Journal of NeuroVirology, 9: 404–407, 2003

ISSN: 1355-0284 print / 1538-2443 online
DOI: 10.1080/13550280390201722

Taylor & Francis
Taylor & Francis Group

Clinical Report

Chronic varicella-zoster virus ganglionitis—a possible cause of postherpetic neuralgia

Donald H Gilden,[1,2] Randall J Cohrs,[1] Anthony R Hayward,[3,4] Mary Wellish,[1] and Ravi Mahalingam[1]

Departments of [1]Neurology, [2]Microbiology, [3]Pediatrics, and [4]Immunology, University of Colorado Health Sciences Center, Denver, Colorado, USA

Postherpetic neuralgia (PHN) is dermatomal distribution pain that persists for months to years after the resolution of herpes zoster rash. The cause of PHN is unknown. Herein, we report clinical, molecular virological, and immunological findings over an 11-year period in an immunocompetent elderly woman with PHN. Initially, blood mononuclear cells (MNCs) contained varicella-zoster virus (VZV) DNA on two consecutive occasions. Random testing after treatment with famciclovir to relieve pain did not detect VZV DNA. However, the patient was reluctant to continue famciclovir indefinitely and voluntarily stopped drug treatment five times. Pain always recurred within 1 week, and blood MNCs contained many, but not all, regions of the VZV genome on all five occasions. Immunological analysis revealed increased cell-mediated immunity to VZV. Chronic VZV ganglionitis–induced PHN best explains the recurrence of VZV DNA in MNCs whenever famciclovir was discontinued; the detection of only some regions of the viral genome in MNCs, compared to the detection of all regions of the VZV genome in latently infected ganglia; the increased cell-mediated immunity to VZV; and a gratifying clinical response to famciclovir. The presence of fragments of VZV DNA in MNCs likely represents partial degradation of viral DNA in MNCs that trafficked through ganglia during productive infection. *Journal of NeuroVirology* (2003) **9,** 404–407.

Keywords: chronic VZV ganglionitis; postherpetic neuralgia

Case report

In December 1990, a 61-year-old woman developed pain over the scalp behind the right ear that extended onto the entire face to just below the mandible. One day later, rash developed in the right ear as well as on the scalp above and behind the ear. One week later, she developed peripheral facial paralysis, loss of taste, and exquisite sensitivity to noise, all on the right side. She was diagnosed with zoster (shingles), and in January 1991, was treated with acyclovir, 800 mg five times daily for 1 week. Two weeks after rash, her grandchildren developed chickenpox. Although her rash resolved and complete facial function returned in 3 months, she continued to experience severe pain as well as increased sensitivity to noise in the right ear and to touch on the right face. Treatment of pain with amitriptyline, 25 mg at night, provided some relief, but she discontinued the drug because it made her lethargic.

At the time of initial neurological evaluation 1 year after the onset of zoster (December 1991), the patient complained of relentless severe pain on the scalp behind the right ear. Except for allodynia on the scalp behind the right ear, the skin and neurological examination was normal. She was diagnosed with postherpetic neuralgia (PHN). Initially, she was treated with topical 16% menthol (Aspercreme) and 10% trolamine salicylate (Flexall 454), which provided partial relief. However, continued pain affected her ability to work as well as other activities of daily living. Carbamazepine, 200 mg

Address correspondence to Dr. Donald H. Gilden, Department of Neurology, Mail Stop B-182, 4200 E. 9th Avenue, Denver, CO 80262, USA. E-mail: don.gilden@uchsc.edu

The current address of AR Hayward is currently at the Division of Clinical Research, National Center for Research Resources, National Institutes of Health, Bethesda, Maryland, USA.

This work was supported in part by Public Health Service grants NS 32623 and AG 06127 from the National Institutes of Health. The authors thank Marina Hoffman for editorial review and Cathy Allen for preparing the manuscript.

Received 13 February 2003; revised 10 March 2003; accepted 12 March 2003.

Table 1 Detection of VZV DNA in blood MNCs of a patient with PHN over a 9-year period

Date	*VZV DNA in MNCs*
12-03-91	+[a]
01-07-92	+[a]
03-11-92	~
03-20-92	~
05-18-92	~
07-07-92	+[b]
07-11-92	~
07-16-92	~
07-27-92	~
08-17-92	~
09-02-92	~
09-11-92	~
03-15-93	~
05-06-93	+[b]
07-28-93	+[b]
08-25-93	~
09-23-93	+[b]
12-06-93	+[b]
06-27-95	~
01-07-00	~

[a]Before starting famciclovir.
[b]After discontinuing famciclovir.

three times daily, did not provide significant pain relief.

In December 1991 and January 1992, varicella-zoster virus (VZV) DNA was detected in the patient's blood mononuclear cells (MNCs) (Table 1), and she was started on famciclovir 500 mg four times daily. Within 1 week, her pain decreased and completely disappeared within 1 month. She was advised to continue famciclovir indefinitely at a dose of 750 mg daily. She has been followed clinically for 11 years. When she takes famciclovir, she is always pain-free. On five occasions, she voluntarily discontinued famciclovir, and pain recurred every time, usually within a few days, and VZV DNA was found in her blood MNCs. In contrast, analysis of blood MNCs on 14 other occasions while she was taking famciclovir and pain-free revealed no VZV DNA (Table 1). Over a 9-year period, blood MNCs were examined 21 times; VZV DNA was detected seven times, twice before the patient started famciclovir, and five times after voluntarily discontinuing the drug. MNCs that contained VZV DNA were tested for two or three VZV regions. Of the seven times that VZV DNA was found, one region was usually detected; on one occasion, two VZV regions were found (Table 2). Once in 2002, the patient again discontinued famciclovir and pain recurred. She was advised to restart famciclovir, which provided complete relief.

Special studies

In January 2000, an enzyme-linked immunosorbent assay of the patient's serum (Forghani, 1986) detected VZV-specific immunoglobin G (IgG), but not IgM, antibody. Polymerase chain reaction (PCR) using primers specific for VZV genes 28, 29, 62 (Mahalingam *et al*, 1992) and 40 (Mahalingam *et al*, 1995) was carried out 21 times during a 11-year period (Table 1) to detect VZV DNA in blood MNCs. In February 2000, cell-mediated immunity to VZV was assessed based on the number of blood MNCs that proliferate in response to VZV antigen as described (Hayward *et al*, 1994). More than one proliferating T cell was found in every 12,500 cells cultured, consistent with increased cell-mediated immunity to VZV (Hayward *et al*, 1991).

Table 2 Analysis of VZV-specific genes in MNCs of a patient with PHN

	Gene		
Date	*28*	*29*	*40*
12-03-91	nd	nd	+
01-07-92	+	~	+
07-07-92	nd	+	~
05-06-93	nd	~	+
07-28-93	nd	~	+
09-23-93	nd	+	~
12-06-93	nd	~	+

nd = not done.

Discussion

Herein, we report the clinical, molecular virological, and immunological findings over an 11-year period in an immunocompetent elderly woman who developed the Ramsay Hunt syndrome (zoster oticus and peripheral facial palsy) followed by PHN. The Ramsay Hunt syndrome is caused by VZV, evidenced by the characteristic vesicular rash on the ear or palate from which VZV can be isolated, as well as by a fourfold rise in antibody to VZV or the presence of VZV DNA in auricular skin, in blood MNCs (Terada *et al*, 1998), in middle ear fluid (Murakami *et al*, 1996), in saliva (Furuta *et al*, 2000), and in saliva and tears (Hiroshige *et al*, 2002) of patients with facial palsy (reviewed in Sweeney and Gilden, 2001). The development of zoster on any part of the body in an elderly patient is associated with a 40% to 44% risk of PHN (Brown, 1976). Our patient was no exception. When first seen, the patient tested positive for VZV DNA in her blood MNCs on two consecutive occasions (Table 1). We considered the possibility that her PHN was secondary to chronic VZV ganglionitis (see below) and treated her with famciclovir. Within days, her pain was relieved and subsequent testing of blood MNCs at random intervals was always negative for VZV DNA. However, when our patient voluntarily discontinued famciclovir, pain always recurred within 1 to 3 days, and blood MNCs became positive for VZV DNA.

The detection of VZV DNA in MNCs was first reported in immunocompromised children with zoster (Feldman *et al*, 1977). Later, Southern and dot-blot hybridization detected VZV DNA in MNCs for 1 to

23 days after rash in immunocompetent patients with zoster (Gilden *et al*, 1987), and *in situ* hybridization identified VZV DNA in ~1/100,000 MNCs up to 38 days after rash in these patients (Gilden *et al*, 1988). Immunoprecipitation also demonstrated the presence of the VZV late glycoproteins gpI and gpIV in MNCs in a zoster patient 2 weeks after rash (Vafai *et al*, 1988). The presence of VZV DNA and antigens in MNCs from zoster patients indicates that these cells are productively infected, although infection appears to be short-lived.

The mechanism of PHN remains unknown, although VZV-specific DNA (Vafai *et al*, 1988; Devlin *et al*, 1992; Mahalingam *et al*, 1995) and VZV-specific late glycoproteins (Vafai *et al*, 1988) have been detected in MNCs of PHN patients 1 to 8 years after zoster. In contrast, VZV DNA has been detected in MNCs only up to 38 days after zoster in patients who did not develop PHN, and not at all after disappearance of zoster pain (Gilden *et al*, 1988). Because one study reported the detection of VZV DNA in blood MNCs of two elderly sick individuals without a history of zoster (Devlin *et al*, 1992), a more extensive study was conducted of zoster patients with and without PHN; in fact, PCR analysis revealed VZV DNA in MNCs up to 8 years after zoster in 11/51 patients with PHN, but not in MNCs of 19 zoster patients without PHN who were analyzed 1 to 31 years after zoster, or in any of 11 elderly age- and gender-matched subjects with no history of zoster (Mahalingam *et al*, 1995). Further evidence that longstanding radicular pain reflects a chronic ganglionitis came from the detection of VZV DNA in both blood MNCs and cerebrospinal fluid of patients with zoster sine herpete (pain without rash) (Gilden *et al*, 1994; Terada *et al*, 1998).

Although both Mainka *et al* (1998) and Schunemann *et al* (1999) did not detect VZV DNA or RNA in MNCs of 16 PHN patients, we studied a larger number of patients over a longer period of time, including our patient reported here in whom VZV DNA was detected in MNCs on multiple occasions. Based on cumulative data from ours and other laboratories (Gilden *et al*, 1988, 1994; Vafai *et al*, 1988; Mahalingam *et al*, 1995; Terada *et al*, 1998), we suggest that the detection of VZV DNA in MNCs of PHN patients likely reflects the trafficking of MNCs, particularly antigen-presenting cells, through productively infected ganglia where viral persistence accounts for the continuous pain. Such a notion is supported by the detection of several, but not all, regions of the VZV genome in MNCs at different times in our patient compared to the detection of every region of the VZV genome in latently infected human ganglia (Mahalingam *et al*, 1990).

Immunological studies of our patient's serum revealed antibody to VZV, normally found in serum of elderly adults. More importantly, our patient exhibited heightened cell-mediated immunity to VZV after years of PHN, consistent with repeated exposure to virus (Hayward *et al*, 1991). The notion that exposure to VZV might boost specific immunity was first proposed by Hope-Simpson (1965). A recent case-controlled study indicated that reexposure of adults to people with varicella or zoster protects latently infected individuals against zoster (Thomas *et al*, 2002). Given the sporadic presence of virus in blood MNCs that followed her intermittent discontinuation of famciclovir, the patient's increased cell-mediated to VZV is not unexpected.

Finally, the gratifying response of our patient to famciclovir further supports the notion that a chronic VZV ganglionitis causes PHN. On the other hand, not all PHN patients respond to oral famciclovir, possibly due to insufficient doses or to a suboptimal route of administration. With respect to the later, two patients with zoster sine herpete treated at our institution with oral acyclovir and famciclovir improved only after acyclovir was given intravenously (Gilden *et al*, 1994).

References

Brown GR (1995). Herpes zoster: correlation of age, sex, distribution, neuralgia and associated disorders. *South Med J* **69:** 576–578.

Devlin ME, Gilden DH, Mahalingam R, Dueland AN, Cohrs R (1992). Peripheral blood mononuclear cells of the elderly contain varicella-zoster virus DNA. *J Infect Dis* **165:** 619–622.

Feldman S, Chaudary S, Ossi M, Epp E (1977). A viremic phase for herpes zoster in children with cancer. *J Pediatr* **91:** 597–600.

Forghani B (1986). Varicella-zoster virus antibody. In: *Methods of enzymatic analysis*, Vol. 10, 3rd ed. Bergmeyer H (ed). Weinheim: Verlag Chemic, pp 267–284.

Furuta Y, Ohtani F, Mesuda Y, Fukuda S, Inuyama Y (2000). Early diagnosis of zoster sine herpete and antiviral therapy for the treatment of facial palsy. *Neurology* **55:** 708–710.

Gilden DH, Devlin M, Wellish M, Mahalingam R, Huff C, Hayward A, Vafai A (1988). Persistence of varicella-zoster virus DNA in blood MNCs of patients with varicella or zoster. *Virus Genes* **2:** 299–305.

Gilden DH, Hayward AR, Krupp J, Hunter-Laszlo M, Huff JC, Vafai A (1987). Varicella-zoster virus infection of human mononuclear cells. *Virus Res* **7:** 117–129.

Gilden DH, Wright RR, Schneck SA, Gwaltney JM Jr, Mahalingam R (1994). Zoster sine herpete, a clinical variant. *Ann Neurol* **35:** 530–533.

Hayward A, Levin M, Wolf W, Gilden DH (1991). Varicella zoster virus specific immunity following herpes zoster. *J Infect Dis* **163:** 873–875.

Hayward AR, Zerbe GO, Levin MJ (1994). Clinical application of responder cell frequency estimates with four years of follow up. *J Immunol Methods* **170:** 27–36.

Hiroshige K, Ikeda M, Hondo R (2002). Detection of varicella zoster virus DNA in tear fluid and saliva of patients

with Ramsay Hunt syndrome. *Otol Neurotol* **23:** 602–607.

Hope-Simpson RE (1965). The nature of herpes zoster: a long-term study and a new hypothesis. *Proc R Soc Med* **58:** 9–20.

Mahalingam R, Wellish M, Brucklier J, Gilden DH (1995). Persistence of varicella-zoster virus DNA in elderly patients with postherpetic neuralgia. *J Neuro Virol* **1:** 130–133.

Mahalingam R, Wellish M, Wolf W, Dueland AN, Cohrs R, Vafai A, Gilden DH (1990). Latent varicella zoster virus DNA in human trigeminal and thoracic ganglia. *N Engl J Med* **323:** 627–631.

Mahalingam R, Wellish MC, Dueland AN, Cohrs RJ, Gilden DH (1992). Localization of herpes simplex virus and varicella zoster virus DNA in human ganglia. *Ann Neurol* **31:** 444–448.

Mainka C, Fuss B, Geiger H, Hofelmayr H, Wolff MH (1998). Characterization of viremia at different stages of varicella-zoster virus infection. *J Med Virol* **56:** 91–98.

Murakami S, Mizobuchi M, Nakashiro Y, Doi T, Hato N, Yanagihara N (1996). Bell's palsy and herpes simplex virus: identification of viral DNA in endoneurial fluid and muscle. *Ann Intern Med* **124:** 27–30.

Schunemann S, Mainka C, Wolff MH (1999). No acute varicella-zoster virus replication in peripheral blood mononuclear cells during postherpetic neuralgia. *Acta Virol* **43:** 337–340.

Sweeney CJ, Gilden DH (2001). Ramsay Hunt syndrome. *J Neurol Neurosurg Psychiatry* **71:** 149–154.

Terada K, Niizuma T, Kawano S, Kataoka N, Akisada T, Orita Y (1998). Detection of varicella-zoster virus DNA in peripheral mononuclear cells from patients with Ramsay Hunt syndrome or zoster sine herpete. *J Med Virol* **56:** 359–363.

Thomas SL, Wheeler JG, Hall AJ (2002). Contacts with varicella or with children and protection against herpes zoster in adults: a case-control study. *Lancet* **360:** 678–682.

Vafai A, Wellish M, Gilden DH (1988). Expression of varicella-zoster virus in blood mononuclear cells of patients with postherpetic neuralgia. *Proc Natl Acad Sci U S A* **85:** 2767–2770.