Ocular Manifestations of Enterovirus: An Important Emerging Pathogen

Enteroviruses (EV) are members of the *Picornaviridae* family and consist of a nonenveloped positive single-stranded RNA. The EV genus contains 4 species (A−D) and 3 rhinovirus species (A−C).[1] Manifestations of EV ocular infections have been rarely described in the literature. Enterovirus-D70 has been shown to replicate in the conjunctival and corneal epithelial cells and cause conjunctivitis.[2] The purpose of our retrospective cohort study is to describe the prevalence and clinical presentation of EV polymerase chain reaction (PCR)-positive ocular infections.

Ocular viral multiplex PCR specimens collected at The Royal Victorian Eye & Ear Hospital and processed at St Vincent's Pathology, Melbourne, Australia, between April 2015 and May 2020 were examined. The multiplex tests for herpes simplex virus type 1 (HSV1), HSV type 2, varicella−zoster virus (VZV), cytomegalovirus (CMV), adenovirus, and EV were performed. Subtyping was not performed on EV-positive specimens. The Royal Victorian Eye and Ear Hospital's Human Research Ethics Committee deemed ethical approval was not required. This study adhered to the tenets of the Declaration of Helsinki.

A total of 12 289 ocular viral PCR specimens were processed during the study period. Of them, 3687 (30.0%) were positive: 1197 were HSV1 positive (9.74%), 16 were HSV type 2 positive (0.13%), 434 were VZV positive (3.53%), 45 were CMV positive (0.36%), 1914 were adenovirus positive (15.57%), and 81 were EV positive (0.66%). The 81 EV-positive samples included 52 from conjunctival samples (64.20%), 28 from corneal samples (34.50%), and 1 from an aqueous sample (1.23%). There were no positive vitreous samples. The mean patient age was 46.2 years (median 46; range 1−89 years) with a male-to-female ratio of 1.6:1.0. Similar to previous studies reporting on EV infections,[3] conjunctivitis was the most common presentation. Forty-nine patients (60.50%) presented with conjunctivitis, whereas 30 patients (37.0%) presented with corneal signs (Table 1). Two patients initially presented with conjunctival injection and lid lesions or follicles but developed anterior uveitis at their subsequent follow-up visit. Seventy-two (88.9%) patients presented with unilateral signs; 9 patients presented with bilateral disease, including 1 patient with coinfection with *Streptococcus pneumoniae*, and 1 patient who was also adenovirus PCR positive. A history of systemic symptoms was not recorded routinely in the clinical notes. It is known that systemic EV infections may be asymptomatic or present with clinical manifestations comprising fever, exanthem, headache, respiratory illness, sore throat, myocarditis, vomiting, and diarrhea.[1]

Eight eyes (9.9%) also tested positive for HSV1, HSV type 2, VZV, CMV, or adenovirus, including 1 patient who was positive for EV, CMV, and adenovirus (Table S2, available at www.ophthalmologyscience.org). Eight (9.9%) patients with keratitis also had positive bacterial growth on corneal scrapes and culture.

Excluding patients with significant preexisting visual impairment and patients with coinfection with other viruses or bacteria,

the mean best corrected visual acuity in the affected eye was 0.13 logarithm of the minimum angle of resolution (range = −0.18 to 1.18) for conjunctivitis and 0.34 (range −0.18 to 1.48) for keratitis cases. At the final follow-up visit, the best corrected visual acuity improved to 0.07 logarithm of the minimum angle of resolution (P value = 0.018, range = −0.18 to 0.18) for conjunctivitis and 0.22 (P value = 0.057, range = −0.08 to 0.18) for keratitis cases. Only 3 patients had lost >2 lines of vision.

There is no known effective treatment for EV infections. Enteroviruses are usually self-limiting although persistent infections in nonocular (pancreatic and cardiac cells) have been reported.[4] In our cohort, the ocular signs were similarly self-limiting, except for patients with concurrent HSV disease who were treated with antivirals (acyclovir ointment or oral valaciclovir) and patients with concurrent bacterial infection who were treated with topical ofloxacin as per standard clinical practice. For EV conjunctivitis and keratitis patients who attended a follow-up appointment (n = 17 and 15, respectively), the time to resolution of clinical signs was a median of 7 and 13 days. The 2 uveitis patients resolved after 8 days and 121 days.

There were 4 (4.9%) patients who had a prolonged recovery period. Each of these patients had a concurrent viral or bacterial infection. The first presented with EV and *Staphylococcus epidermidis* keratitis and recovered after 94 days. The second presented with keratouveitis and was also VZV PCR positive, and recovered over 121 days. The third patient was initially positive only for EV but a subsequent corneal scrape isolated *S. epidermidis* and they recovered over 151 days. The fourth presented with EV and HSV1 coinfection and recovered over 182 days. There were 2 patients who underwent corneal transplants for endothelial failure.

States of latent infection and episodic reactivation have been reported in the coxsackievirus subtype of EV which has been implicated in outbreaks of acute hemorrhagic conjunctivitis along with EV-D70.[5,6] In our cohort, there were only 4 (4.9%) patients who re-presented with recurrent disease. The first patient presented with EV-positive conjunctivitis. They re-presented 16 months later with recurrent viral conjunctivitis and tested positive a second time for EV. The recurrent episode was self-limiting. The second patient presented with conjunctivitis and was PCR positive for EV and HSV1. They improved after 7 days. They re-presented 4 years later with recurrent EV PCR-positive conjunctivitis. A third patient presented with keratitis and was positive for EV and HSV1, and re-presented 3 months later with keratitis although the repeat swabs were negative for both EV and HSV1. A fourth patient presented with keratitis, where a corneal swab was positive for EV and a corneal scrape positive for *S. epidermidis*. They improved over 10 days. They re-presented 8 months later with suspected bacterial keratitis that was viral and bacterial swab negative.

The human conjunctiva has been shown to have a relatively sparse bacterial or viral population in comparison to other mucosal surfaces.[7] There has been no prior study on the presence nor duration of EV shedding in the tear film. Although PCR testing is sensitive in detecting the presence of viral RNA, it does not

Table 1. Clinical Findings in Patients with Enterovirus-Associated Ocular Disease

Conjunctivitis Cases	n = 49
Pseudomembrane	4 (8.1%)
Follicles	40 (81.6%)
Conjunctival injection	48 (97.9%)
Eyelid swelling	10 (20.4%)
Eyelid lesion	4 (8.1%)
Keratitis cases	**n = 30**
Epithelial defect only	11 (36.6%)
Epithelial defect + stromal infiltrate	9 (30.0%)
Epithelial defect + corneal edema	3 (10.0%)
Epithelial defect + stromal infiltrate + corneal edema	4 (13.3%)
Stromal infiltrate only	1 (3.0%)
Corneal edema	2 (6.6%)
Uveitis cases	**n = 2**
Conjunctival injection + anterior chamber cells	2 (2.46%)

indicate active infection or prolonged infectiousness, nor equate to its ability to transmit infection, which may be influenced by numerous factors, such as virus load, exposure time, and host situations. Interpreting the difference between ongoing viral shedding of noninfectious RNA and ongoing replicating viable virus is difficult.

This study implicates EV in cases of conjunctivitis, keratitis, uveitis, and corneal endothelial failure. It is predominantly a self-limiting disease. Uncommonly, it can lead to recurrent or persistent disease.

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