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Evidence Based Management of Herpes Zoster Ophthalmicus

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PERMISSION

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Abstract

This literature review was conducted based upon the successful completion of an Objective Structured Clinical Examination (OSCE) and oral defense, under the supervision of a program instructor. The case report was analyzed and the topic of effective management of herpes zoster ophthalmicus was developed. Research was conducted through the databases CINAHL and PubMed. Limits were applied to every search, including only articles within the last 5 years and articles available in full text. The reference lists of relevant articles were also reviewed for further pertinent articles with useful research. A total of twelve research articles were used for the purpose of this literature review.

Herpes zoster ophthalmicus (HZO) is a debilitating dermatomal rash that affects the V1 ophthalmic region of the face, unilaterally affecting the forehead, upper eyelid, and nose. HZO poses a risk for severe ocular complications, as it can affect any structure of the eye through the nerve pathways. This can lead to long term ocular complications, including vision loss. This literature review identifies proper antiviral treatment to reduce associated complications, timely treatment, steroid use, and additional self-management. It additionally addresses the importance of an ophthalmology referral for thorough assessment and proper treatment of ocular complications. Implementing evidence-based management of HZO provides the patient with the best potential outcome of this complicated disease process.

Keywords: herpes zoster ophthalmicus, management, treatment, ocular complications

Background

Herpes zoster, also known as shingles, is a painful vesicular rash that appears in about 33% of people in the United States in their lifetime (Freund & Chen, 2018). Pain, itching, or tingling often precede the appearance of the rash, followed by the appearance of little blisters that will rupture and turn into scabs within the next seven to ten days (CDC, 2019). Associated symptoms include fever, headache, chills, and/or upset stomach (CDC, 2019). As age increases, so does the risk of developing shingles, as well as the risk for complications associated with shingles (CDC, 2019). About 10-18% of people will develop postherpetic neuralgia, the nerve pain associated with shingles and the most common complication of shingles that can last for months to years following the resolution of the rash (CDC, 2019).

Those who have a history of chicken pox, which is about 99% of people born before 1980, are at risk for developing shingles (CDC, 2019). Varicella zoster virus is the chickenpox virus that lays dormant after infection, and years later may reactivate as herpes zoster to cause shingles (CDC, 2019). It spreads through direct contact with the fluid-filled blisters of the herpes zoster rash (CDC, 2019). Furthermore, it is only infectious when the blisters are present or weeping (CDC, 2019). Herpes zoster can cause chickenpox in an adult or child who does not have immunity to chickenpox, either through history or vaccine, but it cannot cause another person to develop shingles (CDC, 2019). There are two vaccines in the United States for prevention of shingles in those over age 50: zoster vaccine live (Zostavax) and recombinant zoster vaccine (Shingrix) (CDC, 2019; Li, 2018). Zostavax has a prevention rate of 51% since 2006, whereas Shingrix is more effective at up to 97% prevention since it was released in 2017 (Freudn & Chen, 2018; CDC, 2019; Li, 2018).

The risk for complications increases if the rash is on a person's face, specifically around or near the eye – known as herpes zoster ophthalmicus (HZO). Approximately 10-20% of all herpes zoster cases are diagnosed as herpes zoster ophthalmicus (HZO) with 50% experiencing ocular involvement (Freund & Chen, 2018). Complications of HZO due to ocular involvement can threaten vision and require urgent assessment by an ophthalmologist, including symptoms such as decreased vision, redness or pain in the eye, or neurologic symptoms (Freund & Chen, 2018). The goals of HZO management are simply stated: shorten the course, pain relief, and prevent complications (Johnson, Amzat, & Martin, 2015). This paper explores the evidence-based management of herpes zoster ophthalmicus in order to reduce and prevent associated complications.

PICO QUESTION: In adult patients presenting to the primary care setting with herpes zoster ophthalmicus, what are the evidence-based guidelines for optimal management of the condition?

Case Report

The following report is a novel case developed for the purpose of this evidence-based literature review.

Chief Complaint: A healthy 70-year-old female presented to the clinic complaining of right eye pain and rash.

HPI: The patient's rash started two days prior, when she woke up in the morning. The rash was located above her right eyebrow, on her right eyelid, and followed along the right side of her nose. She described the pain as "on and off," itchy and burning. It was aggravated by touch and laying down at night on her pillow. She denied radiating pain. For relief, the patient tried using Tylenol and ice, with little improvement. She rated her pain at 6/10.

Past Medical History:

1. Essential hypertension
2. Rheumatoid arthritis

Past Surgical History:

1. Hysterectomy

Medications:

1. Lisinopril 20mg PO daily
2. Prednisone 10mg PO daily PRN
3. Tylenol 650mg PO q6h PRN

Allergies: NKA

Social History: Widowed x 5 years, retired nurse x 8 years. Patient lives at home alone. She denied current or history of tobacco use. She did admit to alcohol use only on special occasions. For exercise, the patient likes to walk 20 minutes daily.

Review of Systems: The patient admitted to recent blurring vision in the right eye, sharp pain in the right eye, and occasional photophobia in the right eye. She denied similar symptoms in the left eye. She had a burning pain and erythematous rash on the right side of her forehead, right upper eyelid, and along the right side of her nose. Patient also reported associated fatigue and headaches. She denied fever, nausea, vomiting, and generalized myalgias.

Physical Exam: Vital signs: BP 154/90, pulse 78, temp 99.1˚F, respirations 18, O2 96%. She weighed 148 pounds and measured at 5’7” tall. Physical exam revealed a scattered vesicular rash on her forehead above her right eyebrow, upper right eyelid, and along the right side of her nose down to the tip of the nose (+Hutchinson sign). The vesicles were clear, grouped in different areas, with an erythematous base. The rash appeared to follow the V1 ophthalmic dermatome of the trigeminal nerve, unilaterally on the right side. Patient was tender upon palpation.

Ophthalmologic exam revealed irritation to right conjunctiva, some redness without drainage. PERRLA, EOM's intact. Cranial nerves III-XII grossly intact, with a deficit in CN II as follows. Visual acuity 20/20 in the left eye, 20/50 in the right, and 20/20 when using both eyes together. Patient does not use contact lenses, and only uses reading glasses at home. Fundoscopic exam was normal in bilateral eyes. The remaining physical exam was unremarkable.

Plan: The patient was diagnosed with herpes zoster ophthalmicus. Since it has been less than 72 hours since the rash first appeared, the patient was treated with an antiviral to help reduce symptoms and prevent associated complications. She was given valacyclovir 1000mg PO q8h x 7 days. An urgent referral was placed to ophthalmology for evaluation and management of ocular involvement. Patient was instructed to use Tylenol as needed for pain relief. She may try cold compresses to the rash for relief of pain and irritation. Patient to avoid excess exposure to heat, such as hot showers as this may aggravate the rash. Patient was educated on avoiding contact with children, pregnant individuals and immunocompromised individuals, as she may spread the varicella virus causing chicken pox. She should avoid touching the rash and practice good hand hygiene. Patient was told to follow up in 1 week for reevaluation of the rash in clinic, and follow up as instructed by ophthalmology. Patient was in agreeance with the plan of care, and had no further questions at that time.

Literature Review

Intro

This literature review seeks to identify the best practice for management of herpes zoster ophthalmicus for the purpose of the novel case report on the 70-year-old female patient. As 50% of cases of herpes zoster ophthalmicus (HZO) have ocular involvement, an accurate diagnosis is essential for proper assessment, follow up and treatment (Freund & Chen, 2018). A positive

Hutchinson sign, or finding of the herpes zoster rash on the tip of the nose, is strongly correlated with ocular involvement from HZO (Vrcek, Choudhury, & Durairaj, 2016). HZO usually presents as a dermatomal rash in V1: including the frontal, lacrimal, and nasociliary branches (Davis & Sheppard, 2019). The frontal branch has the supratrochlear and supraorbital sub-branches, which innervate the skin of the upper eyelid, forehead, and central scalp (Davis & Sheppard, 2019). The lacrimal branch innervates the lacrimal gland, lateral upper eyelid, and lateral conjunctiva of the upper eyelid (Davis & Sheppard, 2019). Lastly, the nasociliary branch has multiple sub-branches that supply the pathway for the varicella virus to access the eye, as well as the external nasal nerve to the tip of the nose (Davis & Sheppard, 2019). Other manifestations include the typical vesicular rash of herpes zoster, burning, tingling, or shooting pain in one dermatome, and may be accompanied by fatigue, fever, headache, etc. (Vrcek, et al., 2016). Aggressive treatment of herpes zoster ophthalmicus is essential to reduce the duration and severity of the acute infection, as well as prevent postherpetic neuralgia and significant visual impairment associated with HZO (Schuster, et al., 2016). Treatment of HZO is varied among providers, and different trials have reported different efficacies among therapy alternatives.

Treatment - Antivirals

Based upon many randomized control trials, antivirals are the mainstay of treatment for acute herpes zoster and HZO and are approved by the FDA (Lo, Jeng, Gillespie, Wu, & Cohen, 2019). There are three commonly used antiviral agents to prevent the replication of the virus, varying in cost and convenience: Valacyclovir (1g PO TID x 7 days), famciclovir (500mg PO TID x 7 days), or acyclovir (800mg PO 5x/day x 7 days) (Fruend & Chen, 2018; Schuster, et al., 2016; Li, 2018). Lo et al. (2019) identified the current practice patterns of providers for management of HZO. The majority of respondents (45.5%) used topical steroids and high dose

antivirals for acute HZO associated keratitis, while 23.6% using low dose antivirals and topical steroids (Lo, et al., 2019). In this study, valacyclovir 1,000mg was the most frequent used antiviral due to provider preference (Lo, et al., 2019).

Schuster, et al. (2016) conducted a large study comparing valacyclovir versus acyclovir, evaluating the efficacy of its treatment in HZO. They compared ocular involvement, dendritic ulcers, uveitis, pain at 24 weeks, and adverse effects between the two antivirals (Schuster, et al., 2016). Valacyclovir is an altered drug of acyclovir, in which it is converted to acyclovir after PO administration (Schuster, et al., 2016). This mechanism allows for increased plasma concentration of acyclovir, without the inconvenience of taking acyclovir five times per day with a lower plasma concentration due to first-pass metabolism (Schuster, et al., 2016). The study hypothesized that valacyclovir is likely equal in efficacy to IV acyclovir, and might be more efficacious than oral acyclovir (Schuster, et al., 2016). They concluded that the evidence in this one study is similar between the oral antivirals, and therefore inconclusive (Schuster, et al., 2016). However, patient compliance may be greater with valacyclovir's TID dose frequency, and the greater bioavailability of valacyclovir is an important consideration (Schuster, at al., 2016).

Another study found valacyclovir to shorten duration of herpes zoster associated pain as well as duration of postherpetic neuralgia, compared to acyclovir (Li, 2018). On the other hand, a following study determined that the results were similar between the antivirals, and the findings in the earlier study were not supported (Li, 2018). Multiple studies have identified that there is no statistical significance among valacyclovir vs. acyclovir, or famciclovir vs. acyclovir (Werner, et al., 2017). Li found that "valacyclovir and acyclovir also appear to have a similar effect in prevention of ocular complications in HZO" (2018, p.331). Werner et al. (2017)

identified a randomized control trial that showed the benefit of systemic acyclovir over topical acyclovir for the ocular complications associated with HZO.

In regards to time, antiviral therapy can significantly reduce the risk of complications in HZO if they are started within 72 hours of the onset of herpes zoster (Catron & Hern, 2008; Werner, et al., 2017; Johnson, et al., 2015). Reduction in acute pain, decreased risk of postherpetic neuralgia, improved healing of the lesions, decreased viral shedding, and decreased ocular involvement are all associated with prompt treatment with antivirals within the 72 hour window (Catron & Hern, 2008). No evidence has been shown in initiating therapy after this time frame, however many providers will still prescribe for 7-10 days after the onset of symptoms as the adverse effect profile of the antivirals are very low (Werner, et al., 2017; Johnson, et al., 2015; Catron & Hern, 2008). Werner et al. (2017) states expert panels recommend initiation of antiviral therapy after the 72 hour timeframe if new vesicles are still appearing with a complicated course of shingles, such as in patients with cutaneous, visceral or neurological dissemination, in patients with HZ ophthalmicus or HZ oticus, as well as in all immunocompromised patients.

A strong recommendation is also made for local acyclovir 3% ocular ointment to the HZO affected eye 5x/day (Werner, et al., 2017). Varicella DNA has been found to remain in the cornea for up to one month in the elderly and immunocompromised, for whom extending oral antiviral therapy beyond 7-10 days may also be beneficial, or with severe complications considering IV therapy (Vrcek, Choudhury, & Durairaj, 2016; Johnson, et al., 2015). IV antiviral therapy is indicated for patients with high risk cases of HZO, including but not limited to: immunodeficiency, patients on immunosuppressive medications, multiple dermatomes affected by herpes zoster, retinal involvement, corneal ulceration, or severe bacterial superinfection

(Catron & Hern, 2008). As one can see, a thorough understanding of potential ocular complications related to HZO and available treatment options are necessary to determine the proper course of antiviral treatment, which can be effectively determined and managed by ophthalmology.

Treatment - Steroids

Topical corticosteroids can be used to decrease inflammation and reduce ocular complications (Ahmad, Suan, & Alexander, 2019). Systemic corticosteroids, such as PO prednisolone or IV methylprednisolone, can be used in cases of "acute-phase pain, debilitating rash, facial palsy or cranial polyneuritis, and severe inflammatory ocular complications" (Ahmad, et al., 2019, p.99). Oral corticosteroids are recommended in conjunction with the antiviral medication to reduce the acute pain associated with HZO, as well as improve skin healing time (Vrcek, et al., 2016; Catron & Hern, 2008). Ophthalmic steroids, only prescribed in direct consultation with ophthalmology, can be beneficial for some ocular complications, such as stromal keratitis, uveitis, and scleritis (Vrcek, et al., 2016). However, these topical steroids can improve some ocular conditions and exacerbate others, so cautious prescribing is necessary (Johnson, et al., 2015). Steroids may be beneficial in HZO complications such as uveitis or scleritis, however steroid use should be avoided in epithelial keratitis, as well as patients with diabetes mellitus or gastritis (Johnson, et al., 2015).

Ophthalmology Referral

Because there are many severe ocular complications associated with herpes zoster ophthalmicus, "early involvement of an ophthalmologist can be useful in avoiding vision-threatening sequelae" (Vrcek, et al., 2016, p.22). Recommended physical exam of the eye includes "external inspection, visual acuity, visual fields, extra ocular movements, pupillary

response, fundoscopy, intraocular pressure, anterior chamber slit lamp exam, and corneal exam with and without staining" (Catron & Hern, 2008, p.175). Due to limited availability of these ophthalmologic resources in the primary care setting, referral to ophthalmology for a complete exam is necessary. This is especially important for HZO patients presenting with a decrease in vision or a red eye (Catron & Hern, 2008). "All patients with the possible diagnosis of HZO require ophthalmologic consultation […] in order to ensure full evaluation for serious complications" (Catron & Hern, 2008, p.176). After consultation, early ophthalmology follow up is important for continued monitoring and management of the disease process and associated complications (Catron & Hern, 2008).

The viral replication can follow the nerves, causing inflammation that can affect multiple structures of the eye, including: the cornea, sclera, conjunctiva, iris, retina, and/or optic nerve (Vrcek, et al., 2016). If the nasociliary nerve is affected by HZO, the rash will appear on the tip of the nose: a positive Hutchinson sign (Li, 2018). Likewise, the nasociliary nerve also involves the cornea, conjunctiva, sclera and uvea – hence the association of a positive Hutchinson sign with HZO ocular involvement (Li, 2018). Ocular involvement can range from a cutaneous rash of the eyelid, to retinal disease leading to permanent vision damage (Vrcek, et al., 2016). As there is a strong correlation between herpes zoster ophthalmicus and ocular involvement, consultation with and an urgent referral to ophthalmology are recommended (Vrcek, et al., 2016).

Associated Ocular Complications

Associated complications of herpes zoster ophthalmicus include "conjunctivitis, keratitis, iritis/uveitis, episcleritis/scleritis, extraocular motor nerve palsies, retinal perivasculitis and necrosis, and optic neuritis. The most common ocular findings of HZO are conjunctivitis seen in

35-70% of patients, uveitis in 18-47%, and keratitis in 13-75%" (Li, 2018, p.329). Artificial tears and erythromycin ophthalmic ointment may be recommended to keep the eye moist and prevent superinfection, such as in conjunctivitis (Vrcek, et al., 2016).

For HZO with keratitis, endotheliitis, or anterior uveitis, topical ophthalmic steroids are recommended to be implemented by ophthalmology management, as significant ocular adverse effects - such as cataracts and steroid-induced glaucoma - may occur (Werner, et al., 2017; Li, 2018). When using topical ophthalmic corticosteroids, a provider should prescribe the lowest effective dose in order to prevent rebound inflammation (Li, 2018). Li (2018) recommends topical ganciclovir 0.15% gel for effective management, even following a course of antivirals that had little effect. They conclude that further research is necessary to determine most effective treatments for HZO related ocular complications (Li, 2018).

Optic neuritis affects 1.9% of HZO affected eyes (Vanikiete, et al., 2018). The pathophysiology of optic neuritis is not well understood, but one such theory is that the virus replicates on the ophthalmic branch of the trigeminal nerve, spreading to the orbit and causing direct injury to the optic nerve causing vision impairment (Vanikieti, et al., 2018). Treatment for optic neuritis is a combination of corticosteroids and acyclovir x 10 days to 2 months, depending on visual compromise (Vanikieti, et al., 2018). However, visual recovery two months after antiviral treatment is usually excellent (Vanikieti, et al., 2018).

HZO can cause vascular and neural inflammation in its associated dermatome leading to arterial occlusion, or central retinal artery occlusion as a very rare complication of HZO (Ahmad, et al., 2019). Recommended treatment includes antivirals and steroids, with the use of IV acyclovir for severe HZO in these patients (Ahmad, et al., 2019).

One study by Grose (2018) found a correlation between HZO and risk for ischemic stroke: of 658 patients with HZO, 8.1% experienced an ischemic stroke within a year following their HZO diagnosis, compared to only 1.7% in those who did not have HZO. One week of antiviral treatment did not appear to reduce the risk of stroke, however the long-term antiviral treatment to reduce the risk of stroke has yet to be evaluated (Grose, 2018). The only known reduction of stroke risk related to HZO is prevention through herpes zoster vaccination, therefore preventing secondary stroke (Grose, 2018).

Self-Management

Providing instructions for patients who will be caring for their disease at home will continue to promote healing, in addition to medication therapy. They may continue their usual daily activities as tolerated (Johnson, et al., 2015). Patients should be counseled to avoid contact with the immunocompromised, pregnant patients, and those who do not have a history of chickenpox infection or vaccination (Johnson, et al., 2015). Skin care can include wet-to-dry dressings to the herpes zoster lesions with saline or Burow's solution for 30-60 minutes up to six times per day (Johnson, et al., 2015). Another topical option is calamine lotion for its antipruritic effect, although the therapeutic effect is not well supported by evidence (Johnson, et al., 2015). Proper education and instruction, in addition to medication management, can improve patient healing at home and aid in prevention of herpes zoster ophthalmicus associated symptoms.

Conclusion

- Herpes zoster ophthalmicus is the herpes zoster rash appearing along the V1 ophthalmic dermatome of the trigeminal nerve, affecting ocular and periocular structures, with 50% resulting in ocular complications.

- Vaccination against herpes zoster remains the pivotal method for preventing herpes zoster and HZO, and subsequently reducing HZO complications.
- Treatment with an antiviral within 72 hours can significantly reduce the risk of HZO associated ocular complications.
- Acyclovir, valacyclovir, and famciclovir are equally effective in the treatment of HZO.
- Oral and topical corticosteroid treatment may aid in HZO associated pain and swelling, but should be prescribed under care of an ophthalmologist.
- Consultation and referral with an ophthalmologist are essential for thorough ophthalmologic examination, management, and treatment of the patient with HZO, as many potentially severe ocular complications need specific attention.

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