Herpes Zoster Ophthalmicus—Diagnosis and Management

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Abstract
Varicella-zoster virus (VZV) infections are widely distributed in the general population. The lifetime risk of herpes zoster is estimated to be 10–20 %, increasing with age (1–4). Since herpes zoster ophthalmicus (HZO) accounts for 20 % of all locations of shingles, the lifetime risk of HZO is about 1–2 %. The management of ocular complications of VZV infection is now well codified, but sequellae still can occur, despite an armamentarium effective in limiting viral replication and its immune consequences.

Keywords
Herpes zoster ophthalmicus (HZO), keratitis, post herpetic neuralgia

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Pathophysiology: The three Phases of Varicella Zoster Virus Infection

The Primary Infection
This mostly occurs during childhood and early years of adult life. Varicella zoster virus is a highly contagious infection and spread both by respiratory droplets and direct contact. Primary infection begins with oropharyngeal infection followed by viremia, which leads to the diffusion into the skin (chickenpox) and the nervous system where VZV may ultimately establish a latent infection. Extra-cutaneous manifestations are infrequent and include neurological, pulmonary, hepatic and ocular complications. They are rare and proteiform, including conjunctivitis, episcleritis, dendritic keratitis and/or stromal non-necrotic, sclerokeratitis, anterior uveitis, or retinitis. However, most primary infections remain asymptomatic. Primary varicella infection during pregnancy can rarely result in intrauterine infection of the fetus, presenting as congenital varicella syndrome with micromelia, microcephaly, skin scarring and dysautonomic syndrome. Recently, the varicella vaccine has significantly modified the epidemiological data in countries where vaccination is usual. In US, the number of severe cases of varicella (i.e. with neurologic or pulmonary lesions) was reduced by 90 % since the vaccine was approved by the US food and drug administration (FDA) in 1995.

Latency and Clinical Quiescence
Varicella zoster virus has the capacity to become latent in the nervous system. Studies based on molecular biology techniques have shown that almost all people over 60 years are latently infected with Varicella zoster virus. Although numerous neurological tissues have been described as sites of latency for VZV, the sensory neurons of the trigeminal and spinal sensory ganglia seem particularly concerned.7

Viral Reactivations
At the biological level, they occur fairly frequently, but are most often quickly controlled by the immune system, according to the model originally described by Hope-Simpson. The clinical episodes of reactivation (shingles) occur when the immune system is not efficient enough. This explains the increased frequency of herpes zoster with age and/or with other causes of immunosuppression (immunosuppressive treatment, HIV infection, cancerous conditions).

Compared to the number of latently infected neurons, reactivation of VZV is a rare event. It occurs in the sensory ganglia of the clinically affected dermatomes. HZO corresponds to a reactivation in the trigeminal ganglia. During reactivation, a new phase of viremia can lead to atypical presentations with multifocal visceral complications, or conversely without cutaneous signs (zoster sine herpete), among which anterior uveitis or necrotizing retinitis.

Epidemiology
In countries where large-scale vaccination is not recommended, chickenpox mainly affects people under 20 years with an annual incidence estimated between 1.3 and 3.4 per 1000 people. For shingles, the annual incidence increases with age. It ranges from around 1 per 1000 people among persons 20 to 30 years to 11 per 100 in people over 70 years. Age is the major risk factor for shingles. The incidence is growing rapidly after 60 years and it reaches 50 % in patients over 85 years who had
not been previously affected.\textsuperscript{4,17} Immunosuppression is a risk factor of recurrent herpes zoster, which incidence rises from 2–4\% in the general population to 25\% among severely immunocompromised patients.\textsuperscript{6,18} The lifetime risk of herpes zoster is estimated to be 10–20\%.\textsuperscript{2} Since HZO accounts for 20\% of all locations of shingles, the risk of HZO is comprised between about 1 and 4\% over a lifetime.

**Presentation**

**General and Dermatologic Signs**

The prodromal phase of HZO usually includes an influenzalike illness with fatigue, malaise, and low-grade fever prior to the development of unilateral rash over the forehead, upper eyelid, and nose (the first division of trigeminal nerve dermatome).

Dermal pain can also precede the eruption. Subsequently, erythematous macules appear and progress to form clusters of papules and vesicles. These lesions then evolve into pustules, which quickly lyse and crust over. New blisters continue to appear over a period of 1–2 weeks, up to six weeks in some patients, see Figure 1.\textsuperscript{4,19} Necrotic skin lesions can be seen in immunocompromised or elderly patients. Lesions may resolve rapidly and completely, or may lead to a chronic course and linger for years. As with chickenpox, once crusting occurs, the lesions cease to be infectious. Scarring with hypopigmentation or hyperpigmentation may persist over a long period.

**Ocular Manifestations**

Ocular manifestations affect about 50\% of patients with HZO and can be isolated. This proportion reaches 80\% in case of appearance of the Hutchinson Sign. This latter reflects the involvement the naso-ciliary branch and is characterized by eruption on the side and the tip of the nose.\textsuperscript{20–22} Cornea

Corneal complications are seen in up to 50\% of patients with HZO. Corneal involvement patterns are multiple and may reflect different mechanisms of the disease. Residual scarring occurs in 15\% of cases.\textsuperscript{19,23} Epithelial punctate or dendritic keratitis are the most frequently encountered lesions (50\%), followed in descending order by stromal keratitis (40\%), neurotrophic keratitis and corneal muquous plaques (13\%).\textsuperscript{24} Punctate and pseudo-dendritic types of keratitis are mainly observed during the early eruptive phase. Punctate epithelial keratitis is usually peripheral and corresponds to swollen epithelial cells where VZV replicates. Pseudodendrites are the results of the coalescence of previous punctate epithelial keratitis. They are smaller and more superficially ulcerated than herpes simplex dendrites. Additionally, they typically do not show terminal bulbs.\textsuperscript{25–28} These keratitis should respond to antiviral therapy associated with lubricant eyedrops.

Subepithelial infiltrates may develop following the resolution of the epithelial keratitis, in the previously affected zones. Lesions may become chronic with a nummular pattern, corresponding to a probable immunologic stromal reaction to viral antigens.\textsuperscript{6,19} Topical corticosteroids associated with antiviral therapy are usually efficient.

**Figure 1: Herpes Zoster Ophthalmicus Vesicular Rash in the V1 Trigeminal Dermatome Sign**

**Stromal and disciform keratitis, endothelitis and keratouveitis.** These clinical pictures usually appear in the weeks or months following the eruptive stage. Descemet’s fold associated with stromal and epithelial edema may be diffused or localized with underlying keratic precipitates and anterior chamber inflammation. Concomitant trabeculitis may cause a major increase of the intraocular pressure that may become irreversible.\textsuperscript{29} Varicella zoster virus related stromal keratitis are quite similar to those related to HSV1 (see Figure 2) except that they show a higher tendency toward intense inflammation with major corneal neovascularization and subsequent lipidic keratopathy.\textsuperscript{23} All these manifestations may be the consequence of a variable immune reaction to residual viral production and should be treated with inflammation-adjusted corticosteroid therapy and antiviral drugs.\textsuperscript{1,19}

**Serpiginous keratitis** is a rare but dreadful form of Varicella zoster virus related corneal complication that presents as a peripheral ulcerative keratitis with infiltration and thinning, adjacent to a zone of limbal vasculitis. It may progress to neovascularization or perforation.\textsuperscript{79} Treatment is challenging and should be tailored to the risk of perforation. It incudes local or systemic corticosteroids, systemic antiviral therapy, autologous serum eyedrops and conservative surgical procedures such as amniotic membrane grafting.\textsuperscript{23} Corneal muquous plaques are another rare but classic HZO complication.\textsuperscript{30,31} This epithelial keratopathy occurs several months after the eruptive stage and is characterized by mucuous plaques of variable size and location, migratory in nature. It is frequently associated
and appear in average three days after the onset of the rash.33 It is accompanied by perturbations of epithelial cicatrization, leading to corneal abnormality ranging from punctate superficial keratitis to persistent epithelial defects with vascularization and perforation.34 A stepwise treatment should be considered, beginning with eviction of all potential epithelial toxicity: antiviral and preservative-containing should be withdrawn. Conversely, lubricant eyedrops are necessary to wash out all the inflammatory mediators staying at the ocular surface. If the ulceration still progresses, instillation of autologous serum eye drops or amniotic membrane graft can be used to promote healing.35 Finally, corneal perforations may be treated with cyanoacrylate tissue adhesive if small, whereas larger perforations may require surgical correction with either multilayered inlay grafting of amniotic membrane or full thickness corneal patch graft.23,36–38

Conjunctiva, Episclera, Sclera

All types of conjunctival changes may be seen in HZO, ranging from simple papillary or follicular conjunctivitis to pseudomembrane formations with cicatrizing conjunctivitis.39–41 Episcleritis and scleritis may occur soon after the eruptive stage. Scleritis is painful and usually diffuse anterior or nodular anterior in nature but can become necrotizing.39,42 Scleral thinning and atrophy may result of chronic and/or severe scleritis.4,23,24

Eyelids

While eyelid swelling with ptosis is common during the acute eruptive stage, cicatrical changes caused by dermal retraction are more prone to cause ectropion, entropion, ectopic lashes leading to corneal irritation and/or exposure keratopathy, which is more pejorative when corneal sensitivity is also impaired. Lagophthalmos may also result from associated facial nerve palsy. Numerous surgical techniques have been described to improve eyelid disorders and prevent corneal perforation.23

Neuro-ophthalmologic Manifestations

Optic neuritis can be isolated or be associated with necrotizing retinitis or other neurological signs.79,80

Post Herpetic Neuralgia

Post herpetic neuralgia (PHN) is the most common and one of the most dreadful complications of herpes zoster. It is defined as pain persisting beyond one month after rash onset or rash resolution.57,58 Pain is located in the dermatome affected by the rash. Symptoms range from allodynia (hypersensitivity to superficial stimuli) and spontaneous sensations of electric shock, stinging, itching, and burning to deep intermittent lancinating or sharp pain. Post herpetic neuralgia deeply impacts the quality of life of patients affected and may cause suicide in elderly people. The risk of PHN increases with i) the age of the patient, ii) the extension and the severity of the rash, iii) the presence of early neuralgia and the decline in corneal and cutaneous sensation.5,69–71 The prevalence of PHN decreases with time, from 30% at six weeks to 9% at one year of HZO rash.52 Pathogenesis of PHN is not completely elucidated but it may result from chronic inflammation persisting in the trigeminal pathways after the acute infection has resolved. Some studies even demonstrated granulomatous arteritis and lymphocytic infiltration around the trigeminal tract and in the mesencephalic nucleus months and even years after the clinical manifestations of herpes zoster ophthalmicus.58,53 This chronic inflammation may be associated with a low grade viral replication.53,54
**Treatment of Herpes Zoster Ophthalmicus**

The main objectives of HZO treatment are lowering the viral replication, accelerating healing, limiting severity and duration of pain and reducing the complications.

**Antiviral Drugs: Mechanisms and Practical Use**

*Acyclovir (ACV)* is the first antiviral drug which showed efficacy against VZV in randomized controlled clinical trials. It is a synthetic guanosine analogue which activation requires three phosphorylations. Once activated, it becomes a potent inhibitor of the viral DNA polymerase, a key enzyme for VZV replication.47,55

The first phosphorylation is mainly achieved by the viral thymidine kinase (TK), expressed in productively infected cells, thus conferring its selectivity to acyclovir. Nevertheless, acyclovir may also be activated to a lesser extent by cellular kinases, inducing toxicity in rapidly renewing tissues such as corneal epithelium. However, this toxicity is much lower than that of first generation, directly active, antiviral drugs. For treatment of HZO, 800 mg of oral acyclovir should be prescribed five times daily (4 g per day), allowing plasmatic concentrations of 6.9 to 0.96 µmol/l, which are active on the majority of VZV strains.56–59

According to clinical study versus placebo, for 7–10 days of treatment with this dosage significantly reduces the risk of ocular complications such as dendritic keratitis at the acute phase and the delayed inflammatory eye disease such as stromal keratitis, uveitis, episcleritis and scleritis.60–64

The treatment should be started as soon as the rash begins because any delay may increase the risk of ocular complications.65–66 Even if studies failed to demonstrate a benefit to treat patients for a longer period than seven days elderly patients, who are more prone to develop late complications, should benefit from a longer treatment.2

*Valacyclovir (VACV)* is a prodrug of ACV obtained by valine esterification, that has a 3–5 times greater oral bioavailability than oral acyclovir.66–68 Consequently, 1 g tid (3 g per day) of VACV is bio-equivalent to 800 mg five times a day (4 g per day) of Acyclovir. A multicentric randomized controlled trial has shown the clinical equivalence of VACV (3 g per day) and ACV (4 g per day) in HZO. Furthermore, this therapeutic scheme improved patient's compliance.69 Other studies indicate that VACV could be more efficient than ACV in preventing PHN for other locations of herpes zoster.47,70 Nevertheless, plasmatic concentrations obtained with 3 g per day of oral VACV do not surpass those obtained with 5 mg/kg/8h intravenous ACV.66 As a result, the oral maximal dose of VACV should not be used instead of the classic 10 mg/kg/8h intravenous ACV which is required for severe ocular complications of VZV infection (such as necrotizing retinitis) and/or in immunocompromised patients.

*Famciclovir* is another antiviral drug that can be use to treat herpes zoster. It is a prodrug form of penciclovir with improved oral bioavailability. Like ACV, its phosphorylation requires a viral kinase.47 As with other antiviral drugs, treatment should be started as soon as possible and last seven days. Some randomised and controlled studies showed that 500 mg t.i.d. or even b.i.d of famciclovir was noninferior to 4 g per day of oral aciclovir.71,72

**Antalgic Treatments: Practical Use**

Antiviral drugs and occasionally corticosteroids are the main treatments used to relieve the pain associated with the acute phase of herpes zoster. If pain is not controlled, antalgic treatments become necessary, ideally in collaboration with a physician specialized in pain control.62,73 Topical treatments, essentially based on lidocaine or capsaicin, can relieve...
superficial paresthesia (itching and burning sensations).\(^{47}\) Counter-stimulation can be a helpful adjunct at this stage.

In case of more severe pain, tricyclic antidepressants and antiepileptic drugs may be useful. The former are indicated in sharp or lancinating pain and are more effective if started promptly. The latter are mostly efficient on allodynia.\(^{47}\) Finally, opioids can be used orally or topically (block anesthesia), in resistant PHN or in case of uncontrollable pain in the acute phase.\(^{47}\)

**Corticosteroids: Practical Use**

Topical corticosteroids are used to treat inflammatory components of delayed ocular complications such as stromal keratitis, uveitis, epithelial keratitis and scleritis (see above).

Systemic corticosteroids, such as oral prednisone or intravenous methylprednisolone, are indicated for the treatment of resistant acute phase pain,\(^{74,75}\) debilitating rash, facial palsy or cranial polyneuritis\(^ {47}\) and severe inflammatory ocular complications.\(^ {1}\)

Corticosteroids should systematically be used in association with an antiviral cover, to limit the risk of viral replication enhancement, even once the rash has resolved.

**Varicella and Herpes Zoster Vaccination: Advantages and Limits**

A live attenuated vaccine (OKA strain) for varicella was approved by the FDA of the USA and incorporated into the recommended immunization schedule for children starting in 1995. It was also approved in France in 2003. The vaccine has prevented disease in 80–85 % of patients receiving the vaccine. it was also approved in France in 2000 June;107(6):1164–70.

A vaccine against herpes zoster was approved by the US FDA in 2006 for the prevention of immunocompetent individuals over 60 years of age. It also uses the OKA strain, but 14 times more concentrated than the varicella vaccine. A randomized, placebo-controlled, multicenter trial, found that the vaccine reduced by 50 % the overall incidence of herpes zoster and the incidence of PHN by 66 %.\(^ {77}\) As for chickenpox, vaccinated patients who developed herpes zoster, had milder forms of the disease.

Paradoxically, models have projected that the incidence of zoster could rise over time as a result of childhood vaccination against varicella (due to the lack of boosting of immunity in adults through exposure to children with chickenpox),\(^ {81-83}\) although empirical data to date have failed to document such an effect.\(^ {84}\) Anyway, people vaccinated against varicella during their childhood, should benefit, at least partially, from a protection against herpes zoster.

**Conclusion**

In summary, HZO can cause visual loss and debilitating post herpetic neuralgia. Early diagnosis and prompt treatment reduce the rate and the severity of these complications. In difficult cases, a multidisciplinary approach including neurologists or pain specialist can be necessary.

Herpes zoster and varicella vaccination will change the epidemiology of these frequent and ubiquitous infections.

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