequent in this group.

Table 4: Factors associated with prolonged visual symptoms (>4 weeks)

Variable	Prolonged symptoms n/N (%)	Adjusted OR (95% CI)	p-value
Initial corneal involvement	38/72 (52.8%)	4.62 (1.94–11.02)	<0.001
Baseline BCVA $\leq$ 6/12	19/33 (57.6%)	2.31 (1.01–5.29)	0.047
Bilateral involvement	34/79 (43.0%)	1.48 (0.67–3.28)	0.332
Pseudomembrane/membrane	14/25 (56.0%)	2.18 (0.87–5.47)	0.097
Age $\geq$ 40 years	18/45 (40.0%)	1.21 (0.55–2.67)	0.634

After adjustment for potential confounding factors, initial corneal involvement was independently associated with

approximately 4.6-fold higher odds of visual symptoms persisting beyond 4 weeks (adjusted OR 4.62; 95% CI 1.94–11.02; $p < 0.001$). Reduced baseline visual acuity was also independently associated with prolonged symptoms.

DISCUSSION

Adenoviral keratoconjunctivitis is generally self-limiting; however, corneal involvement may lead to persistent visual disturbances even after resolution of the acute conjunctival inflammation. In the present study, initial corneal involvement was observed in 55.4% of patients and was significantly associated with a longer duration of visual symptoms.

Patients with initial corneal involvement had a mean symptom duration of 32.6 ± 14.8 days compared with 17.4 ± 9.2 days among those without corneal involvement ($p < 0.001$). Jonas et al,^[8] described corneal involvement as an important component of epidemic keratoconjunctivitis, with immune-mediated corneal changes potentially persisting after active viral replication has subsided. Gonzalez et al,^[9] similarly emphasized that epidemic keratoconjunctivitis caused by different adenoviral types may produce prolonged corneal disease and visual morbidity.

In the present study, 52.8% of patients with initial corneal involvement had visual symptoms persisting for more than 4 weeks, compared with 15.5% without initial corneal involvement. Therapeutic studies by Pepose et al,^[10] and Kovalyuk et al,^[11] have highlighted the clinical importance of controlling inflammation and reducing the duration and severity of adenoviral ocular disease. Nevertheless, persistent or recurrent corneal infiltrates remain an important therapeutic challenge.

Subepithelial infiltrates developed during follow-up in 58.3% of patients with initial corneal involvement compared with 17.2% of those without it. González-López et al,^[12] described subepithelial corneal infiltrates as an important cause of prolonged photophobia, glare, blurred vision, and decreased visual acuity following adenoviral keratoconjunctivitis. Pihos,^[13] also reported that corneal infiltrates may persist for weeks to months and can considerably affect visual quality even after conjunctivitis has resolved.

Persistent corneal abnormalities at 6 weeks were significantly more frequent among patients with initial corneal involvement (33.3% vs 8.6%). This finding is consistent with the clinical course described by Meyer-Rüsenberg et al,^[14] who noted that corneal involvement in epidemic keratoconjunctivitis can persist considerably longer than the acute conjunctival manifestations. Butt and Chodosh,^[15] likewise demonstrated that adenoviral keratoconjunctivitis may have a prolonged course in a subset of patients.

On multivariable analysis, initial corneal involvement was the strongest independent predictor of prolonged visual symptoms, with an adjusted odds ratio of 4.62 (95% CI: 1.94–11.02; $p < 0.001$). Reduced baseline visual acuity was also independently associated with prolonged symptoms. These findings suggest that careful corneal examination at

the first presentation may provide useful prognostic information regarding subsequent visual recovery.

The study was limited by the clinical diagnosis of adenoviral infection without virological confirmation in all patients and the relatively short follow-up period. Longer follow-up would be useful for evaluating persistent or recurrent subepithelial infiltrates and their long-term effects on visual quality.

CONCLUSION

Initial corneal involvement in adenoviral keratoconjunctivitis was significantly associated with prolonged visual symptoms, persistent corneal findings, and subsequent subepithelial infiltrates. Patients with corneal involvement had approximately 4.6-fold greater odds of symptoms lasting more than 4 weeks. Careful assessment of the cornea at initial presentation may therefore help identify patients at risk of delayed visual recovery and guide appropriate counselling and follow-up.

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Conflicts of interest

There are no conflicts of interest.

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