Clinical Manifestations and Treatment Considerations of Herpes Simplex Virus Infection

Anthony Simmons

Herpes simplex viruses (HSV) types 1 and 2 cause infections manifesting as dermatologic, immunologic, and neurologic disorders. Some of the most important manifestations and complications of HSV infection are considered here in a neuroanatomic context. This discussion should aid in understanding the pathogenesis and, in some cases, diagnosis and management of associated HSV-related diseases. The sensory nervous system, rather than skin and mucous membranes, is the primary target of HSV infection. With the intention of extending the benefits of acyclovir, valacyclovir is now being explored in a number of HSV-related conditions. This review extends contemporary thinking about how new antiviral drugs might be put to greater therapeutic use in the future.

Worldwide, 60%–95% of the population is infected by one or more viruses of the herpes viridae family [1]. In an immunocompetent host, herpesvirus infections can often cause debilitating diseases, which may have psychological and physical sequelae in persons with frequent recurrences [2]. Herpesviruses have two unique biologic properties: the ability to invade and replicate in the host nervous system and the ability to establish a site of latent infection. The neurovirulent properties of herpes simplex virus (HSV) enable the virus to cause a disease primarily of the sensory nervous system rather than of the skin [3].

The ability of HSV to lytically infect cells of the central nervous system (CNS) is illustrated by sporadic cases of potentially fatal HSV encephalitis. In more usual circumstances, however, the peripheral nervous system is the main target of the virus [3, 4]. During primary infection, virus is transported via sensory ganglia to establish a chronic latent infection, most commonly in the trigeminal, cervical, or lumbosacral ganglia [5]. Retrograde transport of HSV along nerves and the establishment of latency are not dependent on viral replication in the skin or neurons [6] and it therefore follows that neurons can be infected in the absence of symptoms.

Periodically, HSV may reactivate from its latent state and virus particles then travel along sensory neurons to the skin and other mucosal sites to cause recurrent disease episodes. Recurrent mucocutaneous shedding of HSV can be associated with lesions or asymptomatic shedding and in either scenario is allied with a period when virus can be transmitted to a new host [7, 8].

Acyclovir has been evaluated and is widely used to treat numerous HSV-related conditions (table 1). More recently, newer nucleoside analogues have been investigated as treatments for HSV infections with the aim of building upon the success of acyclovir [9]. Valacyclovir is an oral prodrug formulation of acyclovir that provides up to 5 times greater acyclovir bioavailability [10]. Although not discussed in this review, another new medication for herpesvirus infections is famciclovir. In this review of HSV infections (predominantly in immunocompetent hosts), I discuss the thought that HSV infections are a cause of disease primarily of the nervous system rather than of skin. I also describe the many manifestations of HSV infection in a neuroanatomic framework to aid in the understanding of their pathogenesis and management. Throughout I discuss how newer antiviral compounds such as valacyclovir or famciclovir might help in the discovery of new associations between HSV and disease.

Infections of the Peripheral Nervous System

The peripheral nervous system is bilaterally symmetric and segmental in its organization, with a defined dermatome innervated by each cutaneous sensory nerve. An association between HSV and the peripheral sensory nervous system has been recognized for some time. Attributing herpetic lesions to individual dermatomes on the limbs can pose some difficulties because the distribution of individual nerve roots on the limbs is less straightforward than on the trunk, owing to rotation of the limbs during embryogenesis. The simplest way to correct for the effects of this rotation is to picture the body in the quadruped position, in which the dermatomes return to a logical, sequential arrangement (figure 1).

Recurrences of HSV infection tend to be confined to the dermatome of primary infection but do not necessarily occur at precisely the same anatomic location. In the case of perioral disease, for example, primary infection is usually inside the mouth (gingivostomatitis), whereas spread of HSV within the trigeminal ganglion means that recurrent disease is most com-

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monly associated with lesions on the lip (cold sores). Frequency of recurrence can also depend on the virus subtype (HSV type 1 or type 2) and anatomic sites of infection [11].

Infections of the Trigeminal Nerve

**Gingivostomatitis and orolabial HSV infection.** Gingivostomatitis is a symptomatic primary HSV-1 infection, usually occurring in children, and characterized by lesions in and around the oral cavity. Children are often unable to swallow because of the associated pain and may become dehydrated. In severe cases hospitalization may be required and occasionally autoinoculation can result in conjunctivitis and keratitis. Oral acyclovir treatment (acyclovir suspension 15 mg/kg 5 times/day for 7 days) started within the first 3 days of onset of symptoms shortens the duration of all clinical manifestations by about 50% [12]. Most cases of gingivostomatitis go untreated, undiagnosed, or even unrecognized; the condition is not normally considered serious.

HSV-1 commonly reactivates from the trigeminal ganglion to cause the cutaneous and mucocutaneous manifestations of recurrent facial herpes or cold sores. Cold sores are usually preceded by prodromal symptoms (e.g., tingling, pain, burning sensation, or itching at the site of reactivation), which are thought to be due to early viral replication at sensory nerve endings and in the epidermis or mucosa [13]. Early initiation of antiviral therapy is essential since the therapeutic window is narrow. Ideally, treatment should begin before a lesion is apparent [14, 15].

Cold sores are a common manifestation of HSV infection; symptomatic outbreaks are estimated to affect 20%–40% of adults [16, 17]. Although clinical symptoms are considered mild, frequently recurrent outbreaks are associated with significant morbidity [15]. The benefit of topical treatment of facial herpes outbreaks with acyclovir cream is only modest [18, 19]. Similarly, oral acyclovir appears to offer only limited efficacy on lesion healing [20]. The greater bioavailability of valacyclovir may, however, translate into an improved clinical benefit in that some lesions can be aborted by patients initiating administration of valacyclovir during the prodromal period [21]. In contrast to the equivocal efficacy of episodic oral acyclovir treatment, suppressive acyclovir (400 mg twice/day) is useful in preventing recurrent cold sores [22]. Recent data also show that oral valacyclovir, administered more conveniently as 500 mg once a day over 4 months, effectively suppresses recurrent herpes labialis outbreaks [23].

Recurrences of HSV infection in the distribution of the trigeminal nerve have greater impact in circumstances where mu-

**Table 1.** HSV infections of the peripheral sensory nervous system

<table>
<thead>
<tr>
<th>Disease manifestation</th>
<th>Acyclovir effective?</th>
<th>Potential for valacyclovir?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trigeminal nerve</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gingivostomatitis</td>
<td>+</td>
<td>Possible, pediatric formulation required</td>
</tr>
<tr>
<td>Recurrent cold sores</td>
<td>+</td>
<td>Controlled trial data available</td>
</tr>
<tr>
<td>Corneal infections</td>
<td>+</td>
<td>Possible</td>
</tr>
<tr>
<td>Facial resurfacing</td>
<td>+</td>
<td>Possible, limited data available</td>
</tr>
<tr>
<td>HSV gladiatorum*</td>
<td>?</td>
<td>Possible, limited data available</td>
</tr>
<tr>
<td>7th cranial nerve</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facial paralysis</td>
<td>+</td>
<td>Possible</td>
</tr>
<tr>
<td>Cervical and thoracic sensory nerves</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpetic whitlow</td>
<td>+</td>
<td>Possible</td>
</tr>
<tr>
<td>Nipple infection</td>
<td>+</td>
<td>Possible</td>
</tr>
<tr>
<td>Lumbosacral sensory nerves</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genital herpes</td>
<td>+</td>
<td>Controlled trial data available</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eczema herpeticum</td>
<td>+</td>
<td>Possible, anecdotal evidence</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome</td>
<td>+</td>
<td>Possible</td>
</tr>
</tbody>
</table>

* Can also affect cervical and thoracic sensory nerves.
crocuteaneous immune defenses are locally impaired. For example, severe recurrences of HSV infection may complicate laser-resurfacing surgery. Gilbert and McBurney [24], in an uncontrolled study, found that prophylactic valacyclovir (500 mg twice/day) started either the day before or the day of facial resurfacing and continued for 14 days thereafter almost completely eliminated the risk of HSV recurrence following this procedure. Further controlled trials are needed to optimize the duration and start time of therapy, together with a dosage regimen of valacyclovir [25].

**Ocular HSV infections.** HSV is a major cause of corneal scarring and visual loss, the result not only of a direct viral cytopathic effect but also an immune-mediated response [26]. In contrast to early antiviral agents, which demonstrated unacceptably high levels of systemic toxicity, acyclovir, when introduced almost 20 years ago, was shown to be highly selective for herpesviruses with low systemic toxicity. Although originally developed as an ophthalmic ointment formulation outside the United States, subsequent studies with oral acyclovir showed good intraocular and tissue penetration [27, 28]. The low systemic toxicity of acyclovir also made it an ideal candidate for long-term use in patients experiencing frequent ocular HSV recurrences.

More recently, a large controlled study investigating long-term suppressive oral acyclovir therapy for recurrences of HSV epithelial keratitis and stromal keratitis was reported [29, 30]. This randomized, placebo-controlled trial concluded that acyclovir (400 mg twice/day for 12 months) was effective in reducing the rate of recurrences, especially in persons with a prior history of HSV stromal keratitis. Continuous suppression rather than intermittent dosing was suggested as the preferred therapeutic option.

Oral valacyclovir administration provides improved bioavailability of acyclovir, suggesting that valacyclovir should be evaluated as therapy for ocular HSV infections. In a randomized study in which patients about to undergo cataract surgery received valacyclovir (1000 mg 3 times/day) or acyclovir (800 mg 5 times/day) to achieve steady-state concentrations, acyclovir concentrations in aqueous humor were about 40% of those in plasma at the same, near maximum, time point [31]. Thus, intraocular acyclovir concentrations appear to rise in parallel with plasma concentrations.

Aqueous humor concentrations of acyclovir after valacyclovir administration were almost twice those found after oral acyclovir (mean ± SD, 9.18 ± 3.17 vs. 4.59 ± 2.97 μM) and after valacyclovir dosing exceeded the value of 7.5 μM previously reported for acyclovir ophthalmic ointment [32]. While corneal tissue concentrations of acyclovir would be more relevant for assessing the potential efficacy of valacyclovir in ocular HSV disease, acyclovir penetration into ocular fluids after valacyclovir administration should ensure a substantial excess given the in vitro IC₅₀ acyclovir susceptibility range of ≤1 μM for most HSV-1 strains. Randomized controlled trials evaluating valacyclovir for the acute treatment or prevention of ocular HSV outbreaks are warranted.

**Herpetic facial paralysis.** Reactivation of HSV-1 from the geniculate ganglion has been implicated in the pathogenesis of idiopathic facial palsy or Bell’s palsy. During the acute phase of the disease, shedding of HSV-1 into saliva was detectable by polymerase chain reaction in 40% (n = 47) of cases examined [33]. Inflammation appears also to play a major role in pathogenesis of facial paralysis, and corticosteroids have been a mainstay of therapy, although views on efficacy remain controversial.

One study compared acyclovir (400 mg 5 times/day) and placebo given in combination with oral prednisone and concluded that the combination of acyclovir and prednisone was more efficacious than oral prednisone alone [34]. A recent meta-analysis of prospective trials of steroids, acyclovir, and surgery for facial palsy identified the complete absence of any adequately powered study. The analysis concluded that, from available evidence, steroids were probably effective and acyclovir (with prednisone) was possibly effective in improving facial function outcome [35]. Clearly, there is a role for antiviral therapy in the treatment of this disease; however, several issues need clarification, including the determination of the proportion of facial palsies attributable to HSV and how they can be differentiated at the outset from idiopathic (Bell’s) palsy. Further prospective trials are needed that substitute valacyclovir for acyclovir so as to offer a less cumbersome dosing schedule. Such a study might also be designed to formally assess the contribution of corticosteroids in herpetic facial paralysis.

**HSV gladiatorum.** Another cutaneous manifestation of HSV infection affecting persons who participate in contact sports (e.g., wrestling or rugby football) is herpes gladiatorum [36]. This disease may involve the trigeminal, cervical, or lumbar dermatomes and is arbitrarily considered here. Commonly, HSV-1 is inoculated via abraded skin during the “lock position” and lesions appear in 1–2 weeks. Recurrences are frequent enough to be troublesome and may be unsightly, particularly when on the face, neck, and ears. Prophylactic use of valacyclovir (500 or 1000 mg once or twice/day) during the sports season has been helpful in such cases. The higher dose regimen should be considered in cases of more recent primary acquisition of infection (unpublished data) [37, 38].

**Cervical and Thoracic Sensory Nerves Infections**

**Herpetic whitlow.** This condition, caused by HSV-1 or -2, is a painful infection of the digits seen predominantly in health care professionals [39] (figure 2). Rowe et al. [40] reported that the incidence of the disease is higher in dental personnel than in the general population [40], although their study was done before the routine use of disposable gloves in dental clinics. Another study reported that of 46 patients seen by a dental...
Hygienist was subsequently found to have herpetic whitlow [41]. Primary and recurrent herpetic whitlows are often associated with painful neuritis in the affected digit and forearm. The condition may last 3 weeks or more and patients may benefit from episodic or suppressive acyclovir. Several cases have been successfully treated with intravenous acyclovir regimens, including a 13-month-old girl [42] and a 35-year-old male dentist [43]. While there have been no appropriate controlled clinical trials with oral acyclovir or valacyclovir, the increased bioavailability of valacyclovir can be expected to offer advantages in dosage and perhaps efficacy in treating herpetic whitlow.

**HSV infection of the nipple.** Reports of HSV infection of the nipple, while extremely uncommon, most often relate to transmission of HSV from infant to mother during breast-feeding [44]. Although treatment has not been defined in the literature, there is no reason to infer that acyclovir or valacyclovir would be ineffective. If treatment of the mother were considered, dosages would be those recommended for HSV management at other anatomic sites. Transfer of acyclovir to the infant via breast milk should be recognized [45] but not be considered a contraindication to treatment when the infection is severe.

**HSV Infections of the Lumbosacral Sensory Nerves**

Of primary importance in the neuroanatomic context is how the organization of the peripheral sensory nervous system relates not only to the pathogenesis but also to the diagnosis of genital herpes. The sensory nerves arising from the sacral and lower lumbar spinal segments innervate the genitalia in males and females as well as a substantial part of the lower body, including the buttocks, thighs, and perianal mucosa (figure 1). As a consequence, when the lumbosacral ganglia become infected with HSV, lesions can occur at seemingly very different anatomic sites. The buttocks, thighs, and perianal mucosa are common sites of recurrent blistering that may not always be recognized as “genital herpes” without an understanding of the neuroanatomy involved. This is further compounded by the fact that lesions are often atypical in appearance. In order to maximize the chances of correct diagnosis and treatment, recurrent itching, burning, blistering, or erythema at any site below the waist should be regarded as genital HSV infection until proven otherwise. A swab taken from a recent eruption is essential for confirmatory diagnosis. Serologic testing may provide useful insight in diagnosing “recurrent genital discomfort” when the classic vesicular lesions of genital herpetic infections are not apparent. HSV-2 seroprevalence minimum estimates for general adult populations, suggesting genital HSV infection, are about 5%-25% in Western countries [46].

Two issues should be highlighted. First, perianal herpes does not necessarily imply direct anal inoculation of HSV given infection in lumbosacral sensory nerves. Second, symptomatic herpetic infections in the sacral dermatome may sometimes be accompanied by asymptomatic shedding from the genital mucosa. The importance of asymptomatic HSV reactivation and shedding in sexual transmission of genital herpes and public health is reviewed elsewhere [47, 48].

To extend the neuroanatomic theme further, several cases have been reported of HSV infections affecting the toes [42, 49, 50]. While it was generally assumed that autoinoculation was the source of infection, it is likely that the sacral nerves of the toes were responsible for the location of the lesions.

The role of antivirals in the management of genital herpes, which effectively includes all HSV infections below the waist, is discussed in detail elsewhere [51]. There have been several recent advances in nucleoside analogues used for the treatment of primary and recurrent genital herpes. In particular, valacyclovir was found to be as effective as acyclovir in the acute treatment of primary and recurrent infections, with the advantage of a more convenient, twice daily dosing regimen [52, 53]. In addition, valacyclovir is effective when administered once daily for suppressive management of recurrent genital herpes [54, 55]. Ongoing research initiatives for new therapeutic strategies in genital herpes focus on modification of the immune response (e.g., by therapeutic vaccination or local immune response modification) [56, 57] and on the potential for suppressive antiviral therapy to influence sexual HSV transmission risk [47].

Neonatal HSV infections, although rare, can have grave consequences. Infection occurs via three distinct routes: in utero infection, intrapartum contact, and postnatal acquisition. In each case, although the mother is the most common source of infection [3], there is usually no evidence of shedding at the time of delivery [58]. Shedding may also occur from the uterine cervix where lesions, if present, are hidden from view. Although the safety and ease of administration of intravenous acyclovir (10 mg/kg every 8 h) make it the treatment of choice for neonatal HSV infection, recent discussions have identified the ideal of prevention of infection [59]. Although it has been suggested that prophylaxis with an antiviral agent should be of-

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**Figure 2.** Herpetic whitlow, an infection of the digits, seen primarily in health care professionals.
ferred to pregnant women who have a history of genital herpes or are seropositive for HSV-2, this strategy highlights areas where information is needed on the ability of nucleoside analogues to interrupt vertical transmission of HSV infection and on the safety of prolonged exposure of the preterm fetus to antivirals.

Complications of HSV Infections of the Peripheral Sensory Nervous System

Eczema herpeticum. HSV infection is a particularly troublesome complication of atopic eczema [60] and frequently affects the head and neck if associated with autoinoculation from orolabial herpes (figure 3). Eczema herpeticum is a potentially serious and progressive disease for which suppressive therapy with acyclovir may be indicated. In some patients, recurrences are so severe that they cannot be suppressed adequately with acyclovir. Some cases have been managed successfully with suppressive valacyclovir (1000 mg twice/day) (unpublished data).

Erythema multiforme and Stevens-Johnson syndrome. Erythema multiforme, an acute, usually self-limiting inflammatory syndrome, and Stevens-Johnson syndrome (SJS) are recognized as being part of a continuum of immunologically mediated diseases of the skin. SJS is at the more severe end of the spectrum. SJS is defined as erythema multiforme associated with mucosal involvement, visceral involvement, or both, and can be fatal. Viral infections including HSV-1 are recognized as triggers for these severe cutaneous conditions [61]. The efficacy of continuous acyclovir therapy (600 mg twice/day for 6 months) in preventing outbreaks was demonstrated for recurrent erythema multiforme and in some cases resulted in complete disease remission [61, 62].

Choy et al. [63] used suppressive acyclovir (200 mg twice/day) following acute treatment (200 mg 5 times/day) at the onset of herpetic oral lesions to treat a patient with recurrent HSV-associated SJS. The interval between the onset of herpetic lesions and erythema multiforme prior to acyclovir intervention was 7–13 days. The patient was followed for 6 months (February–July) and, following acyclovir intervention, erythema multiforme did not occur in April, May, or July despite oral herpetic lesions in March, April, May, and July. Single-case statistical analysis demonstrated a reduction of the HSV lesions and erythema multiforme with acute and prophylactic acyclovir regimens. Although effective, the acyclovir regimens evaluated in erythema multiforme and SJS might be improved by the greater bioavailability of valacyclovir, which offers more convenient dosing and better control of HSV reactivation.

HSV Infections of the CNS

Herpes simplex encephalitis is a life-threatening manifestation of infection usually caused by HSV-1 [64]. In neonates, encephalitis accounts for 35% of babies with HSV infection [65]. Progressive neurologic impairment is recognized as a sequel to herpes simplex encephalitis [64]. It has been hypothesized that this occurs as a result of accumulating damage caused by frequent reactivations of HSV in the brain. This issue is being studied in adults in a randomized controlled trial by following the initial intravenous treatment of encephalitis with a prolonged course of oral suppressive valacyclovir therapy (Whitley R, personal communication). Two anecdotal reports hint at the potential of this approach with valacyclovir for prevention of further seizures [66, 67].

The possibility of an association between acute episodes of multiple sclerosis (MS) and reactivations of herpesviruses continues to be a topic of interest. HSV, Epstein-Barr virus, and human herpesvirus type 6 are all implicated [68]. In one study, HSV-1 was detected in the blood of MS patients only during acute episodes of the disease [65], suggesting that this virus reactivates during acute exacerbations of MS. However, it is unclear whether herpesvirus reactivation might precipitate the
episode. Further trials of antiviral compounds in MS patients with dosage regimens that facilitate CNS penetration of active compounds seem warranted.

Conclusions

An intimate relationship with the sensory nervous system is the common thread linking many manifestations of HSV infection. Acyclovir has been used to treat herpesvirus infections for about 20 years and knowledge regarding its clinical utility is well documented. Acyclovir is highly specific for herpesvirus-infected cells and sets the standards for efficacy and safety. The development of valacyclovir should ensure a less onerous treatment schedule and better compliance, without loss in clinical benefit, alongside maintenance of the highly acceptable safety profile of acyclovir. Future strategies for combating HSV are likely to continue through the search for effective vaccines and immune modifying agents and ideally will target the control of HSV infection at the level of the sensory nerve ganglia.

References


