Herpes simplex virus and varicella-zoster virus cause dermatitis, blepharoconjunctivitis, keratitis, uveitis, glaucoma, and retinitis. These conditions are encountered frequently by the ophthalmologist in clinical practice. It should not be overlooked that herpesviruses can also produce an extraordinary variety of neuroophthalmological signs and symptoms. What follows is an overview of the most common and important neuroophthalmological manifestations of herpesvirus infection.

Ophthalmoplegia

Palsy of an ocular motor nerve occurs occasionally after an attack of herpes zoster (Fig 1). It is exceedingly rare after chickenpox or herpes simplex infection. Virtually all cases have been associated with herpes zoster ophthalmicus, although palsy has been claimed to occur without eye involvement or skin lesions. In herpes zoster ophthalmicus, extraocular eye muscle palsy has been reported in 13, 2 14, 3 and 33% 4 of patients. In the author's experience, these incidence rates are unusually high, probably because of referral bias.

In approximately 290 cases, Edgerton 2 found the following distribution of ocular nerve palsies: nerve III (47%), IV (10%), VI (23%), and multiple nerves (20%). Sixteen cases of complete ophthalmoplegia have been recorded in the literature. 5 The onset of ocular motor palsy occurs usually 1 to 3 weeks after the eruption of the herpes zoster rash. When the third nerve is involved, there is always ptosis. The pupil is often dilated partially. After recovery, aberrant regeneration of the third nerve is rare but has been observed in some cases.

The mechanism of ocular motor nerve involvement is controversial. Edgerton 2 proposed that herpes-induced inflammation spreads from the trigeminal nerve to contiguous ocular motor nerves in the cavernous sinus. Another possibility is that herpesvirus induces an occlusive vasculitis
that causes an ischemic neuropathy. The few cases studied at autopsy have shown monocytic infiltration, demyelination, axonal degeneration, and vasculitis of vasa nervorum. Virus particles have not been demonstrated in postmortem specimens of ocular motor nerves.

The prognosis for eventual recovery from ocular motor nerve palsy is excellent. Spontaneous resolution of diplopia usually occurs in 6 to 12 months. There is no evidence that antiviral drugs or steroids hasten improvement, although these agents are often employed.

Herpesvirus Reactivation After Surgical Manipulation

Cushing observed reactivation of herpes simplex virus after nerve root section for trigeminal neuralgia. In this phenomenon, vesicles appear in areas where sensory innervation remains intact but are absent in denervated skin. This observation implies that surgical manipulation of the sensory root triggers latent virus to replicate and travel distally along intact nerve fibers. After microsurgical decompression for trigeminal neuralgia, approximately 50% of patients develop herpesvirus reactivation. Virus can also be cultured from oropharyngeal secretions in this setting.

In addition, herpesvirus reactivation can occur from spinal surgery
and aneurysm clipping,\textsuperscript{12} indicating that direct trigeminal manipulation is not required to reactivate latent herpesvirus. Indeed, herpes reactivation can complicate any type of surgery, although it is most common in neurosurgery (Fig. 2).

Many patients receive steroid medications routinely during and after major neurosurgical procedures. Steroids may enhance the likelihood of herpesvirus reactivation by producing immunosuppression. One might postulate that herpesvirus reactivation occurs because of steroid treatment rather than from physiological stress or physical manipulation. However, surgical reactivation of herpesvirus was described long before the introduction of steroids in medicine, proving that steroids play a secondary role.

Herpetic outbreak after surgery is a distressing iatrogenic complication. Patients should be treated with antiviral medications. Steroids should be discontinued, when possible.

### Herpetic Optic Neuropathy

Visual loss from herpetic optic neuropathy is rare; there are no reliable data concerning the incidence. Bilateral cases have been reported,\textsuperscript{13} although they are exceptionally rare. Onset usually occurs weeks after the development of a herpetic rash or uveitis. Impairment of acuity is often

![Figure 2](image_url)

**Figure 2.** (A) An 82-year-old man with complete right ophthalmoplegia, facial numbness, and vesicles on the nose and upper lip caused by pituitary apoplexy. (B) Magnetic resonance imaging shows hemorrhagic pituitary adenoma. The patient was thought to have herpesvirus reactivation and ophthalmoplegia caused by abrupt compression of cranial nerves from an adenoma expanding into the cavernous sinus.
fairly severe. Vitritis, retinitis, and neuretinitis are frequently present. In some patients, swelling of the optic disc can occur in conjunction with an arcuate pattern of retinal edema, necrosis, and hemorrhage that follows the nerve fiber layer (Fig 3). The fundus appearance can be normal in the retrobulbar form of herpetic optic neuropathy.

The mechanism of optic neuropathy in association with herpesvirus is uncertain. It may result from an immune-mediated inflammatory reaction in the optic nerve. In some cases, the herpesvirus may invade the optic nerve, as it does the retina. Some cases have shown evidence of granulomatous inflammation of the optic nerve, giving rise to the idea that some cases may represent a form of anterior ischemic optic neuropathy.

Ophthalmologists frequently worry about the possibility of herpesvirus infection in patients who present with acute visual loss from an optic neuropathy of unknown cause. One does not want to overlook a treatable optic neuropathy. As a general rule, optic neuropathy from herpesvirus never occurs without retinal necrosis, uveitis, or a recent herpetic skin rash. The only exceptions occur in patients who are immunocompromised.

In patients with the acquired immunodeficiency syndrome or other forms of immunocompromise, optic neuropathy from herpesvirus can occur in the setting of acute retinal necrosis syndrome. It is even possible for the optic neuropathy to precede the development of acute retinal necrosis. Such patients may present with retrobulbar visual loss. The cause of visual loss should be investigated aggressively with magnetic resonance imaging and lumbar puncture. Empirical therapy with antiherpes virus drugs should be instituted if the diagnosis is unclear.

**Ramsay Hunt Syndrome**

In 1907, Hunt described the simultaneous occurrence of unilateral facial nerve palsy and herpetic vesicles on the pinna. The skin of the
external auditory canal and central pinna is supplied by a small sensory branch of the facial nerve. The cell bodies of these fibers, located in the geniculate ganglion, are believed to harbor latent herpesvirus. Ramsay Hunt syndrome, therefore, is a rare form of herpetic skin eruption accompanied by facial paralysis. Corneal exposure is the major ocular complication of Ramsay Hunt syndrome.

In recent years, evidence has mounted that idiopathic Bell’s palsy (without herpetic vesicles) may represent a herpetic mononeuritis (varicella-zoster virus or herpes simplex virus) of the seventh nerve. There is a growing literature to support the treatment of Bell’s palsy with antiviral agents.20–24 Typical regimens are acyclovir (4,000 mg/day for a week) or valacyclovir (3,000 mg/day for a week) in combination with prednisone (1 mg/kg).

### Cerebral Vasculitis

A delayed cerebral vasculitis can occur 1 to 2 months after herpes zoster. This complication was reported by Womack and Liesegang25 in 4 of 86 patients with herpes zoster ophthalmicus. Patients may present with contralateral hemiplegia, aphasia, or confusion. Neuroimaging demonstrates a fresh infarct. Angiography usually shows multiple areas of segmental narrowing of the middle cerebral artery, anterior cerebral artery, or their branches. The posterior circulation is affected less frequently, but occipital infarct with homonymous hemianopia has been reported.26

Autopsy studies have shown that infarcts in herpetic cerebral vasculitis are caused by a focal necrotizing granulomatous angiitis. In one study, varicella-zoster virus particles were identified by electron microscopy in smooth muscle cells of the vessel wall.27

### Meningitis and Encephalitis

Primary skin infection by herpes simplex virus is accompanied by aseptic meningitis in approximately 10% of patients. The term Mollaret’s meningitis refers to a phenomenon of recurrent episodes of headache and stiff neck caused by aseptic meningitis from herpesvirus. Cerebrospinal fluid analysis shows a lymphocytic pleocytosis and herpes simplex virus type 2 DNA on polymerase chain reaction.28

Rarely, herpes simplex causes encephalitis. Any region of the brain can be affected, but there is a predilection for temporal lobe involvement. Pathological specimens show a hemorrhagic, necrotizing encephalitis with Cowdry type A inclusion bodies in neurons. These are intranuclear bodies containing viral particles.

The diagnosis of herpetic encephalitis is difficult, because cutaneous
evidence of viral infection is usually absent. The virus is difficult to culture from the cerebrospinal fluid. The enzyme-linked immunosorbent assay method may show rising titers of IgG and IgM antibodies. Molecular techniques (e.g., polymerase chain reaction amplification of viral DNA followed by restriction enzyme analysis) can provide the diagnosis.\textsuperscript{29,30} The diagnosis can also be made by brain biopsy. Because of the obvious disadvantages of brain biopsy, many neurologists recommend empirical treatment with acyclovir in all cases of unexplained encephalitis.\textsuperscript{31}

Chickenpox is complicated by central nervous system involvement in 1 of 1,000 patients. It can produce acute cerebellar ataxia, optic neuritis,\textsuperscript{32} meningitis, myelitis, delayed cerebral vasculitis, or encephalitis (Fig 4). Similar neurological sequelae can occur after attacks of herpes zoster.

\section*{Postherpetic Neuralgia}

Herpes zoster is usually heralded by the onset of pain. When the trigeminal nerve is affected, a physician may suspect temporal arteritis, until telltale vesicles appear on the skin. Pain may persist after the skin lesions have healed, especially in older patients. This pain, defined as postherpetic neuralgia, is described variously as burning, itching, aching, or lancinating. Although skin sensation is reduced, trivial stimulation provokes a painful response (dysesthesia). The mechanism of postherpetic neuralgia is not understood.\textsuperscript{33} It is believed that damaged peripheral C-fiber afferents may be abnormally sensitized or that deafferented central neurons may signal pain through increased spontaneous activity.

It is uncertain whether postherpetic neuralgia can be prevented. Nucleoside analogs such as acyclovir appear to mitigate attacks of herpes zoster and reduce acute pain. However, it is unclear whether these agents reduce the incidence of postherpetic neuralgia.\textsuperscript{34} Corticosteroids do not reduce the likelihood of developing postherpetic neuralgia.\textsuperscript{35}

Patients with postherpetic neuralgia can be incapacitated by pain. Treatment with tricyclic antidepressants (amitriptyline) is beneficial in most patients. Capsaicin cream is also helpful, although it produces intolerable burning on application in many patients. Stabbing pain may respond to anticonvulsants (carbamazepine).

\section*{Monkey Herpes B Virus}

Cercopithecine herpes B virus is widespread in Old World monkey colonies. The disease can be communicated to humans. More than a dozen fatalities have been reported in the medical literature. The disease should be suspected in any patient with evidence of herpes infections and a history of occupational exposure to monkeys (e.g., zookeepers, laboratory researchers).
The most recent death from this virus occurred in 1997. A 22-year-old scientist felt a drop splash into her right eye while transferring a rhesus monkey in a cage. Ten days later, the eye became injected. She consulted an ophthalmologist, who observed no dendritic corneal lesions. Two weeks after exposure, she developed nausea, photophobia, and worsening right retroorbital pain. A vesicular rash erupted in the right V₁ and V₂ distribution. Despite treatment with ganciclovir, the patient developed paralysis and respiratory failure resulting in death 6 weeks after exposure. The diagnosis of cercopithecine herpes B virus infection was confirmed by Western blot analysis of serum.

Figure 4. (A) A 20-year-old college student with blindness, urinary retention, weakness, and confusion 2 weeks after an attack of chickenpox. (B) A T₂-weighted magnetic resonance imaging scan shows lesions scattered throughout the white matter. (C, D) Bilateral optic disc edema. Visual acuity was hand motions OD, no light perception OS. The patient was treated with intravenous acyclovir and hospitalized for supportive care. After 3 months, he made a complete recovery.
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