

Visual Outcome in Herpes Zoster Optic Neuritis

A case report and systematic review

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Background: Optic neuritis in herpes zoster ophthalmicus (HZO) has been rarely reported in immunocompetent individuals. It is a potentially blinding disease. Visual outcomes for herpes zoster optic neuritis since the advent of acyclovir have only been mentioned through case reports. The role of systemic steroids is still unclear.

Objective: To present a case of herpes zoster ophthalmicus associated optic neuritis in an immunocompetent patient combined with systematic literature review to assess treatment outcomes.

Case: 62 year-old male presents with left optic nerve edema concurrently with HZO. An MRI shows enhancement of the optic nerve consistent with optic neuritis. Pt is treated with systemic acyclovir and steroid with minimal visual acuity benefit. End result was light perception vision and optic nerve pallor.

Methods: An exhaustive MEDLINE literature search of cases of HZO optic neuritis in immunocompetent patients were reviewed and selected. Cases were excluded the patient was immunocompromised, had extensive intracranial or orbital sequelae or in which sufficient information not available (n=2). Cases were separated by those having been treated with systemic acyclovir and those which were not. These were used to assess differences in visual prognosis based on mean visual acuity, recovery duration and treatment outcomes.

Results: A total of 26 cases met selection criteria, including this case. In the acyclovir treatment group there were 13 cases as well as 13 cases in the non-acyclovir treatment group. Both populations were comparable for gender and age at disease onset. The onset and recovery times were similar in each group. The mean visual acuity of the acyclovir treatment group was 0.66 logMAR compared to 1.38 in the non-acyclovir treatment group. This was statistically significant at $P < 0.005$. Subset analysis of a systemic steroid only group and a systemic acyclovir + steroid group showed a mean logMAR visual acuity of 1.77 (n=6) and 0.7 (n=10) respectively. Legal blindness (logMAR 1.0) occurred in 23% of the acyclovir treatment group compared to 69% of the non-acyclovir treatment group. Optic atrophy was also more prevalent in cases not treated with acyclovir, 69%, compared to 31% if given systemic acyclovir.

Conclusion: Systemic acyclovir has dramatically reduced the morbidity of HZO optic neuritis. Although recovery time with the use of acyclovir was not significantly reduced, final visual acuity is much better when systemic acyclovir is implemented as primary treatment. Treatment with systemic acyclovir also reduced the rate of legal blindness and optic atrophy by almost 50%. The current treatment recommendations are systemic acyclovir for all cases of HZO. This will help reduce the ocular complications of HZO including HZO related optic neuritis.

Introduction

Herpes zoster is an infectious disease acquired from reactivation of the latent varicella virus. Reactivation can occur in individuals who had varicella virus infection “chicken pox” or received a vaccination for the virus earlier in life.^{1,2} The disease has an affinity for the nervous system in particular the sensory ganglia. The essential lesion is acute inflammation of these ganglion and nerves. Histological evi-

dence show lymphocytic infiltration, hemorrhages, and fibrinoid necrosis of the infected ganglia, nerve cells and fibers.^{3,4} A lifelong inhabitation of the sensory ganglia occurs as a result of the initial infection³ and DNA evidence exists that confirms herpes zoster to be the reappearance of the same specific strain of childhood virus contracted years prior.⁵ It is estimated that over 90% of the population has se-

rologic evidence of the disease with over 1 million cases each year in the U.S. alone.^{2,3} It is a disease of the elderly with no seasonal pattern.⁶ As we age, we develop decreased cell-mediated immunity and it is by this mechanism that the virus is allowed to become active after having been held quiescent for many years.^{2,6}

This disease has a prodrome of fever, malaise, headache, and pain along the dermatome a few days before exanthema onset. The skin exanthem presents as an acute, painful, eruption of vesicles along a single dermatome or sensory distribution. Shedding virus can be isolated from the vesicles for up to 14 days but typically lasts only 7 days in healthy individuals.^{3,7} New lesions typically cease formation by day 7, leaving stages of old crusting lesions inter-mixed with more active pustules. In immunocompetent individuals the affected dermatome usually heals in 2-3 weeks but the lingering post herpetic neuralgia (PHN) may last for months to years.^{2,8} Immunocompromised individuals often suffer worse manifestations of the disease including pneumonitis, meningoencephalitis, hepatitis, ocular and cranial nerve complications.⁹ Herpes zoster can affect any spinal or cerebral ganglia but has a disproportionate attraction for the trigeminal ganglia, specifically the ophthalmic division (V1) called herpes zoster ophthalmicus (HZO).

HZO accounts for 17-50% of herpes zoster cases.^{10,11} Like herpes zoster it increases with age, with the majority occurring over the age of 50. It is more common in females although when HZO occurs early in life it occurs more commonly in males.⁸ The exanthem develops most commonly in the frontal branch of the ophthalmic nerve and does not cross the midline. It is potentially the most devastating form of herpes zoster due to its ocular complications which have a prevalence of up to 50%.^{2,8} It is well known that herpes zoster involving the nasociliary portion of the ophthalmic nerve carries an increased likelihood of ocular involvement.¹² In one study, there was a 76% chance of ocular complications if the nasociliary nerve was involved compared to a 36% chance if it were not.⁸ This nerve innervates the skin of both eyelids and tip of the nose, conjunctiva, sclera, cornea, iris, ciliary body and choroid. The virus reaches the globe via branches of the nasociliary called ciliary nerves. Ocular signs appear on average 1.8 weeks after onset of exanthema with approximately 28% of eyes becoming chronically involved.⁸ In a recent study on visual outcomes,

Miserocchi et al.,¹³ reported a rate of 20% legal blindness in cases of HZO with ocular involvement.

The ocular complications of HZO are related to multiple mechanisms including viral spread, ischemic vasculitis, neural inflammation and tissue scarring.^{2,3,13} Chronic sequelae can be attributed to an epithelioid and giant cell granulomatous reaction within the cornea, ciliary body, choroid, retina and central nervous system. Nerves become thickened and fibrotic with ischemic vascular changes.^{3,14} Viral DNA has been identified at some stage in all ocular tissues. Even 10 years after the onset of HZO, viral-DNA has been identified in several ocular structures.¹⁵ The most common ocular complications of HZO are conjunctivitis, keratitis and uveitis but others include: edema of the eyelid, ocular hypertension, trabeculitis, pseudodendritis, keratouveitis, scleritis, retinal vasculitis, central retinal artery occlusion, choroiditis, acute retinal necrosis and optic neuritis.¹⁶

Optic neuritis is an uncommon complication of HZO. Since Hutchinson originally described it in 1886,¹² HZO optic neuritis has been documented but rarely reported. Reports in the past have documented devastating effects on visual acuity. Tunis et al.,¹⁷ in a literature search reported final visual acuities of 20/200 or worse in 71% and no light perception (NLP) in 24% of patients with HZO related optic neuritis. Systemic steroids were the best option for treatment before the discovery of anti-viral medications.^{17,18,19} The invention of acyclovir dramatically changed the outcomes of HZO in general as it decreasing viral shedding. New skin lesions were reduced as well as decreased incidences of ocular and late complications.^{7,20} Visual outcomes of HZO optic neuritis since the advent of acyclovir have not been reported except in case reports. Reported here is a case of HZO optic neuritis combined with a literature review assessing visual prognosis in immunocompetent patients with this potentially blinding disease.

Case Report

A 62 year-old male presented to our corneal clinic for evaluation of herpes zoster ophthalmicus. He is a previously healthy individual with no significant past medical history. Five days earlier he was diagnosed with conjunctivitis of his left eye which subsequently evolved into a vesicular rash distributed over the first trigeminal nerve. His eyelids had be-

cause this could potentially confound and contribute to the final visual outcome. Cases of immunocompromised patients and those with insufficient data were also excluded. Data extracted is shown in table 1 and included: age, sex, worst visual acuity, final visual acuity, onset of optic neuritis, estimated recovery from optic neuritis, findings, treatment, and end results.

Visual acuity measures from each report were converted to a standard logMAR equivalent for comparison. Visual acuities reported as count fingers (CF), hand motion (HM), light perception (LP) and no light perception (NLP) were assigned logMAR values of 2.0, 2.1, 2.2 and 2.3 respectively. These values were given in sequential order above the highest visual acuity reported in the selected cases which was 1.82. This allowed the possibility of certain statistical calculations across cases. Time was also converted to days in each case.

Cases were separated based on treatment and divided into 2 major groups; those treated with systemic acyclovir and those that were not. In each group, we calculated the mean visual acuity, time to onset, time to recovery and percentage of eyes that became legally blind (logMAR 1.0) or had optic atrophy. Subset treatment groups of systemic steroids only and systemic acyclovir + steroids were also formed from the data. These were assessed in the same manner with regards to visual acuity, onset and recovery.

Results

A total of 26 reported cases met inclusion criteria, including the one reported here. The baseline characteristics and findings are shown in table 1. There were 13 eyes included in the systemic acyclovir treatment group and 13 cases in the non-acyclovir treatment group. Both populations were comparable for gender and age at disease onset. The average age at disease onset was 53 and 58 years for the acyclovir and non-acyclovir treated groups respectively. These averages excluded the 5 reported cases that occurred in children. There were 7 females and 6 males in each group. The onset and recovery times were also similar in each group. Days to onset in the acyclovir group averaged 30 days with recovery occurring 151 days later. Onset was on average a few days earlier in the non-acyclovir treatment group at 23 days with recovery in 128 days (table 2).

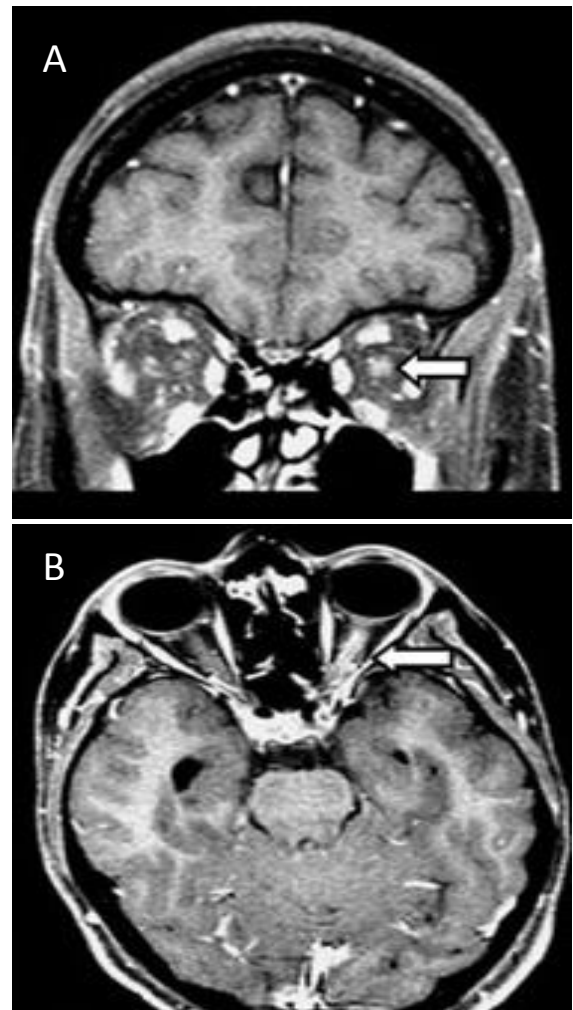


Figure 2. A. Contrast-enhanced T1-weighted, fat-suppressed coronal MRI through the orbits shows contrast enhancement of the left optic nerve (arrow). B. Contrast-enhanced fat-suppressed axial MRI through the orbits shows contrast enhancement of the left optic (arrow).

Optic atrophy was assessed in each group occurring in a total of 14 of 26 eyes. In the acyclovir treatment group optic atrophy was the end result in 4 of 13 cases (31%) compared to 9 of 13 (69%) in the non-acyclovir treated group (table 2). Optic atrophy correlated well with visual acuity measures in each group.

The mean visual acuity of the acyclovir treatment group was 0.66 logMAR compared to 1.38 logMAR in the non-acyclovir treatment group (figure 3). This difference was statistically significant ($P < 0.005$). Visual acuities in each group ranged from normal (0.0 logMAR) to NLP. Subset analysis of a systemic steroid only treatment group showed a mean

Table 1. A comparison of literature reporting optic neuritis with herpes zoster ophthalmicus

Reference	Age/ Sex	Worst V/A	Final V/A	Onset of ON	Estimated Recovery	Findings	Treatment	Final result	Year
Veasey [31]	40/F	NLP	NLP	7 days	28 days	Central scotoma, Normal fundus	Mercurial inunctions, Pilocarpine sweats	Optic atrophy and central scotoma	1919
Jensen [32]	9/F	6/60	6/60	21 days	180 days	Disc edema, foveal exudates	Unknown	Optic atrophy	1948
Parry [33]	52/F	LP	6/60	24 days	56 days	Slight blurring of disc	Unknown	Optic atrophy, Central scotoma, Abn color v/a	1948
Sasso [34]	4/F	20/50	Normal	10 days	19 days	Disc edema and blurring, Peripapillary hemorrhage, Exudate	Cortisone	Normal fundus	1958
Ramsell [19]	78/F	LP	6/18	120 days	455 days	Blurred disc margin	Topical/sub-conjunctival steroids	Defined disc margin	1967
Monroe [35]	9/M	CF	CF	14 days	30 days	Disc edema with hemorrhage	Topical steroids	Disc margin sharp, Hemorrhage resolved	1979
Carroll [36]	55/M	CF	6/9	9 days	28 days	Central scotoma, APD, Abn VEP, EOG and color v/a	Unknown	Improved but abn VEP, EOG and color v/a	1979
Schmidt [4]	73/F	LP	1/60	28 days	240 days	Thickening of optic nerve, Central scotoma, Disc edema, Abn amplitude on VEP, APD	Systemic steroids, Vidaribine ointment	Optic nerve atrophy, Central scotoma	1983
Scharf [37]	73/M	CF	NLP	10 days	365 days	+APD, Optic nerve edema	Systemic steroids	Optic atrophy	1987
Tunis [17]	19/M	NLP	CF	24 days	90 days	Altitudinal scotoma, Absent VEP, APD	Systemic steroids	Optic atrophy	1987
Atmaca [38]	58/M	CF	NLP	9 days	90 days	APD, Disc edema, Hyperfluorescent optic disc, CRAO	Systemic steroid, Periocular steroid	Optic atrophy	1992
Gunduz [23]	48/M	0.1	0.4	5 days	90 days	Central scotoma, APD, Abn VEP	Topical steroid, Acyclovir ointment	Temporal disc pallor, Decreased VEP	1994
Menon [39]	48/F	LP	LP	30 days	90 days	Absent VEP, APD, Central scotoma	Systemic steroid, B vitamins	Temporal disc pallor, central scotoma	1995
Deane [40]	73/M	HM	20/600	150 days	365 days	Disc edema, Splinter hemorrhages Abn VEP, Central scotoma, Abn color v/a, APD	Intravenous acyclovir and steroid	Improved visual field, Optic atrophy	1995
Deane [40]	73/M	20/200	20/80	42 days	365 days	Disc edema, Splinter hemorrhages, Abn VEP, Central scotoma, Abn color v/a	Intravenous acyclovir and steroid	Improved visual field, Optic atrophy	1995
Dhar [30]	30/F	NLP	5/60	9 days	28 days	APD, Disc edema, Peripapillary hemorrhage, Exudates, Absent VEP, Abn color v/a	Systemic Acyclovir, Systemic steroid	Improved color and contrast v, VF scotoma, Enlarged blind spot	1996
Mori [41]	50/F	NLP	20/33	42 days	240 days	APD, Central scotoma	Systemic acyclovir, Systemic steroid, SGB	Optic atrophy, Disc pallor, Abn color v/a	1997
Wang [42]	72/M	2/60	6/8.6	14 days	90 days	APD, Disc edema, VF constricted, Late staining disc, Enhanced optic nerve sheath on MRI	Systemic acyclovir, Systemic steroid	Normal visual field	2000
Wang [42]	69/M	6/15	6/6.7	12 days	30 days	APD, Central scotoma, Enhanced optic nerve on MRI, Abn color v/a	Systemic acyclovir, Systemic steroid	Resolution of APD and color deficit	2000
Zaal [43]			0.3	7 days	180 days	Optic neuritis	Systemic Acyclovir	Stable vision loss	2003
Saenz-Frances [44]	65/F	20/80	20/50	Onset	7 days	Disc edema, Peripapillary hemorrhage	Systemic valacyclovir, Topical acyclovir	Resolved disc edema, Altitudinal scotoma	2007
Hong [45]	6/F	0.4	0.8	7 days	30 days	Disc edema, Hyperfluorescent optic disc	Systemic acyclovir, Systemic steroid	Normal fundus	2010
Vitor [46]	74/F	CF	20/60	45 days	10 days	Disc edema, Hyperfluorescent optic disc, Abn VF and VEP	Systemic acyclovir, Topical steroid	Disc pallor	2011
Gupta [47]	34/F	20/200	20/40		300 days	Optic neuritis	Systemic acyclovir, Systemic steroid	Resolution of optic neuritis	2011
Gupta [47]	33/F	20/800	20/80		300 days	Optic neuritis	Systemic acyclovir, Systemic steroid	Resolution of optic neuritis	2011
Our Study	62/M	LP	LP	6 days	30 days	APD, Optic disc edema, Central scotoma,	Systemic acyclovir, Systemic steroid	Disc pallor, Central scotoma	2011

V/A=vision; NLP=no light perception; LP=light perception; HM=hand motion; FC=finger counting; VEP=visual evoked potential; VF=visual field; SGB=stellate ganglion block; EOG=electrooculogram; APD=afferent papillary defect; M=male; F=female; ON=optic neuritis; Abn=abnormal; CRAO=central retinal artery occlusion

Table 2. Characteristics extracted from table 1. Note the significant decrease in both legal blindness and optic atrophy in the acyclovir treated group compared to the non-acyclovir treated group. Legal blindness based on logMAR 1.0 or 20/200.

	Acyclovir treated group (n=13)	Non-acyclovir treated group (n=13)
Average Age (years)	53	58
Gender	6 Male/7 Female	6 Male/7 Female
Rate of legal blindness	23%	69%
Optic atrophy	31%	69%

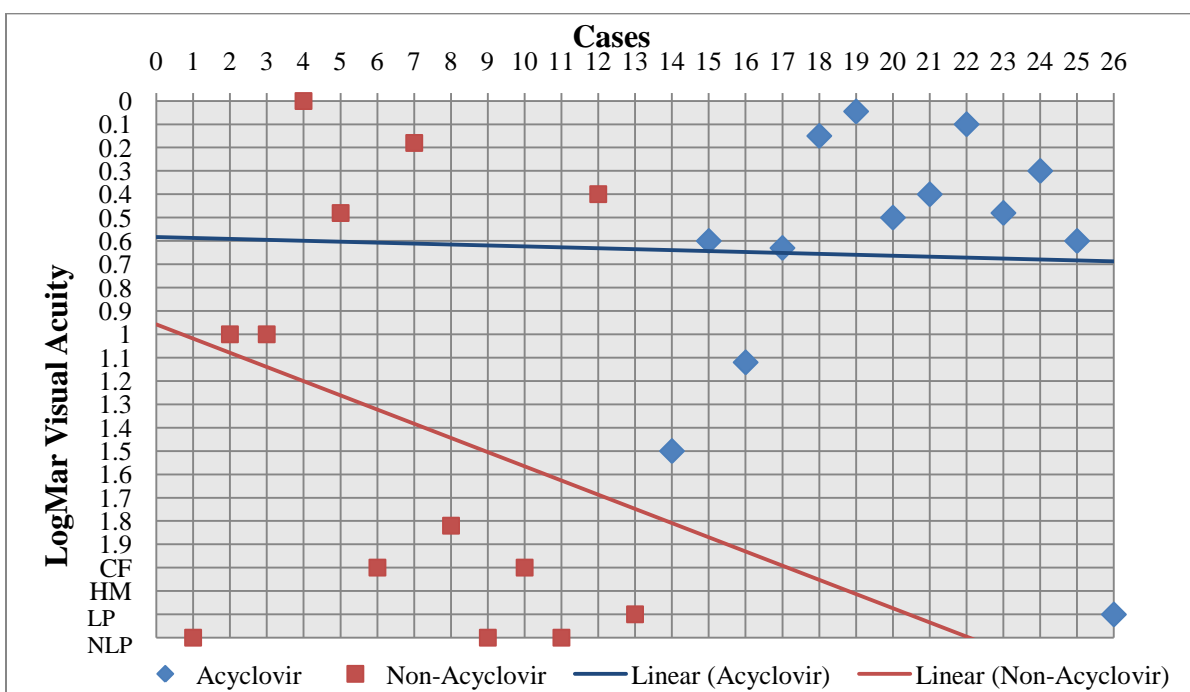


Figure 3. LogMar visual acuity equivalent data points for each case report selected. Most of the cases treated with acyclovir were also treated with systemic steroids. Of those not treated with systemic acyclovir, about half received systemic steroids. Most of the cases treated with acyclovir maintained stable useful vision as shown in the trendline analysis.

logMAR visual acuity of 1.77 (n=6). Most cases treated with systemic acyclovir were also given systemic steroids (n=10). This subset had a logMAR visual acuity of 0.72 (figure 4). Legal blindness (logMAR 1.0) occurred in 23% of the acyclovir treatment group compared to 69% of the non-acyclovir treatment group (table 2).

Discussion

Herpes zoster related optic neuritis is a rare complication occurring more often in the elderly and

immunosuppressed as cell-mediated immunity falls.^{2,3,21} Because of its uncommon nature, the incidence is unknown but estimated at far less than 1%.^{4,11} Advances in technology however may indicate that inflammation of the optic nerve occurs more often than its clinical presentation. Wenkel et al.¹⁵ performed histological examination and immunohistochemistry of 9 ocular specimens with a history of HZO. Their evaluation found over 50% of these eyes had evidence of optic neuritis confirmed by viral DNA detected at the optic disc. In this study viral DNA was identified in many other structures

including: the anterior chamber, corneal stroma, episclera, posterior ciliary nerves and arteries, and meninges causing a granulomatous inflammation. Viral DNA was even identified in some specimens up to 10 years after the onset of HZO. This may account for the chronic recurrent nature of the disease. Naumann et al.²² also discussed the histopathology of 21 enucleated eyes after HZO. Seven of these eyes demonstrated evidence of optic neuritis although none had clinical symptoms before enucleation. In this study inflammation was also found around the posterior ciliary nerves and vessels with patchy necrosis of the iris suggestive of generalized ischemia.

HZO optic neuritis may be unilateral, bilateral, intraocular or retrobulbar.^{4,23} The optic nerve may become involved by several different mechanisms. Direct extension, hematogenous, cerebral spinal fluid and transneuronal spread have all been implicated. Studies by Wenkel et al. and Naumann et al. confirmed vascular inflammation resulting in ocular ischemia. Cerebral spinal fluid may allow spread of the herpetic family. Transneuronal spread has been implicated as evident on MRI. Concurrent MRI T2 signal enhancement of the optic nerve, tracts, lateral geniculate body, optic radiations and calcarine fissure support this theory.²⁵ Direct extension of the virus through the cavernous sinus also occurs as evident in herpes zoster associated orbital apex syndrome.¹⁴ Despite the lack of histological evidence in our case, papillitis secondary to direct viral induced neuritis and vasculitis is suspected.

Acute optic neuritis usually develops as a post-herpetic complication. In this analysis the onset of optic nerve disease occurred from 5 days to 5 months but the average time was about 4 weeks (figure 5). This confirms previous reported post-herpetic onset times ranging from 2 to 4 weeks.¹⁷ Time to resolution was similar in each group. This data was probably confounded by variability in patient follow up, meaning the exact time of resolution was probably overestimated. The severity and course of ocular inflammatory complications depends on the interaction between reactivated virus, the immune response elicited and the timing and efficacy of anti-viral therapy.

Before the development of anti-viral therapy, herpes zoster related optic neuritis had a dismal out-

come. Most ended with less than 20/200 vision secondary to optic atrophy.^{4,23} This study confirmed that without acyclovir, visual prognosis is poor and optic atrophy likely (figures 3 and 4). Table 2 shows that legal blindness is 3 times higher when anti-viral therapy is not used to treat optic neuritis. Acyclovir has become standard of care for the treatment of HZO.

Acyclovir is a specific antiviral agent against herpetic infections that inhibits viral DNA polymerase.^{25,26} High doses of acyclovir are needed to treat the virus because acyclovir has a poor bioavailability and the zoster virus is less susceptible than other herpetic infections to this medication.^{1,25,26} A dose of 800 mg of oral acyclovir 5 times daily or 10 mg per kilogram intravenously every 8 hours has been shown by multiple studies to be affective.^{25,27,28} The duration of treatment has also been studied. These studies have proven a 7 day course to be effective and that longer durations have no additional benefit.^{28,29} The benefits of acyclovir are best achieved if treatment is begun within 72 hours of skin exanthem.^{25,27} At the appropriate dose, acyclovir not only decreases viral shedding but also decreases the severity of ocular sequelae.⁷

Our study supports evidence of acyclovir's efficacy (figures 3 and 4). Visual outcomes are significantly improved when systemic acyclovir is used to treat herpes zoster related optic neuritis. A gain of more than 3 lines on a Snellen equivalent eye chart was achieved using this treatment when compared to non-treated groups. The prevalence of optic atrophy and legal blindness both fell by over 50% with the advent and implication of acyclovir treatment (table 2). Steroids have also commonly been used in adjunct to acyclovir (table 1). Steroids alone do not have promising visual outcomes but may help decrease the vasculitis associated with HZO related optic neuritis when used with acyclovir (figure 4).³⁰ Our patient despite treatment with acyclovir and steroid did not regain useful vision. Perhaps because acyclovir therapy was delayed and significant viral load had already been established, damage was inevitable. Despite our best efforts however, herpes zoster related optic neuritis frequently leaves the patient with some amount of permanent vision loss.

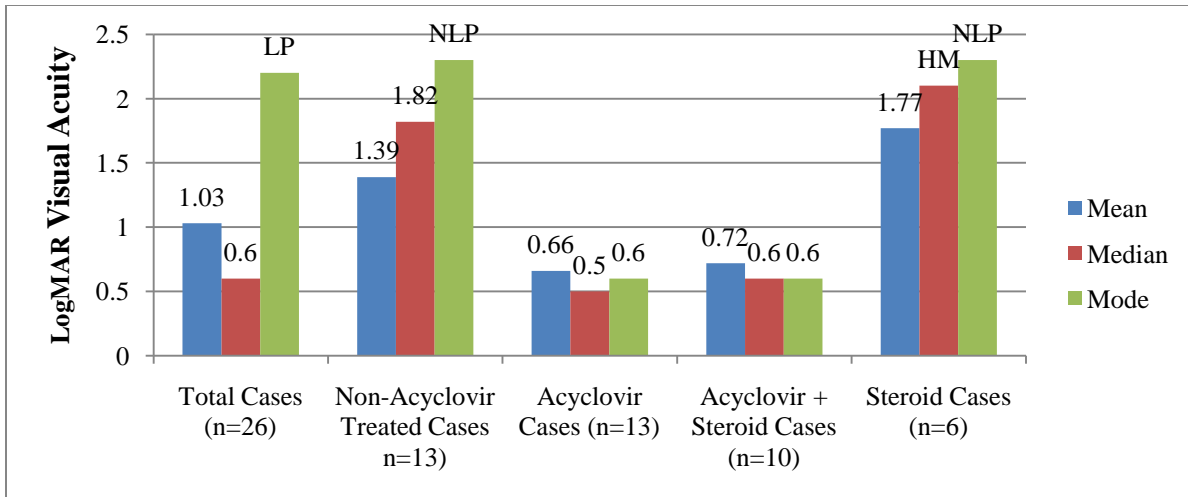


Figure 4. A comparison of visual acuities over selected treatment groups. Most of the cases treated with acyclovir were also treated with systemic steroids. The visual acuity benefits are attributed mostly to acyclovir as the steroid only group performed poorly.

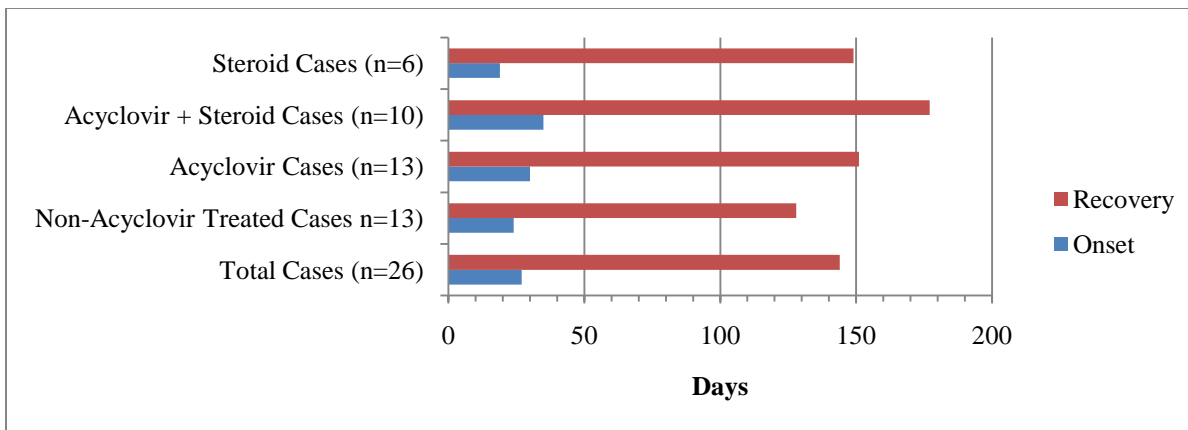


Figure 5. Estimated Optic Neuritis Onset and Recovery. Mean onset and recovery were comparable. Recovery time is based on patient follow up and probably is overestimated.

Prevention would be ideal in fending this virus. To date, we cannot prevent herpes zoster reactivation. There is no rapid zoster test to catch it during its prodromal stage. Vaccines however may provide a boost in cell-mediated immunity for the elderly and immunocompromised so the body can maintain at bay this latent virus.^{2,3}

Conclusion

Systemic acyclovir has dramatically reduced the morbidity of ocular complications caused by HZO. Any ocular structure can be involved. The optic nerve is less commonly affected by HZO resulting in papillitis, neuroretinitis or retro-bulbar neuritis.

When herpes zoster does infect the optic nerve the consequences can be devastating. High dose systemic acyclovir is currently the treatment of choice for this condition and can improve chances of good visual outcomes as well as quality of life in immunocompetent persons.

Comments

No potential conflict of interest relevant to this article was reported. This study met IRB exemption requirements because it involves the collection of existing data, documents and records. The information is expressed in such a manner that subjects cannot be identified directly or through identifiers.

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