Severe Complications of Herpes Zoster

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KEY WORDS
▮ *HERPES ZOSTER* ▮ *COMPLICATIONS* ▮ *CUTANEOUS* ▮ *VISCERAL* ▮ *NEUROLOGICAL* ▮ *OCULAR* ▮ *HERPES OPHTHALMICUS*

SUMMARY
The usual presentation of herpes zoster is as a self-limiting vesicular rash, often accompanied by post-herpetic neuralgia (PHN), its most common complication. However, herpes zoster can give rise to other complications, many of which have unusual presentations and serious sequelae. The incidence and burden of many of these less common complications are poorly understood. Ocular complications of ophthalmic zoster are relatively frequent but, with early antiviral therapy, need not be sight-threatening. Delayed contralateral hemiparesis is a rare complication of ophthalmic zoster that may present as stroke, temporally remote from the zoster episode. Ramsay Hunt syndrome is caused by reactivation of varicella zoster virus (VZV) involving the facial nerve; facial paralysis, ear pain and vesicles in the ear are diagnostic. Facial paralysis in the absence of vesicles may indicate zoster sine herpete, which can be mistaken for Bell's palsy. Herpetic facial palsies may respond to combination therapy with an antiviral plus steroid, but further research is needed to determine the benefit of such treatments.

Introduction

HERPES ZOSTER, CAUSED by the reactivation of latent varicella zoster virus (VZV), usually presents as a self-limiting, dermatomally localized vesicular rash, accompanied by neuropathic pain. The most common complication, particularly in the elderly, is persistent chronic pain or post-herpetic neuralgia (PHN), which can last for many months after the rash has healed. However, herpes zoster can give rise to other complications, many of which have serious sequelae. The most common complications of herpes zoster, other than PHN, include ophthalmic zoster (with delayed contralateral hemiparesis, myelitis and secondary bacterial infection), large and small vessel encephalitis, and cranial and peripheral nerve palsies (including Ramsay Hunt syndrome and Bell's palsy). Prompt identification of these complications and appropriate early treatment are essential to decrease their severity and improve outcomes.

The Incidence and Burden of Herpes Zoster Complications

- Further research is required to define the incidence and burden of herpes zoster complications, other than post-herpetic neuralgia (PHN), in different regions and populations (research need recommendation)

The most common herpes zoster complications are listed in Table 1.[1,2] In general, the incidence and burden of herpes zoster complications other than PHN are poorly studied and, consequently, reliable epidemiological information is scarce. An observational, retrospective analysis of 1401 herpes zoster cases recorded by dermatologists and general

Table 1: Complications of herpes zoster[1,2]

Cutaneous	Visceral	Neurological	Ocular
Cutaneous VZV dissemination	Neural extension of VZV infection	Post-herpetic neuralgia	Loss of corneal sensation
	Bronchitis	Aseptic meningitis	Panophthalmitis
Bacterial superinfection	Oesophagitis	Meningo-encephalitis	Keratitis
Scarring	Gastritis	Transverse myelitis	Scleritis
Cellulitis	Colitis	Ascending myelitis	Uveitis
Zoster gangrenosum	Cystitis	Peripheral nerve palsies	Chorioretinitis
Septicaemia	Myositis	Diaphragmatic paralysis	Iridocyclitis
	Pericarditis	Cranial nerve palsies	Optic neuropathy
	Pleuritis	Sensory loss	Ptosis
	Peritonitis	Deafness	Mydriasis
	Visceral VZV dissemination	Cicatricial lid scarring	Secondary glaucoma
	Pneumonia	Vestibular dysfunction	Acute retinal necrosis
	Hepatitis	Granulomatous cerebral angiitis	Progressive outer retinal necrosis
	Myocarditis		
	Pericarditis		
	Arthritis		

VZV, varicella zoster virus

STATEMENTS AND RECOMMENDATIONS*

- Further research is required to define the incidence and burden of herpes zoster complications, other than post-herpetic neuralgia (PHN), in different regions and populations (research need recommendation)
- Oral antiviral therapy should be offered to patients presenting with herpes zoster ophthalmicus (even if >72 h and up to 7 days following rash onset) to reduce ocular complications (category 2 recommendation)
- Early treatment with aciclovir in combination with prednisolone (even if >72 h and up to 7 days following rash onset) should be offered to patients with Ramsay Hunt syndrome to improve outcome (category 2 recommendation)
- The efficacy of antiviral treatment of Bell's palsy requires more extensive study (research need recommendation)

RECOMMENDATIONS AND STATEMENT CATEGORIES

Category 1

Consistent evidence from controlled clinical trials. For example, for an antiviral this would include results from at least one well-designed, randomized, clinical trial, and, in the case of laboratory studies, consistent evidence from comparative studies.

Category 2

Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytical studies (preferably from more than one centre), or from multiple time-series studies or dramatic results from uncontrolled experiments.

Category 3

Evidence from opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.

Research Need

Area in which research is warranted.

*Ratified by participants at an IHMF® Workshop in May 2006 and at the 2006 IHMF® Annual Meeting; these recommendations do not necessarily reflect the individual views of the authors or editors in this publication.

practitioners in Italy showed that the most frequently occurring zoster-related complications, excluding PHN, were ocular complications (5.7%) and facial palsy (0.6%), with the risk increasing with age (Table 2).[3]

Table 2: Complications of herpes zoster in Italian clinical practice[3]

Incidence of zoster-related complications (%)		Total (*n*=1401)
Overall		26.1
By gender:	Male	26.1
	Female	27.3
By age (years):	<35	8.9
	35–44	14.9
	45–54	23.9
	55–64	22.1
	≥65	35.1
Individual complication rates:		
	Post-herpetic neuralgia[a]	19.6
	Ocular complications	5.7
	Facial palsy	0.6
	Others	2.1

[a]Defined as pain lasting at least 30 days after the onset of skin lesions

Individuals aged >65 years had almost four times the risk of complications as those aged <35 years.[3] A separate, retrospective analysis of 859 patients with herpes zoster showed that the risk of zoster-related complications is also elevated in immunocompromised individuals and in those with trigeminal involvement of zoster rash.[2]

Interestingly, much lower rates of zoster complications were observed in the recent Shingles Prevention Study.[4] In this North American placebo-controlled vaccine study, more than 38 500 vaccinated and unvaccinated adults (aged >60 years) with herpes zoster were followed for an average of 3 years. The most frequent zoster-related complications, excluding pain, were neurological (1.4%) and ocular (0.7%) in unvaccinated individuals, and cutaneous (0.7%) and neurological (0.5%) in vaccine recipients (Table 3).[4] Ocular complications were markedly lower in this North American population than in Italian clinical practice, which could be attributed to the prompt use of antiviral drugs for the majority of patients; however, it could also reflect regional variations, differences in study selection criteria, or some other unidentified cause.

Herpes Zoster Ophthalmicus

- Oral antiviral therapy should be offered to patients presenting with herpes zoster ophthalmicus (even if >72 hours and up to 7 days following rash onset) to reduce ocular complications (category 2 recommendation)

Table 3: Rate of herpes zoster complications in the Shingles Prevention Study[4]

	ZOSTAVAX™ (*n*=19 270)		Placebo (*n*=19 276)	
Zoster-related complication	*n*	Incidence[a]	*n*	Incidence
Neurological[b]	29	0.5	82	1.4
Cutaneous	39	0.7	116	2.0
Ocular	14	0.2	40	0.7
Visceral complications	9	0.2	28	0.5
Sacral dermatome involvement	6	0.1	24	0.4

[a]Incidence per 1000 person-years (total population).
[b]Excluding pain.

Herpes zoster ophthalmicus, or ophthalmic zoster, arises from VZV reactivation in the first division of the trigeminal nerve. Ophthalmic zoster accounts for 1%–10% of all cases of herpes zoster and the rate of complications is high, with 50%–90% of patients developing some form of ocular complication if left untreated (Table 4).[5–9]

Skin lesions extending to the nose (Hutchinson's sign) are present in about one-third of patients with ophthalmic zoster, and are a powerful predictor of ocular inflammation and corneal denervation (relative risks: 3.35 [CI 95%: 1.82, 6.15] and 4.02 [CI 95%: 1.55, 10.42], respectively).[10,11] Corneal complications of ophthalmic zoster occur in approximately 65% of patients and stromal keratitis in 25%–30% of patients.[12]

TREATMENT

Evidence supporting the use of early antiviral therapy in preventing complications in ophthalmic zoster has been reviewed in a previous IHMF® Management Strategies publication and so will be summarized only briefly here.[13]

Early treatment with antiviral therapy reduces the incidence of ocular complications in ophthalmic zoster. Current IHMF® guidelines recommend that all patients with herpes zoster ophthalmicus presenting within 1 week of rash onset should be offered antiviral therapy with one of the following to reduce the incidence of ocular complications (category 2 recommendation):[13]

- Aciclovir 800 mg five times a day for 10 days;
- Valaciclovir 1000 mg three times daily for 7 days; or
- Famciclovir 500 mg three times daily for 7 days.

In placebo-controlled studies, oral aciclovir, valaciclovir and famciclovir, initiated within the first 72 h of rash onset, considerably reduce the incidence of ocular complications in patients with ophthalmic zoster compared with placebo or historical untreated controls (reviewed in a previous IHMF® Management Strategies publication).[13] A retrospective comparison of ocular outcomes in 202 treated and 121 untreated ophthalmic zoster patients in Olsted County, Minnesota, USA, showed that patients treated with antivirals had a significantly lower risk of severe visual loss or other adverse outcome at 5 or 10 years than untreated patients (2.1% versus 8.9%, respectively, P=0.009).[14] Furthermore, among treated patients, the development of serious inflammatory complications appeared to be associated with a delay in antiviral treatment, emphasizing the importance of early treatment.[14]

Delayed Contralateral Hemiparesis

Delayed contralateral hemiparesis (large-vessel encephalitis or granulomatous arteritis) is a rare, but serious, complication of herpes zoster ophthalmicus that can occur weeks or months (average 7 weeks) after the initial episode. The condition usually presents as headache and hemiplegia secondary to stroke on the side contralateral to the original rash. Diagnostically, computerized tomography (CT) or magnetic resonance imaging (MRI) show evidence of infarction,[15,16] angiography reveals inflammation and narrowing of the middle or anterior cerebral arteries, and cerebrospinal fluid (CSF) shows mononuclear cell pleocytosis (white blood cell count <100) and is polymerase chain reaction (PCR)-positive for VZV-DNA.[17]

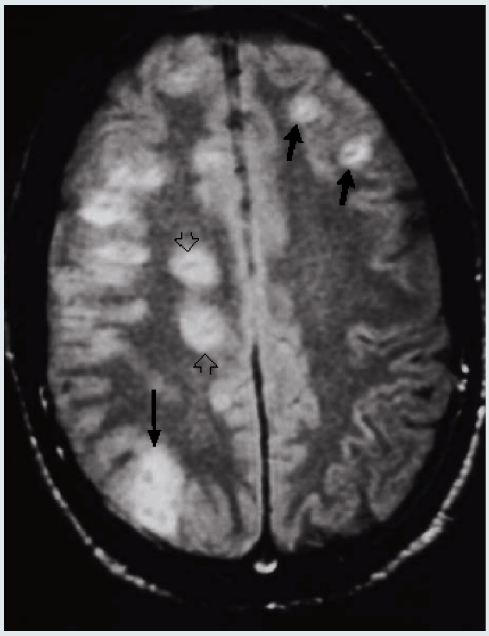
As VZV is present in the inflamed cerebral arteries, treatment with intravenous aciclovir (10–15 mg/kg three times daily for 7 days) and prednisolone (60–80 mg three times daily for 5 days) is indicated,[18] but its benefit is difficult to assess since irreversible cerebral infarction has often occurred by the time of diagnosis. Delayed contralateral hemiparesis has a mortality of 20–25% and a high probability of neurological sequelae among survivors.[15]

Chronic VZV Encephalitis

Chronic VZV encephalitis (small-vessel encephalitis) occurs almost exclusively in patients with immune suppression.[19] Onset may be several months after the herpes zoster episode, which can complicate diagnosis. In 30%–40% of patients there is no history of recent VZV skin disease.[20–22] Clinical presentation is usually subacute with headache, fever, hemiplegia, altered mental status and seizures.[19] Diagnosis by MRI scan reveals infarcts of cortical and subcortical grey and white matter (multifocal leucoencephalopathy) and small-vessel vasculitis (Figure 1).[18] CSF analysis reveals mild mononuclear pleocytosis and is usually PCR-positive for VZV-DNA.[19] The prognosis is poor, with a clinical course of progressive deterioration and death, although anecdotal reports suggest some benefit with high-dose intravenous aciclovir therapy.[23,24]

Table 4: Ocular complications in immunocompetent patients with ophthalmic zoster (adapted from Opstelten *et al.*)[9]

Area affected	Acute	Chronic
Eyelids	Swelling, vesicular rash	Ptosis, eyelid retraction
Conjunctiva	Conjunctivitis	–
Episclera/sclera	Episcleritis	–
	Scleritis	Focal scleral atrophy
Cornea	Epithelial keratitis	Neurotrophic or exposure keratopathy
Anterior chamber	Uveitis	Focal iris atrophy
	Ocular hypertension	Usually self-limiting
Rare complications	Extraocular muscle palsies	–
	Optic neuritis	Optic atrophy
	Retinal vasculitis, retinitis	Retinal atrophy



Long solid arrows: multifocal areas of infarction: a superficial wedge-shaped lesion; open arrows: deep ovoid lesions in white matter; short solid arrows: smaller lesions at junctions of grey and white matter.

Figure 1:
Magnetic resonance image of the brain of an AIDS patient with chronic VZV encephalitis.[18]

Facial Nerve Palsies (Ramsay Hunt Syndrome, Bell's Palsy)

- Early treatment with aciclovir in combination with prednisolone (even if >72 h and up to 7 days following rash onset) should be offered to patients with Ramsay Hunt syndrome to improve outcome (category 2 recommendation)
- The efficacy of antiviral treatment of Bell's palsy requires more extensive study (research need recommendation)

Herpes zoster reactivation involving the seventh cranial (facial) nerve causes herpes zoster oticus or Ramsay Hunt syndrome. Ramsay Hunt syndrome is the second most common cause of non-traumatic peripheral facial nerve paralysis after Bell's palsy, and presents as unilateral facial weakness accompanied by a vesicular rash in the external ear canal, auricle and tympanic membrane, sometimes involving the hard palate or tongue. Other symptoms include malaise and fever, sensorineural hearing loss, tinnitus, vertigo and nystagmus.

Pain associated with secondary VZV infection in the absence of a typical rash is generally referred to as zoster sine herpete. This condition is a variation of the cranial zoster, Ramsay Hunt syndrome, which can occur on its own. The frequency and significance of zoster sine herpete remains controversial.

Zoster sine herpete in the facial region may be mistakenly diagnosed as Bell's palsy (idiopathic facial palsy), especially in the early stages when vesicles may be absent. As reviewed by Gilbert *et al.*,[25] serological and PCR evidence indicates that VZV reactivation occurs in up to 56% of patients who would otherwise be diagnosed with idiopathic, or Bell's palsy (Table 5).[25–28] Zoster sine herpete can be confirmed by the presence of elevated VZV antibody titres in serum or VZV-positive PCR analysis of oropharyngeal swabs.[28] In another study, the proportions of subjects shedding VZV-DNA in saliva and VZV-DNA copies detected were similar in patients with Ramsay Hunt syndrome and in patients with zoster sine herpete.[29] Patients who develop Ramsay Hunt syndrome and those who develop zoster sine herpete have a worse prognosis for recovery than those with classic Bell's palsy.[26]

TREATMENT

There are currently no published prospective, randomized, controlled trials for the treatment of Ramsay Hunt syndrome. Data from case reports and one large retrospective study suggest that early treatment with prednisolone and aciclovir can improve recovery rates and overall prognosis. In a large retrospective study, the combination of oral prednisolone (1 mg/kg/day for 5 days, tapering over 10 days) plus either intravenous aciclovir (250 mg three times daily) or oral aciclovir (800 mg five times daily) was evaluated in 80 patients with Ramsay Hunt syndrome followed up for 6–12 months.[30] Complete recovery was observed in 75% of patients treated within the first 3 days of symptom onset ($P<0.05$), 48% treated at 4–7 days, and 30% of patients whose treatment started after 7 days.

Treatment of Bell's palsy remains controversial (see Gilbert *et al.* for review).[25] Reported recovery rates without treatment are high (80–90%),[31,32] and the few published studies show only relatively modest improvements in recovery rates versus no treatment. The two prospective, controlled studies published to date, which randomized 101 Bell's palsy patients[33] and 99 patients[34] to treatment, indicate that prednisolone (1 mg/kg/day) is more effective than oral aciclovir (2400 mg/day) alone.[33] However, the combination of aciclovir (2000 mg/day) and prednisolone (1 mg/kg/day) is more effective than prednisolone alone in preserving volitional muscle motion and nerve function.[34] More

Table 5: Summary of selected studies showing presence of VZV reactivation in patients with acute facial palsy, in the absence of vesicular rash[25–28]

Reference	Diagnostic method	Number of patients analyzed	Proportion (%) VZV-positive in absence of zoster rash
Robillard *et al.*[26]	Serology (viral titres)	1507 acute facial palsy	12
Morgan *et al.*[27]	Serology (ELISA and complement fixation)	62 acute facial palsy	56.5
		50 controls	20
Furuta *et al.*[28]	PCR (saliva)		29
	Serology (ELISA and Western blot)	142 acute facial palsy	

ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction

recent retrospective studies show that combined treatment with prednisolone (40–60 mg/day) plus either aciclovir (2000 mg/day) or valaciclovir (1000 mg/day), started within 3 days of symptom onset, leads to a 15–20% improvement in complete recovery rates, versus no or later onset treatment, the benefit being most pronounced in individuals aged >60 years.[35,36]

Conclusions

Herpes zoster can give rise to unusual complications, many of which have serious or even life-threatening sequelae. The rarity of many zoster complications prohibits epidemiological study and consequently the incidence and burden of these conditions in many regions is unknown. Ocular complications are common in untreated patients with ophthalmic zoster and can be sight-threatening, but are largely prevented with early antiviral therapy. Delayed contralateral hemiparesis may be mistaken for stroke unless it is linked to a recent history of ophthalmic zoster. Ramsay Hunt syndrome, the clinical manifestation of zoster in the facial nerve, responds well to early treatment with aciclovir plus prednisone. Up to half of patients presenting with Bell's palsy may have zoster sine herpete–VZV reactivation in the facial nerve, in the absence of a vesicular rash – which may respond to combination treatment with aciclovir or valaciclovir plus prednisolone. Further research is needed to determine the effectiveness of antiviral treatment in this disorder.

Conflicts of Interest

No conflicts of interest were declared in relation to this article.

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