CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, July 2001, p. 850–851 Vol. 8, No. 4
1071-412X/01/$04.00+0 DOI: 10.1128/CDLI.8.4.850–851.2001

Spinal Cord Involvement in Uncomplicated Herpes Zoster

ISRAEL STEINER,[1]* BETTINA STEINER-BIRMANNS,[1] NETTA LEVIN,[1] KLILA HERSHKO,[2] ISABELLE KORN-LUBETZKI,[3] AND IFTAH BIRAN[1]

Departments of Neurology[1] and Dermatology,[2] Hadassah University Hospital, and The Neurological Service, Bikur Cholim Hospital,[3] Jerusalem, Israel

Received 28 March 2001/Accepted 9 May 2001

We prospectively evaluated herpes zoster patients during the acute phase of the disease for central nervous system involvement. Of 24 patients with spinal zoster, 13 (54%) had spinal cord abnormality, which was asymptomatic in 12 of the 13. Age but not lack of acyclovir treatment was associated with such involvement. In all but 2, neurological involvement resolved within 6 months. Although the mechanism responsible for the neurological abnormalities is unknown, findings may support the hypothesis that zoster is associated with spread of viral infection into the spinal cord and therefore support the possibility that zoster is due to active viral replication in the ganglion.

The three neurotropic herpes viruses, herpes simplex virus type 1 (HSV-1), HSV-2, and varicella-zoster virus (VZV), reside latently in peripheral sensory ganglia (PSG) and reactivate to produce recurrent mucocutaneous disease (for reviews, see references 2, 4, and 7). However, although they belong to the same family of viruses and colonize the same tissue, there are major clinical differences between the reactivation of HSV-1 and -2 and that of VZV. Unlike cold or genital sores, herpes zoster is usually a single episode affecting the entire dermatome and is associated with severe sensory symptomatology and sometimes with short or even long-lasting sensory abnormalities. Moreover, while HSV-1 and -2 reactivations are usually not associated with meningitis, herpes zoster is accompanied by cerebrospinal fluid pleocytosis in at least a third of patients (3). The site of latency for HSV-1 in PSG is ganglion cells. However, some data suggest that in addition to neurons, nonneuronal cells also harbor the latent VZV genome (1, 6). Based on these differences, several groups proposed that nonneuronal cells might give rise to reactivated VZV, leading to active viral replication, propagation of infectious viral particles throughout the ganglion, and spread of the infection via nerve axons to the entire respective dermatome and the meninges. (5). On the other hand, HSV-1 reactivation is associated with either restricted or no viral replication in the ganglion and spread of viral particles to the cutaneous distribution of a single neuron.

If indeed the cause of herpes zoster is infectious viral particles that spread from the ganglion into the periphery, one might expect a similar spread orthodromically from the ganglion into the spinal cord in cases of spinal herpes zoster and into the brain stem in cranial herpes zoster. We therefore examined central nervous system (CNS) involvement in patients with uncomplicated herpes zoster.

Between the years 1997 and 1999, we enrolled all patients who presented to the neurological and/or dermatological departments and outpatient clinics in our institute, within the first week of herpes zoster. Patients underwent a thorough neurological examination and were followed up for at least 6 months after the herpes zoster episode by the same neurologist at time intervals of 1 to 2 months. In all patients, diagnosis of zoster infection was confirmed by histological evaluation and/or PCR for VZV nucleic acids in the infected lesion. Clinical evidence for CNS involvement included long tract signs, sensory level, pyramidal limb weakness, and/or sphincter dysfunction. Patients who presented more than 1 week after initiation of zoster symptoms and patients with a history of a previous neurological disorder were excluded from the study.

Twenty-eight patients (15 females) with an age range of 22 to 83 years (median, 66) were studied. Only four patients were immuno compromised. A history of chicken pox was available in 14 patients. In all but one, the episode was the first herpes zoster infection. Infection involved thoracic dermatomes in 16 patients, cervical dermatomes in 4, lumbar dermatomes in 3, and sacral dermatomes in 1. The ophthalmic branch of the trigeminal nerve was affected in 4 patients. Thirteen patients were treated with acyclovir.

None of the four patients with ophthalmic zoster had brain stem involvement. Thirteen patients (46.5% of the entire group) had evidence of spinal cord involvement. Symptoms and signs for such cord dysfunction, beside brisk deep tendon reflexes present in all 13 patients and limb weakness in 6, included at least one of the following: long tract signs in 12 patients, sensory level at the segment supplying the cutaneous distribution of the zoster rash in 6 patients, and sphincter abnormalities consisting of urinary retention and constipation in 2 patients

Clinically symptomatic spinal cord disease was evident in only one patient, a 67-year-old immunocompetent male who developed a D7 herpes zoster on the right side complicated by mild paraparesis with urinary retention. It resolved within 2 weeks. Four months later he was left with only a right extensor plantar response. Two patients had symptomatic meningitis. Age (68 versus 58 years), but not lack of acyclovir treatment, was associated with increased incidence of CNS involvement.

In all patients neurological signs and symptoms faded within a half year of follow up. In 11, all signs of cord involvement resolved within 4 months. In the remaining two, an extensor

* Corresponding author. Mailing address: Laboratory of Neurovirology, Department of Neurology, Hadassah University Hospital, P.O. Box 12000, Jerusalem, 91120, Israel. Phone: 972/2/6776952. Fax: 972/2/6437782. E-mail: isteiner@md2.huji.ac.il.

plantar response persisted but was not accompanied by motor weakness.

Thus, of the 24 patients with herpes zoster affecting spinal dermatomes, 13 (54%) had clinical evidence of disease, usually subtle, asymptomatic, and transient, since only one patient developed paraparesis, involving the respective spinal segment of the ganglion which gave rise to VZV reactivation. In all, the spinal cord signs were noted during the active cutaneous viral infection and not at a delayed period. None of the four patients with ophthalmic zoster had evidence of brain stem abnormality during the acute infection. Though the number of patients is small, this result may suggest that brain stem tissue has the ability to limit VZV spread more effectively than the spinal cord.

The mechanism responsible for the spinal cord involvement in cutaneous zoster is unknown and could be either immune mediated or infectious. However, the occurrence of the neurological signs during the active skin disease and presence of the sensory level at the segment supplying the cutaneous distribution of the zostiform rash favors the second alternative. Therefore, these findings may support the hypothesis (5) that during reactivation, herpes zoster is accompanied by release of infectious viral particles that enable spread of the virus to the entire ganglion and infection of many neurons culminating not only in a peripheral disease within the distribution of the entire PSG but also in disease of the spinal cord within the distribution of the same segment. Unlike HSV-1 reactivation, where reactivation takes place within one neuron and is therefore likely to evade the host immunological response, VZV reactivation may involve spread of virus throughout the tissue (and can be altered by the immune response), and this may lead to extension of the infectious process in both directions: the periphery and the spinal cord.

REFERENCES

1. **Croen, K. D., J. M. Ostrove, L. J. Dragovic, and S. E. Straus.** 1988. Patterns of gene expression and sites of latency in human nerve ganglia are different for varicella-zoster and herpes simplex viruses. Proc. Natl. Acad. Sci. USA **85:** 9773–9777.
2. **Gilden, D. H., B. K. Kleinschmidt DeMasters, J. J. LaGuardia, R. Mahalingam, and R. Cohrs.** 2000. Neurologic complications of the reactivation of varicella-zoster virus. N. Engl. J. Med. **342:**635–645.
3. **Gold, E.** 1966. Serologic and virus isolation studies of patients with varicella or herpes zoster infections. N. Engl. J. Med. **274:**181–185.
4. **Kennedy, P. G. E.** 1987. Neurological complications of varicella-zoster virus. p. 177–208. *In* P. G. E. Kennedy and R. T. Johnson (ed.), Infections of the nervous system. Butterworths, London, United Kingdom.
5. **Kennedy, P. G. E., and I. Steiner.** 1994. A molecular and cellular model to explain the differences in reactivation from latency by herpes simplex and varicella-zoster viruses. Neuropathol. Appl. Neurobiol. **20:**368–374.
6. **Meier, J. L., R. P. Holman, K. D. Croen, J. E. Smialek, and S. E. Straus.** 1993. Varicella-zoster transcription in human trigeminal ganglia. Virology **193:**193–200.
7. **Steiner, I.** 1996. Human herpes viruses latent infection in the nervous system. Immunol. Rev. **152:**157–173.