Ocular complications from primary varicella infection
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Varicella-zoster virus (VZV) is one of eight herpes viruses known to cause human infection. VZV infection has two distinct forms: primary varicella infection (chickenpox) and herpes zoster (shingles). Primary varicella infection results in a diffuse vesicular rash, while herpes zoster occurs as a result of endogenous reactivation of latent VZV, which typically manifests as a unilateral dermatomal rash. Prior to the introduction of the varicella vaccine, national seroprevalence data in developed countries showed that over half of the population are infected by chickenpox by the age of three, and by the age of 15, seroprevalence is over 90%.1,2

The typical course of primary varicella infection starts off with a prodromal phase of fever, malaise, pharyngitis and loss of appetite. This is followed by the development of a generalised vesicular rash. The course can be complicated by skin infections, neurological complications, pneumonia and hepatitis.3 Ocular complications such as conjunctivitis, uveitis, ophthalmoplegia, retinal necrosis and optic neuritis have also been reported.4–7

The aim of this study was to determine the rate of ocular complications secondary to primary varicella infections at Auckland District Health Board. Secondly, we compiled a case series of severe ocular complications that required long-term treatment or have resulted in permanent vision loss.

Methods
A 10-year retrospective case series of all subjects reviewed at the Department of Ophthalmology, Auckland District Health Board with ocular complications secondary to primary varicella infection was undertaken. The inclusion criteria were a preceding chickenpox infection. The exclusion criterion was the presence of another more likely diagnosis or cases classified as herpes zoster.

The majority of cases were identified from previous discharge records, according to a clinical coding of “chickenpox”, “VZV” or “varicella”, from the period of March 2009 to March 2019. A standardised proforma was used to extract relevant data from the clinical records. Ethical approval was obtained from the Auckland District Health Board ethics approval committee.

Results
A total of 30 subjects were reviewed with complications secondary to primary VZV infection in this 10-year period. The problems were unilateral in 24 cases (80%) and bilateral in six cases (20%). The total number of eyes involved was 36. The median age at presentation was six years old (range 3–48 years old). There were 18 females (62.1%) and 11 males (37.9%). In terms of ethnicity, New Zealand Europeans were most commonly affected (60.0%), followed by Indians (16.7%), Pacific Islanders (13.3%), Māori (6.7%) and Chinese (3.3%). The median duration from onset of rash to ocular symptom onset was five days and some variation was seen according to site of ocular involvement (range 1–136 days).

The clinical presentation of subjects are listed in Table 1. The most common presentation was conjunctivitis, which was usually mild and self-limiting. There were two cases of preseptal cellulitis, which required hospital admission and treatment with antibiotics. The majority of subjects with uveitis had an uncomplicated course after being treated with topical steroids. There were seven cases that went on to develop serious complications, including one case of moderate vision loss (visual acuity ≥6/15) and two cases of severe vision loss (visual acuity ≥6/60).
Case 1
A five-year-old New Zealand European girl presented with left eye photophobia, redness and irritation one week after a chickenpox infection. On presentation, her left eye had small pseudodendrites, grade 1 anterior chamber reaction and stromal keratitis. Her left eye visual acuity was 6/7.5. She was started on a tapering course of topical steroids. She then developed chronic uveitis and raised intraocular pressures (IOP). She remained on topical steroids for two years before transitioning to systemic immunosuppression with Methotrexate. Her IOP remained poorly controlled despite being on maximal medical therapy (three classes of IOP lowering drops and oral Azetozolamide). She developed a left cataract secondary to chronic uveitis. At the age of eight, she had a left eye combined cataract and glaucoma drainage implant (Molteno tube) surgery. Her best corrected visual acuity improved from 6/38 to 6/30. Despite this treatment, she ended up developing corneal scarring and band keratopathy. Her final left visual acuity was counting fingers.

Case 2
A three-year-old Māori girl was referred from her general practitioner with a red left eye and persistent discharge. She was diagnosed with chickenpox approximately four months prior. She was initially managed as a bacterial conjunctivitis with chloramphenicol drops after a difficult examination. A repeat examination one month later revealed left disciform keratitis. She was started on long-term topical steroids and topical acyclovir, as well as a six-month course of oral acyclovir. Her Snellen visual acuity deteriorated to 6/36 and she was prescribed Atropine 1% eye drops daily to her fellow eye to manage amblyopia. She remained on the same treatment for a further three years. Over that time, she developed worsening central cornea scarring. At the age of six, she underwent a partial thickness corneal transplant (deep anterior lamellar keratoplasty). She was weaned off topical steroids a year after the operation and her last recorded Snellen visual acuity was 6/18.

Case 3
A 48-year-old Indian man presented with bilateral red and painful eyes a week after having chickenpox. His right and left visual acuity was 6/7.5 and 6/6 respectively. His intraocular pressures (IOP) were elevated at 48mmHg and 29mmHg respectively. On slit lamp examination, his right eye had pseudodendrites, mixed fine and large corneal keratic precipitates, as well as a grade 2 anterior chamber cell reaction. His

Table 1: Clinical presentation.

<table>
<thead>
<tr>
<th>Ocular involvement</th>
<th>Number of eyes</th>
<th>Onset after rash (days)</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lid lesions</td>
<td>3</td>
<td>1–2</td>
<td>Topical antibiotics</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>10</td>
<td>1–11</td>
<td>Topical antibiotics and lubricants</td>
</tr>
<tr>
<td>Conjunctival pox</td>
<td>5</td>
<td>2–10</td>
<td>Topical antibiotics and lubricants</td>
</tr>
<tr>
<td>Preseptal cellulitis</td>
<td>2</td>
<td>4–6</td>
<td>Intravenous antibiotics</td>
</tr>
<tr>
<td>Uveitis</td>
<td>12*</td>
<td>7–41</td>
<td>Topical steroids +/- oral antiviral treatment +/- topical cycloplegic agent</td>
</tr>
<tr>
<td>Keratitis</td>
<td>3*</td>
<td>8–136</td>
<td>Topical steroids and antivirals</td>
</tr>
<tr>
<td>Early cataract</td>
<td>3*</td>
<td>300+</td>
<td>Cataract extraction and intraocular lens implantation</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>1</td>
<td>26</td>
<td>Systemic steroids</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>1*</td>
<td>300+</td>
<td>Intracocular pressure lowering medication and glaucoma tube drainage surgery</td>
</tr>
<tr>
<td>Autoimmune retinopathy</td>
<td>2</td>
<td>28</td>
<td>Systemic steroids and mycophenolate mofetil</td>
</tr>
</tbody>
</table>

*Some subjects had more than one complication.
left eye had a grade 1 anterior chamber cell reaction. There were no signs of inflammation in the vitreous or retina. Gonioscopy revealed open iridocorneal angles.

He was diagnosed with bilateral hypertensive uveitis secondary to primary varicella infection and was started on hourly topical steroids and Brimonidine eye drops twice daily to both eyes. He continued to have a chronic bilateral uveitis, ocular hypertension and secondary cataracts, which required treatment with topical steroids, oral acyclovir, two pressure lowering eye drops and oral acetazolamide. He underwent bilateral cataract operations in the subsequent two years. Prior to his second operation, he developed recurrence of his right anterior uveitis, which was successfully treated with oral steroids. His final visual acuity was 6/6 in his right eye and 6/7.5 in his left eye.

Case 4
A two-year-old, normally fit and well, Samoan boy was initially admitted under the paediatric team for left eye swelling and redness six days after developing chickenpox. He was started on intravenous Augmentin and Aciclovir. He was reviewed by the acute eye service and was found to have a swollen left eyelid with surrounding cellulitis. His CT orbit scan showed preseptal collections but no extension into the orbit. His wound swabs grew Streptococcus pyogenes, which was sensitive to penicillin. After three days of medical treatment, his left eyelid remained swollen and he developed an upper eyelid abscess. He underwent an incision and drainage procedure of this abscess. Intraoperative findings included copious amounts of pus in loculations. He recovered well after that and had mild residual scarring on his left upper eyelid.

Case 5
A 16-year-old New Zealand European female presented with painful eye movements and blurred vision in her left eye one month after a chickenpox infection. Visual acuity was hand movements in the left eye and 6/6 in the fellow eye. She had a left relative afferent pupillary defect (RAPD) and optic nerve head swelling. She was treated with three daily doses of 1g intravenous methylprednisolone (IVMP) followed by a tapering course of oral steroids over one week. Bartonella and syphilis serology was negative. An MRI brain scan revealed left optic neuritis with no other foci of demyelination. Two weeks later, her visual acuity improved to 6/5 and she had trace left RAPD and mild disc swelling. Her visual field test results at this point were normal. Her final diagnosis was a post-infectious optic neuritis.

Case 6
A 28-year-old Indian man initially presented to his optometrist after noticing left blurry vision following a chickenpox infection. His vision was 6/6 in both eyes and there were no signs of ocular inflammation on slit lamp examination. Three months later, he presented to the eye clinic after suddenly noticing poor vision in his left eye. His visual acuity was 6/6 on the right eye and hand movements in his left eye. On examination, he had occasional vitreous cells and atypical macular appearances in both eyes. Further tests including fundus autofluorescence, optical coherence tomography and electrophysiology suggested outer retinal inflammation that tracked along the retinal blood vessels. This led to outer retinal thinning and retinal dysfunction, especially in the left eye. Retinal auto-antibodies tests, Quantiferon gold, whole body CT scan and MRI brain scan results came back normal. He was diagnosed with autoimmune retinopathy and started on a course of oral prednisone and Mycophenolate Mofetil, which managed to slow the progression of visual field loss on his right eye. He had further right eye visual field loss a year later, after failing to attend appointments and stopping his medication. Fortunately, his clinical course stabilised after restarting treatment and he maintained a visual acuity of 6/6 in his right eye and count fingers in his left eye.

Case 7
An eight-year-old Cook Island Māori girl presented with two days of an itchy, red left eye as well as a dilated left pupil a week after a chickenpox infection. On examination, she had a mildly injected left conjunctiva, grade 2 anterior chamber cells and an irregular, dilated left pupil. She was diagnosed with a left acute anterior uveitis, and was started on topical steroid eye drops four times daily and oral acyclovir 800mg four times daily. On follow-up appointments a week and one month later, her anterior
chamber reaction improved, but her left pupil remained dilated. Her final left visual acuity was 6/12. Unfortunately, she failed to attend further follow up appointments.

Discussion

Ocular complications from primary varicella infection are rare. According to a 2013 census, the acute eye clinic at Greenlane Clinical Centre caters for an Auckland population of 1,400,000, with 21% being under the age of 15. The total number of chickenpox cases over 10 years would be 407,000 after applying the seroprevalence rate of 83% for those aged 10–14 from an Australian study. We collected 30 patients with ocular complications from primary varicella over 30 years. Furthermore, 15 out of 30 referred patients only had conjunctivitis or lid lesions, which would have settled with observation. Based on these figures, there is an estimated 1 in 27,000 cases of primary varicella that would require active treatment for ocular complications. A similar study carried out at a paediatric ophthalmology clinic in Canada showed that out of the 24 children referred for review, only six subjects required topical steroid treatment for uveitis and one required oral antibiotics for a secondary bacterial skin infection.

In our case series, two young subjects developed chronic disciform keratitis that progressed to corneal scarring and permanent vision loss. Lowenstein described a similar case in a four-year-old boy who made a full recovery. Another case report by Willhemus in 1991 showed that three out of five patients with disciform keratitis required a prolonged course of topical steroid. However, none of them suffered from severe vision loss. Prompt diagnosis is critical to the outcome in these cases, and subjects presenting with red eye following primary varicella require assessment of vision and referral as necessary.

The delayed onset of stromal keratitis following primary varicella infection suggests an immunologic cause, rather than infective. Frandsen theorized that it was driven by the activation of the immune system 10–14 days after the initial infection towards remnant virus. Hence, the course may be prolonged and recurrent compared to ocular complications that arise during the early phase of chickenpox, such as conjunctival vesicles and conjunctivitis.

Bacterial superinfection during the acute phase of chickenpox infection is common. In fact, our case four shared close similarities to another case report, with both being the same age and having the same treatment. Group A streptococci, which includes Streptococcus Pyogenes, and Staphylococcus aureus are the most common causative pathogens. The former being able to cause streptococcal toxic shock syndrome that requires rapid fluid resuscitation and intensive care admission.

Our case of optic neuritis closely resembles previous case studies. However, the disease can manifest in a few different ways. The visual symptoms can present before, during the acute phase of rash (within seven days) or a few weeks after rash resolution. It can be unilateral or bilateral. Most affected individuals have full recovery of visual acuity but some have long-term visual loss. It can be associated with other neurological complications such as acute transverse myelitis, encephalomyelitis, ataxia, and retinopathy. Optic disc changes have been documented even before the onset of visual symptoms.

Pupillary dilatation following chickenpox infection can occur in isolation or with other ocular manifestations. Affected patients have been found to have poor recovery and permanent loss of accommodative ability. However, most achieve good visual acuity with corrective lenses.

Autoimmune retinopathy is rare type of retinopathy, characterised by vision loss, visual field deficits, photoreceptor dysfunction and the presence of circulating anti-retinal antibodies. The fundal appearance is usually normal with minimal inflammation. Our case is the only published case of autoimmune retinopathy following primary varicella infection. Although the anti-retinal antibodies tests were negative, the diagnosis was made based on the electoretinogram findings, observed clinical improvement on immunosuppressants and absence of any other ocular signs.
The ocular complications of primary varicella infection are rare with 1 in 13,500 cases requiring assessment by ophthalmology and only 1 in 27,000 necessitating active treatment. Half of referrals to the eye clinic for primary varicella eye sequelae were mild cases of conjunctival or lid involvement, which can be treated conservatively.

Our case series demonstrates that ocular complications from primary varicella infection can be severe and permanent. Three subjects developed vision loss from disciform keratitis, and another one had vision loss from autoimmune retinopathy. Our other subjects recovered their vision on appropriate treatment, although some were left with long-term sequelae. Primary care clinicians should refer all patients with eye pain, floaters, redness or drop in visual acuity, especially if this persists for more than a week following a primary varicella infection.

Competing interests:
Nil.

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