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Short Communication

Neurological complications of varicella-zoster virus in human immunodeficiency virus–infected patients: Changes in prevalence and diagnostic utility of polymerase chain reaction in cerebrospinal fluid

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Neurological complications caused by varicella-zoster virus (VZV) were diagnosed in 13 human immunodeficiency virus (HIV)–infected patients in our hospital. There was a favorable influence of highly active antiretroviral therapy (HAART) in the prevalence of these disorders among acquired immunodeficiency syndrome (AIDS) patients: Since 1996, only 1 of 961 AIDS patients had VZV neurological disease, compared to 9 of 1088 patients before that year ($P = .02$). Polymerase chain reaction (PCR) detected VZV DNA in cerebrospinal from 4 of 5 patients with VZV neurological disease, and from 2 of 130 HIV-infected patients with other neurological diseases (sensitivity 0.8, specificity 0.98 [95% confidence intervals 0.45–1 and 0.96–1, respectively], positive predictive value 0.94). *Journal of NeuroVirology* (2003) **9,** 129–135.

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A wide spectrum of neurological complications of varicella-zoster virus (VZV) have been reported in human immunodeficiency virus (HIV)–infected patients, including encephalitis (Amlie-Lefond *et al*, 1995; Gray *et al*, 1992; Kleinschmidt-DeMasters *et al*, 1996; Mouligner *et al*, 1995; Rosenblum, 1989), aseptic meningitis (Glesby *et al*, 1995), optic neuritis (Franco-Paredes *et al*, 2002), myelitis (Devinski *et al*, 1991; Gilden *et al*, 1994), and meningoradiculitis (Snoeck *et al*, 1994). VZV encephalitis is actually a vasculopathy that affects either large or small cerebral arteries and sometimes both (Amlie-Lefond *et al*, 1995; Kleinschmidt-DeMasters *et al*, 1996). Large artery disease produces large-sized ischemic and hemorrhagic infarctions (Kleinschmidt-DeMasters *et al*, 1996). Vasculopthy is also a pathologic finding in VZV myelitis. Most reports of VZV neurological disease included patients who were not receiving highly active antiretroviral treatment. Little is known about the impact of new therapies on the occurrence and clinical manifestations of the neurological complications of VZV.

Diagnosis of these disorders is difficult during patient's life. The presence of herpetic skin lesions is often the clue to suspect the diagnosis, but neurological complications may occur before the cutaneous eruption (Devinski *et al*, 1991; Gómez-Tortosa *et al*, 1994), or even without it (Manian *et al*, 1995; Meylan *et al*, 1995). Recently, demonstration of VZV DNA in cerebrospinal fluid (CSF) using polymerase chain reaction (PCR) has been shown as a potentially diagnostic aid (Gilden *et al*, 1994; Iten *et al*, 1999; Puchhammer-Stöckl *et al*, 1991), but reports based on series of HIV-infected patients have given conflicting results (Burke *et al*, 1997; Cinque *et al*, 1997).

We have reviewed the cases of all HIV-infected patients diagnosed of a neurological disease due to VZV

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Table 1 Patient characteristics, clinical presentation, CSF findings, and course

Patient	*Sex/age*	*CDC stage/CD4 per mm^3*	*VZV skin lesions (days before neurological presentation)*	*Neurological presentation*	*CSF analysis*	*Treatment (days)*	*Course (survival)*
1	M/18	C3/50	Thoracic (2)	Aseptic meningitis	CELLS: 200 LYM PROT: 2.26 g/L GLUC: 68 mg/dl PCR: negative	IV acyclovir (10)	Complete resolution (74 months, alive)
2	F/26	C2/521	Thoracic (2)	Aseptic meningitis	CELLS: 29 LYM PROT: 0.54 g/L GLUC: 39 mg/dl PCR: VZV	IV acyclovir (14)	Complete resolution (24 months, alive)
3	M/28	A3/142	Lumbar (L5) (7)	Aseptic meningitis	CELLS: 156 LYM PROT: 1.17 g/L GLUC: 51 mg/dl PCR: VZV	IV acyclovir (10)	Complete resolution (48 months, alive)
4	M/33	A3/200	Lumbar (L1) (3)	Aseptic meningitis	CELLS: 220 LYM PROT: 1.36 g/L GLUC: 41 mg/dl PCR: *ND*	IV acyclovir (10)	Complete resolution (90 months, alive)
5	M/49	C3/5	Multidermatomal thoracic (11)	Brainstem encephalitis	CELLS: 37 LYM PROT: 4.6 g/L GLUC: 32 mg/dl PCR: *ND*	*ND*	Death (17 days)
6	M/27	A2/260	Disseminated (maxilar, cervical) (0)	Brainstem encephalitis	CELLS: 40 LYM PROT: 0.71 g/L GLUC: *ND* PCR: *ND*	IV acyclovir (15)	Partial recovery Lost for follow-up at day 30
7	M/29	C3/25	Mandibular (30)	Encephalitis	CELLS: 25 LYM PROT: 7.62 g/L GLUC: *ND* PCR: VZV	*ND*	Death (4 days)

8	M/33	C3/50	Disseminated (14)	Myelitis	CELLS: 5 LYM PROT: 0.72 g/L GLUC: 56 mg/dl PCR: VZV	Foscarnet (21)	Stabilization (102 days)
9	F/28	C3/27	Sacral (7)	Myelitis Cranial neuritis (bilateral VII nerve)	CELLS: 15 LYM PROT: *ND* GLUC: *ND* PCR: *ND*	IV acyclovir (14)	Acute retinal necrosis Stabilization (137 days)
10	F/36	C3/19	Disseminated (ophthalmic, thoracic) (0)	Meningoradiculitis Cranial neuritis (III and VII nerves)	CELLS: 230 LYM PROT: 12.73 g/L GLUC: 56 mg/dl PCR: *ND*	IV acyclovir (14) Antituberculous drugs	Deterioration (84 days)
11	M/35	C3/1	Lumbar (L5) (390)	Cerebral infarctions (ischemic and hemorrhagic)	CELLS: 3 LYM PROT: 1.31 g/L GLUC: 60 mg/dl PCR: VZV	IV acyclovir (21)	Deterioration (133 days)
12	M/31	C3/31	Ophthalmic (0) Acute retinal necrosis (0)	Cranial neuritis (III nerve)	CELLS: 5 LYM PROT: 0.57 g/L GLUC: 53 mg/dl PCR: *ND*	IV acyclovir (14)	Improvement Acute retinal necrosis and V nerve lesion 3 months later, improved with foscarnet Brainstem encephalitis 4 months later (15 months)
13	M/59	C3/21	Multidermatomal lumbar (7)	Optic neuritis	*ND*	Ganciclovir (21)	No visual improvement Brainstem encephalitis 2 months later (62 days)

CDC: Centers for Disease Control and Prevention; F: female; M: male; LYM: lymphocytes; GLUC: glucose; PROT: proteins; PCR: polymerase chain reaction; VZV: varicella-zoster virus; *ND*: not done.

in a single institution during an 18-year period, with the aims of studying the changes in prevalence and clinical presentations, and evaluating the diagnostic utility of the PCR in CSF.

The records of all HIV-infected patients with a clinical diagnosis of a neurological disorder caused by VZV from 1983 to 2001 were reviewed. For the diagnosis of VZV neurological disease, patients had to fulfil all the following diagnostic criteria: (1) presentation with a neurological disorder reported to be associated with VZV infection. These include encephalitis, aseptic meningitis, cranial neuropathy (including optic neuritis), leukoencephalitis, cerebral infarcts, acute myelitis, and motor radiculopathy or polyradiculopathy. Patients with postherpetic neuralgia were not included; (2) evidence of recent reactivation of VZV, either by the presence of cutaneous zoster, varicella or acute retinal necrosis, appearing concurrent with the neurological disease or in the previous month, or by the demonstration of VZV DNA in CSF by PCR; and (3) exclusion of other possible etiologies of the neurological syndrome.

Thirteen cases of neurological VZV disease have been diagnosed among HIV-infected patients from 1983 to 2000. Table 1 shows patient characteristics, clinical presentation, CSF findings, and course. Ten of these 13 patients had acquired immunodeficiency syndrome (AIDS), representing 0.6% of the 1775 AIDS cases diagnosed in our hospital in that period. After the introduction of highly active antiretroviral therapy (HAART) in 1996, only 2 patients had a diagnosis of neurological VZV disease. Both (patients 2 and 3) were receiving HAART, but only one of them had defined AIDS. Thus, the prevalence of VZV neurological disease among AIDS patients in our hospital in the period 1996–2000 (1 of 961) was significantly lower than in the pre-HAART period 1982–1995 (9 of 1088) ($P = .02$, Fischer's exact test).

Past or concurrent skin herpetic lesions were diagnosed in all patients, although in one case history of herpes zoster was remote. Neurological complications developed in 9 patients despite previous treatment with specific antivirals. Aseptic meningitis (4 patients, 31%) and encephalitis (3 patients, 23%) were the most frequent clinical presentations. Less common presentations were myelitis, cranial neuritis (2 patients each, 15%), meningoradiculitis, and cerebral infarctions (1 patient each, 8%). CSF viral cultures were performed in 9 patients, always with negative results. The patient with meningoradiculitis (patient 10) had multiple asymptomatic hypodense lesions on cranial computed tomography, suggesting VZV vasculopathy. Globally, a favorable response to treatment, defined as either complete or partial recovery, or stabilization, was found in 67% of treated patients.

For the evaluation of the diagnostic utility of PCR in CSF, we used a multiplex PCR for herpesvirus, described elsewhere (Quereda *et al*, 2000; Tenorio *et al*, 1993), which was available routinely since September 1993. The multiplex PCR was performed in 183 CSF samples from 167 HIV-infected patients during the study period. Only the first CSF sample was considered in patients with more than one CSF specimen obtained during a single neurological process, and patients without established neurological diagnoses were excluded. Thus, a total of 135 CSF samples were included for the evaluation of the PCR results. Among patients with VZV-associated neurological disease, the PCR was performed in 6 cases (in the other 7 cases, either the PCR technique was not yet available, or the attendant specialist did not consider the study at the moment of CSF extraction), but the patient with cerebral infarctions was not included in the analysis because a positive PCR was a diagnostic criterium in this case. VZV DNA was detected in CSF in 4 out of 5 patients with VZV neurological disease, and in 2 out of 130 HIV-infected patients with other neurological diagnoses. The diagnoses in this control group were progressive multifocal leukoencephalopathy (36 cases), HIV-associated neurological disease (30 cases), cytomegalovirus (CMV) disease (28 cases), tuberculous meningitis (6 cases), primary cerebral lymphoma or lymphomatous meningitis (6 cases), cerebral toxoplasmosis (5 cases), cryptococcal meningitis (4 cases), sepsis (4 cases), subarachnoid hemorrhage (3 cases), seizures secondary to metabolic or toxic causes (3 cases), bacterial, candida and listeria meningitis, spinal astrocytoma, and tension headache (1 case each). In this group, VZV was amplified in CSF from a patient with tuberculous meningitis and from a patient with CMV encephalitis. Sensitivity of the technique was 0.8 (95% confidence interval: 0.45–1), and specificity 0.98 (95% confidence interval: 0.96–1). Positive predictive value was 0.94, and negative predictive value 0.99. The likelihood ratios for the positive and negative tests were 40 and 0.2, respectively.

Analysing all CSF samples, VZV DNA amplification in CSF was associated with a past history of cutaneous zoster ($P = .002$), although this association was limited to cases in whom lumbar puncture was performed less than 3 months after the onset of the zoster lesions ($P < .001$), and was not found if the zoster had occurred earlier ($P = .1$). However, when only patients without neurological VZV disease were considered, we did not find differences in VZV amplification among patients with or without past history of herpes zoster (1/42 versus 1/134).

The present study shows a low prevalence of neurological complications of VZV in AIDS patients and demonstrates a favorable impact of the introduction of HAART in their prevalence. Our results also demonstrate the diagnostic utility of the use of the PCR in CSF for the diagnosis of these diseases.

The diagnoses of the patients included in this series was based on clinical criteria. This might represent

a limitation of our study. However, in the absence of pathological confirmation, the diagnosis of neurological complications due to VZV is usually a clinical one, as CSF viral cultures usually have a very low diagnostic yield. Search for CSF antibody to VZV, which may aid in the diagnosis of these disorders in HIV-infected patients (Gilden *et al*, 1998), was not performed in our patients. We believe that our diagnostic criteria reflect appropriately the actual clinical setting where a diagnosis of VZV neurological complication is usually made: the patients presented a neurological syndrome known to be caused by VZV, in close temporal association with cutaneous reactivation of VZV (with the exception of one case in which recent reactivation of VZV was demonstrated by VZV DNA amplification from CSF). Additionally, our criteria required exclusion of any evidence of other possible etiologies for the neurological syndrome. HIV infection itself did not explain the neurological disease of our patients.

The low prevalence of neurological complications of VZV in our study, 0.6% of AIDS patients diagnosed in our hospital from 1983 to 2000, might represent an underestimate of the actual prevalence. The lack of autopsy studies and of PCR testing in CSF before 1993, together with a low clinical awareness of these disorders in the early years of the AIDS epidemic, might have influenced the number of patients diagnosed. Estimates of the frequency of VZV neurological complications in HIV-infected patients have varied substantially in other studies (Iten *et al*, 1999; Burke *et al*, 1997; Cinque *et al*, 1997; Levy *et al*, 1985; Petito *et al*, 1986). The demonstration of a decrease in the prevalence of VZV central nervous system (CNS) disease among AIDS patients since the introduction of HAART is not surprising, given the dramatic effect of HAART in the prevalence of other opportunistic infections. However, to our knowledge, no studies had previously assessed the influence of HAART on VZV neurological diseases. Improvement of the immunological status of HIV-infected patients seems to decrease the risk for these disorders, which are frequently associated with advanced stages of HIV infection (69% of patients were in stage C3 in our study) (Iten *et al*, 1999; Cinque *et al*, 1997; De la Blanchardiere *et al*, 2000; Gray *et al*, 1994). The high incidence of herpes zoster reported in patients receiving HAART during the first weeks of treatment (Domingo *et al*, 2001), is not paralleled by an increase in neurological complications caused by VZV. Although VZV neurological disease have occurred in 2 of our patients receiving HAART, in both cases the neurological presentation was aseptic meningitis, a benign disease that may also present in immunocompetent patients. Thus, it appears that HAART may also influence the severity of the neurological complications of VZV if they finally appear.

The present series shows a spectrum of neurological disorders associated with VZV in HIV infection, primarily aseptic meningitis and vasculopathy, and less often cranial nerve palsies. Autopsy studies are obviously biased towards more severe presentations and do not include benign syndromes, such as aseptic meningitis or cranial neuritis (Gray *et al*, 1994). Aseptic meningitis was the most frequent presentation in our study, in contrast with other reports (Brown *et al*, 2001; De la Blanchardiere *et al*, 2000). Encephalitis was the second most frequent presentation (23%). Brainstem encephalitis, common in our series (patients 5, 6, and possibly 11 and 12), has been only occasionally reported (Brown *et al*, 2001; Mouligner *et al*, 1995; Rosenblum, 1989), and may complicate trigeminal zoster, suggesting a trans-synaptic spread of trigeminal infection to the brain (Rosenblum, 1989). Cranial neuritis, including optic neuritis, was also a frequent clinical manifestation among our patients (38%), but it is rarely the only clinical presentation (15%). Less common clinical presentations were myelitis (15%), meningoradiculitis (8%), and cerebral infarction (8%).

Our results confirm the diagnostic value of CSF PCR for the diagnosis of VZV neurological disorders in HIV-infected patients. Previous reports have supported the diagnostic utility of the test in HIV-infected patients (Burke *et al*, 1997; Iten *et al*, 1999), particularly in the absence of concomitant herpes zoster, and in fact this test has already been used as a diagnostic criterium for this disease by some authors (Brown *et al*, 2001; De la Blanchardiere *et al*, 2000). However, VZV DNA has been detected in CSF from HIV-infected patients with other opportunistic diseases, suggesting a subclinical reactivation of VZV infection within the CNS (Cinque *et al*, 1997), and rising concerns about the specificity of the test. In our experience, subclinical reactivation of the virus in patients with other neurological diseases has been rare. We found only two possible cases of unspecific reactivation of VZV among 130 control patients with other neurological diagnoses, and yet in one of them, concomitant CMV and VZV encephalitis cannot be completely ruled out. In a previous report, we found high specificity of CSF VZV DNA amplification for the diagnosis of VZV neurological disease (Quereda *et al*, 2000), but sensitivity could not be evaluated due to a low number of cases with the diagnosis of VZV neurological disease. In the present study we have confirmed the high specificity of the test, and we have found good sensitivity (0,8), albeit with a wide 95% confidence interval (0.45–1), and predictive values.

The demonstrated association between amplification of VZV DNA from CSF and history of recent or concurrent cutaneous zoster might also rise doubt about the clinical utility of the test for the diagnosis of VZV neurological complications, because

it would be as sensitive as the presence of recent zoster, and its specificity would lower due to cases with recent zoster suffering from other neurological diseases. However, our results have shown that, in the majority of cases, VZV amplification has clinical significance independently of the presence or absence of recent zoster. In conclusion, we believe that, although a negative PCR result does not exclude completely the diagnosis of VZV neurological disease, a positive one should prompt this possibility, whether or not there is history of concomitant or recent herpes zoster.

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