Herpes Zoster Ophthalmicus with Orbital Apex Syndrome—Difference in Outcomes and Literature Review

Jie Jie Lim, Yu Ming Ong, M. Zain Wan Zalina & May May Choo

To cite this article: Jie Jie Lim, Yu Ming Ong, M. Zain Wan Zalina & May May Choo (2017): Herpes Zoster Ophthalmicus with Orbital Apex Syndrome—Difference in Outcomes and Literature Review, Ocular Immunology and Inflammation, DOI: 10.1080/09273948.2017.1327604

To link to this article: http://dx.doi.org/10.1080/09273948.2017.1327604

Published online: 16 Jun 2017.
LETTER TO THE EDITOR

Herpes Zoster Ophthalmicus with Orbital Apex Syndrome—Difference in Outcomes and Literature Review

Jie Jie Lim, MD1,2, Yu Ming Ong, MBBS, MOphthal3, M. Zain Wan Zalina, MBCh BAO, MS (Ophthal)3, and May May Choo, MBBS, M.Med, M.Oph, FRCS2

1Department of Ophthalmology, Hospital Selayang, Selangor, Malaysia, 2Department of Ophthalmology, University of Malaya, Kuala Lumpur, Malaysia, and 3Department of Ophthalmology, Hospital Sultanah Bahiyah, Alor Setar, Kedah, Malaysia

Keywords: Herpes zoster ophthalmicus, Orbital apex syndrome, Varicella zoster infection

Herpes zoster ophthalmicus (HZO) is caused by reactivation of latent varicella zoster virus infection in the trigeminal ganglion, involving the ophthalmic division of the trigeminal nerve (V1). Ocular involvement occurs in 20–70% of patients with HZO1 and may include blepharitis, keratoconjunctivitis, iritis, scleritis, and acute retinal necrosis. Neurological complications are less frequent compared to ocular complications and may include ophthalmoplegia, optic neuritis, ptosis, and rarely orbital apex syndrome (OAS). OAS involves dysfunction of V1, the oculomotor nerve (III), the trochlear nerve (IV), and the abducens nerve (VI), as well as dysfunction of the optic nerve (II). Herpes zoster ophthalmicus is a rare cause of OAS. Here, we report two cases of HZO with orbital apex syndrome. We conducted a thorough literature review to assess the prevalence of our reported cases.

METHOD

Case Series

RESULT

Case 1

A 77-year-old woman with underlying hypertension presented with complete left upper eyelid ptosis. Three weeks prior to presentation, she had vesicular skin lesions over the left periorbital region and forehead. She also experienced left eye pain, redness, and progressive blurring of vision. She had reduced oral intake as well. The patient did not seek treatment at that time.

At presentation, there were dried and scarred skin lesions over her left forehead and periorbital region in the distribution of the ophthalmic division of the trigeminal nerve. Visual acuity in the left eye was perception to light. The left eye was proposed with complete ophthalmoplegia and the presence of relative afferent pupillary defect. There was complete left upper lid ptosis. Intraocular pressures were 12 (OD) and 07 (OS) mmHg. Left eye conjunctiva was injected. The cornea was hazy with the presence of epithelial defect and reduced corneal sensation. The posterior segment view was obscured. B-scan ultrasonography showed no obvious posterior segment involvement. Examination of the right eye showed that it was normal. Computed tomographic (CT) scan of the brain and orbit turned out normal (see Figures 1 and 2).

A diagnosis of left herpes zoster ophthalmicus with orbital apex syndrome and neurotrophic corneal ulcer was made. She was treated with oral acyclovir (800mg 5 times a day), oral prednisolone 40mg od and topically, she was treated with artificial tears eyedrops, dexamethasone 0.1% eyedrops, oxytetracycline ointment, and homatropine eyedrops. Patient was maintained on oral acyclovir 800mg 5 times a day and oral prednisolone tapered over a total duration of 2 months.

She was discharged after two weeks, with residual minor epithelial defects. Her left eye vision remained at perception of light at the time of discharge.

The patient was closely monitored as an outpatient with biweekly follow-ups. During this period, she developed secondary bacterial keratitis and was read-

Received 27 December 2016; revised 27 April 2017; accepted 3 May 2017; published online 16 June 2017

Correspondence: Jie Jie Lim, Department of Ophthalmology, Hospital Selayang, Lebuh Raya Selayang-Kepong, 68100 Batu Caves, Selangor, Malaysia. E-mail: jie2lim@gmail.com
<table>
<thead>
<tr>
<th>Case Reports</th>
<th>Age</th>
<th>Gender</th>
<th>Initial VA</th>
<th>Time of onset of OAS</th>
<th>Time of administration of antiviral after the onset of HZO</th>
<th>Administration of systemic steroid</th>
<th>Final VA</th>
<th>Full recovery of EOM</th>
<th>Causes of poor vision</th>
<th>Systemic association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dhingra et al 2008 (5)</td>
<td>63</td>
<td>Male</td>
<td>20/200</td>
<td>5th day</td>
<td>5th day (iv acyclovir and converted to oral acyclovir)</td>
<td>Oral prednisolone for 2 months</td>
<td>HM</td>
<td>Minimal improvement of 4th and 6th cranial nerve</td>
<td>OD pale</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Ugarte et al 2010. (6)</td>
<td>80</td>
<td>Female</td>
<td>HM</td>
<td>2.5 week</td>
<td>1st day (oral acyclovir)</td>
<td>Oral prednisolone for 2 months</td>
<td>6/9</td>
<td>6th month</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Saxena et al 2010 (7)</td>
<td>29</td>
<td>Female</td>
<td>20/640</td>
<td>2 weeks</td>
<td>2nd week (oral acyclovir with HAART)</td>
<td>Oral prednisolone, taper over 10 days.</td>
<td>20/25</td>
<td>4th week</td>
<td>-</td>
<td>HIV</td>
</tr>
<tr>
<td>Kurimoto T et al 2011. (8)</td>
<td>81</td>
<td>Female</td>
<td>6/12</td>
<td>17 days</td>
<td>10th day (iv vidarabine)</td>
<td>Iv prednisolone</td>
<td>6/6</td>
<td>20th week, except for abduction</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Arda et al 2012 (9)</td>
<td>75</td>
<td>Male</td>
<td>CF</td>
<td>2 days</td>
<td>1st day (oral valacyclovir then changed to iv acyclovir after diagnosis of OAS being established)</td>
<td>Oral prednisolone.</td>
<td>CF</td>
<td>5th month, partial improvement of the EOM.</td>
<td>Mature cataract, epithelial defect, fibrinoid reaction in AC</td>
<td>-</td>
</tr>
<tr>
<td>Alexia Merino Iglesias et al Mar 2014 (10)</td>
<td>61</td>
<td>Male</td>
<td>CF</td>
<td>5 days</td>
<td>5th day (iv acyclovir)</td>
<td>Oral prednisolone For 10 weeks</td>
<td>6/12</td>
<td>10th week.</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CY Lee et al Jan 2015 (11)</td>
<td>78</td>
<td>Male</td>
<td>3/60</td>
<td>5 days</td>
<td>5th day (iv acyclovir)</td>
<td>Oral prednisolone 12 weeks</td>
<td>6/30</td>
<td>12 weeks, with residual limitation of abduction and paralysis of the left upper eyelid.</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kalamkar C et al Jun 2016 (12)</td>
<td>65</td>
<td>Male</td>
<td>PL</td>
<td>10 days</td>
<td>10th day (oral acyclovir)</td>
<td>IV methylprednisolone for 3 days, then oral prednisolone tapered over 2 months</td>
<td>PL</td>
<td>3 months, except limited abduction</td>
<td>OD pale</td>
<td>-</td>
</tr>
<tr>
<td>Verhaeghe et al Jun 2016 (13)</td>
<td>80</td>
<td>Male</td>
<td>CF</td>
<td>7 days</td>
<td>1st day (initially oral acyclovir, then admit for iv acyclovir)</td>
<td>IV methylprednisolone for 15 days – started after 7 days of iv acyclovir, then oral for 2 months.</td>
<td>6/15</td>
<td>5 months</td>
<td>OD pale</td>
<td>-</td>
</tr>
<tr>
<td>Our patient of case 1.</td>
<td>77</td>
<td>Female</td>
<td>PL</td>
<td>3 weeks</td>
<td>3 weeks (oral acyclovir)</td>
<td>Oral prednisolone For 2 weeks</td>
<td>PL</td>
<td>6 weeks</td>
<td>Extensive cornea scarring and vascularization secondary to bacterial keratitis</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Our patient of Case 2</td>
<td>65</td>
<td>Male</td>
<td>3/60</td>
<td>4 weeks</td>
<td>1st day (oral acyclovir)</td>
<td>Not initiated.</td>
<td>6/24</td>
<td>6 weeks</td>
<td>Nuclear sclerosis</td>
<td>Diabetes mellitus</td>
</tr>
</tbody>
</table>
mitted to the ward for treatment (see Figures 3 and 4). Her bacterial keratitis resolved after intensive treatment with topical antibiotics (gentamicin eyedrops and ceftazidime eyedrops).

At 2 months, her extraocular muscle movements were full. However, there was still partial ptosis. Her vision remained poor due to extensive vascularization and scarring of the cornea.
Case 2

A 65-year-old Chinese man with underlying diabetes mellitus complained of redness and pain in the left eye for a duration of four weeks. He also had complete left upper lid ptosis, poor vision, and left-sided headache. One week prior to this, there were vesicular lesions which were distributed over the left forehead and left periorbital region. He had been treated with oral acyclovir by his primary care doctor. At the time of
presentation to the ophthalmology clinic, his left vision was 2/60 with no improvement using the pin-hole. Right eye vision was 6/24 and 6/12 with a pin-hole.

There were multiple small healed depressed scars, and some had overlying scabs in the left periorbital region, forehead, cheek, and nose. Complete ptosis was present in the left eye. The left pupil was dilated (7mm) and non-reactive to light. There was reverse Marcus Gunn. The right pupil was 5 mm in size and reactive. The eye was exo-deviated by 15° (Hirschberg corneal light reflex). There was total ophthalmoplegia. Intraocular pressures were 18 (OD) and 20 (OS) mmHg. The left conjunctiva was injected, and left corneal sensation was absent. Small punctate erosions were present on the left cornea, and a small corneal ulcer with thinning was seen infero-nasal to the pupil measuring 1.7 mm × 1.7 mm. The cornea was hazy. Fundus view was also not clear (see Figures 5 and 6). The right eye anterior and posterior segments were normal with no diabetic retinopathy seen.

A provisional diagnosis of left herpes zoster ophthalmicus with orbital apex syndrome was made, and the patient was commenced on treatment with topical acyclovir 5 times a daily and hourly ocular lubricants. A further continuation of oral acyclovir was prescribed for 10 days.

The patient’s vision improved to 6/24 at 3 weeks review, and there was partial recovery of the left oculomotor nerve. The anterior chamber was quiet with no cells detected. Acyclovir ointment was tapered, and topical lubricants were reduced to four hourly intervals as corneal was clear with mild haziness inferonasally. All the epithelial defects had healed. At 6 weeks, there was mild ptosis, but full eye movements were
detected. Vision had remained the same, and this was attributed to worsening of nuclear sclerosis. However, cataract extraction will be deferred for another 6 months in view of the recent inflammatory condition in the eye (see Figure 7).

**DISCUSSION**

Herpes zoster ophthalmicus (HZO) is defined as herpes zoster involvement in the ophthalmic division of the trigeminal nerve. It accounts for 10–20% of herpes zoster cases. It could involve a spectrum of presentation, such as blepharitis, keratoconjunctivitis, iritis, scleritis, and acute retinal necrosis. Diagnosis of herpes zoster ophthalmicus is relatively straightforward and is usually based on typical clinical presentation of rashes and pain. Often no tests are required.

Orbital apex syndrome (OAS) is a rare and serious complication of herpes zoster ophthalmicus. OAS is a spectrum of disease which involves damage to the oculomotor nerve, trochlear nerve, abducens nerve, and ophthalmic division of the trigeminal nerve, in association with optic nerve dysfunction. It was first reported by Ramsell in 1967. Both our patients presented with this rare but severe complication of HZO—orbital apex syndrome. In our cases, imaging had excluded other common causes of OAS such as hemorrhage, neoplasm, and cavernous sinus thrombosis. Others blood investigations turned out normal. Based on clinical presentation, we diagnosed them with herpes zoster ophthalmicus with orbital apex syndrome after the imaging.

Cases of herpes zoster ophthalmicus complicated with orbital apex syndrome are extremely rare. From the literature reviews, we found some reported cases with neuropathy. Womack et al (1983) reported three of 86 patients with HZO seen at Mayo clinic had ocular motor palsies (3.4%)1. Marsh (1977) reported that 9.8% of patients with HZO in the Moorfield Eye Hospital study had extraocular muscle palsy, with cranial nerve III dysfunction in four of the patients. Incidence of cranial nerve II dysfunction was only in 0.4% of the patients in the Moorfield Eye Hospital study.4

HZO associated with orbital apex syndrome has only been reported in isolated cases. Over the past 10 years, there were nine isolated cases of HZO with OAS reported in the literature (see Table 1).5–13

The age range of the patients was 29–81 years old, with most of the patients being elderly. There were two cases reported with background of immunosuppressive state—one of the patients was a HIV patient, while the other patient had multiple myeloma. In both our cases, the patients were elderly and the second patient had underlying diabetes.

Based on Dworkin et al (2007), systemic antiviral therapy is recommended as first-line treatment for all immunocompetent patients with herpes zoster who fulfill any of the following criteria: (1) 50 years of age; (2) have moderate or severe pain; (3) have moderate or severe rash; or (4) have non-truncal involvement.14

The current practice is to treat individuals with a new episode of herpes zoster with 7 to 14 days of antiviral treatment. However, based on Miserocchi et al’s report, it was found that there is a decreased frequency of recurrent episodes from 3.4 to 2.1 episodes per year in patients treated with prophylactic oral acyclovir or valacyclovir for at least 1 year. The optimal time for initiation of systemic antiviral treatment is within 72 hours after the onset of rash.

While the optimal therapy for OAS secondary to HZO remains unclear, the current mainstay of treatment is combined administration of systemic acyclovir and steroids.5,15 In the reported cases, most of the cases showed good improvement in response to the treatment with systemic acyclovir and steroids. One of the reported cases was treated with vidarabine due to compromised renal function. She also achieved good vision at the end of the treatment. Three of these patients did not achieve good vision despite treatment with systemic antivirals and steroids. The poor vision for the three reported cases was all attributed to optic atrophy.

In the cases of our two patients, the first patient presented to us with a severe form of orbital apex syndrome only at the third week after the onset of rashes. Oral acyclovir and systemic steroid treatment were started at the third week of onset. The effectiveness of acyclovir therapy in our patient has been reduced due to the delay in initiation of treatment, while the second case represents a milder case that was probably attributed to early administration of oral acyclovir by the general practitioner. However, the optimal time for initiation of treatment is within 72 hours from the onset of the rash.5,15

The true mechanisms by which optic neuropathy and extraocular muscle paralysis occur in patients with OAS due to HZO are not completely understood. Postulated mechanisms include extensive inflammation around the posterior ciliary nerves and vessels with ocular ischemia, orbital soft tissue edema with direct compression of cranial nerves III, IV, and VI, and direct spread of VZV from cranial nerve V to cranial nerves III, IV, and VI. Different mechanisms may lead to different clinical manifestations and prognoses.4,11

The proportion of patients who achieve resolution of ptosis, ophthalmoplegia, and reduced visual acuity remains unknown.16 Complete or near-complete resolution of ophthalmoplegia due to HZO has been reported to occur in 76.5% of cases and may take between 2 weeks and 1.5 years (mean 4.4 months).5

In our first patient, resolution of ophthalmoplegia took 6 weeks, with residual of partial ptosis. Her
visual acuity did not improve due to extensive scarring and vascularization of the cornea from secondary bacterial keratitis. Our second patient regained complete recovery of ophthalmoplegia at 6 weeks. His visual acuity returned to 6/24 after treatment.

CONCLUSION

Orbital apex syndrome is a rare but severe complication of HZO. The mainstay of treatment is a combined administration of systemic acyclovir and corticosteroids together with topical acyclovir and topical steroids for the anterior segments involvement. Early administration of systemic acyclovir and systemic steroid aid in improving the outcome. Serious and potentially blinding complications of herpes zoster ophthalmicus should be suspected, especially in patients with risk factors such as diabetes mellitus, advanced age and immunodeficiency states. Medical officers or general practitioners should refer patients with herpes zoster ophthalmicus to ophthalmologists as early as possible to commence treatment with antivirals to improve the prognosis.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

REFERENCES