Published in final edited form as:
J Neurol Sci. 2011 May 15; 304(1-2): 22–24. doi:10.1016/j.jns.2011.02.030.

Subclinical reactivation of varicella zoster virus in all stages of HIV infection

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Abstract

Analysis of 200 paired serum and cerebrospinal fluid (CSF) samples from 180 HIV-positive individuals, 136 of whom had AIDS, revealed intrathecal synthesis of antibodies specific for varicella zoster virus (VZV) in 28 (16%) individuals, measles virus in 15 (8%), herpes simplex virus-1 (HSV-1) in 1 (0.6%), and HSV-2 in none. Of the 28 subjects with a positive VZV antibody specificity index, only 1 had zoster rash at the time of serum and CSF sampling; of the total 180 HIV-positive subjects, 146 (81%) had no history of zoster. Based on an estimated 33.4 million HIV-positive individuals worldwide, subclinical reactivation of VZV in even less than 16% of HIV-positive people suggests the possibility that millions of people have active VZV infection of the central nervous system. In cases of VZV vasculopathy, myelopathy and even zoster sine herpete, the CSF is often positive for anti-VZV antibody, but negative for VZV DNA. To rule out VZV infection of the nervous system, CSF must be tested for VZV DNA and anti-VZV IgG and IgM antibody.

Keywords

VZV; HIV; subclinical reactivation; CSF; intrathecal synthesis

1. Introduction

Varicella zoster virus (VZV) is a ubiquitous neurotropic alphaherpesvirus. Primary infection, usually in children, results in chickenpox (varicella), after which the virus becomes latent in ganglionic neurons along the entire neuraxis. As cell-mediated immunity to VZV declines with age or immunosuppression, as in organ transplant recipients or patients with cancer and AIDS, VZV reactivates to produce zoster and often chronic pain

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The findings and conclusions in this report are those of the authors and do not necessarily represent the view of the Centers for Disease Control and Prevention.

(postherpetic neuralgia). The incidence of zoster is considerably increased in HIV-positive adults [1,2] and children [3], and in AIDS patients, zoster is often recurrent and more protracted. VZV reactivation can also produce multiple CNS and ocular disorders which are estimated to occur in up to 11% of HIV-positive subjects [4].

Importantly, all the neurological and ocular diseases that develop when VZV reactivates can occur in the absence of zoster rash [4,5]. VZV can also reactivate without rash or neurological symptoms or signs, as evidenced by a 5-fold increase in VZV-specific antibodies [6] and by the presence of VZV DNA and infectious virus in saliva of healthy astronauts [7,8]. The incidence of subclinical VZV reactivation in HIV-infected individuals and patients with AIDS is unknown. We had the unique opportunity to analyze 200 paired serum and CSF samples from 180 HIV-positive individuals for the prevalence of subclinical VZV reactivation as formally defined by intrathecal synthesis of anti-VZV IgG antibodies in the absence of zoster rash or pain, indicative of active (current) infection.

2. Methods

2.1. Subject population

Two-hundred paired serum and CSF samples from 180 HIV-positive individuals, none of whom received varicella vaccine, from a single neurology clinic were studied. The mean age of all subjects at the time serum and CSF were obtained was 40 years (range 18–71). Table 1 lists the pertinent demographic and clinical features of all subject studied. The diagnosis of AIDS was determined by clinical and/or laboratory criteria, including a CD4 cell count below 200 cells/mm^3. The viral load was also determined in most subjects. HIV-positive subjects were categorized as follows according to clinical criteria established by the Centers for Disease Control and Prevention (CDC) [9]: Category A, asymptomatic; Category B, symptomatic, but not an AIDS indicator condition; and Category C, symptomatic with an AIDS indicator condition. Individuals in our study for whom clinical data were insufficient for category diagnosis were reported as “unknown.”

2.2. Serologic analysis

From October 1995 to January 2003, 200 paired serum and CSF samples were collected on the same day from all individuals, with an average interval between HIV-positive diagnosis and sample collection of 4.6 years (range: 3 days before to 17 years after the detection of HIV-positivity); in 18 individuals, collections were repeated. Serum and CSF were frozen immediately, and virologic analyses were conducted years later at the CDC (Atlanta, GA). Because sera and CSF were analyzed retrospectively, PCR data for VZV DNA and other viruses was not available. ELISA assays were used to detect all antiviral antibodies in serum and CSF. VZV IgG serology was performed as described [10]. HSV-1 and HSV-2 type-specific IgG ELISA was performed using the HerpesSelect assay (Focus Diagnostics, Cypress, CA), and measles IgG ELISA was performed using the kit from Wampole Diagnostics (Princeton, NJ), both according to the manufacturer’s instructions. The antibody specificity index (ASI) was calculated using corrected ELISA optical density readings (sample minus background) as described by Reiber and Lange [11].

2.3. Statistical analyses

Data were analyzed using two-sided t-test for parametric variables and X^2 test for nonparametric variables. Differences were considered significant at $p<0.05$.

3. Results

3.1. Antiviral IgG antibodies in CSF and serum of HIV-positive individuals

Table 2 lists the distribution of antiviral IgG antibodies detected in the serum and CSF of 180 HIV-positive patients against VZV, measles virus, HSV-1 and HSV-2. In the 180 HIV-positive individuals, Table 3 shows that the VZV ASI was ≥1.5 in 28 (16%) subjects, 24 of whom (86%) had no known history of zoster and constituted 13% of the total HIV-positive subjects; the other 4 individuals with VZV ASIs ≥1.5 had a history of zoster (range: 2 months before CSF and serum collection to 8 years after), constituting 2% of the total HIV-positive subjects. One of these 4 HIV-positive individuals had zoster rash at the time of serum and CSF sampling. Of the 136 HIV-positive subjects with AIDS, 21 (15%) had a VZV ASI ≥1.5, while only 3 (18%) of the 17 without AIDS and 4 (15%) of the 27 with unknown AIDS status had a VZV ASI ≥1.5. In the 180 HIV-positive individuals, the ASI was ≥1.5 for measles virus in 15 (8%), for HSV-1 in 1 (0.6%), and for HSV-2 in none of the individuals; 8 had an ASI ≥1.5 for both anti-VZV and anti-measles IgG antibodies.

The prevalence of intrathecal synthesis of anti-VZV IgG (ASI ≥1.5) among HIV-positive subjects in CDC Categories A, B, and C was 21%, 15%, and 15%, respectively, and 15% among unknown. The history of zoster in Categories A, B, C and unknown was positive in 7%, 42%, 20% and 0%, respectively; the increased incidence of zoster in subjects in Category B compared to Category A was statistically significant ($p = 0.04$).

3.2. Additional clinical and laboratory data

The median CD4 count in 21 of 28 (75%) subjects with VZV ASI ≥1.5 was 87 (range 2-346). The median HIV load in 17 of 28 (61%) subjects with VZV ASI ≥1.5 was 10,000 (range 1-500,000). Among the 28 HIV-positive subjects with VZV ASI ≥1.5, 7 (25%) had neurological signs but without a proven etiologic diagnosis. Clinical features included hemiparesis, multiple cranial neuropathies, ataxia, myelopathy, encephalopathy or combinations thereof.

3.3. Individuals with repeated CSF and serum sampling

In 18 HIV-positive subjects, serum and CSF were examined for antiviral IgG antibodies more than once, with an interval between sample acquisitions ranging from 2 weeks to 4 years. In 5 of these 18 HIV-positive subjects, intrathecal synthesis of anti-VZV IgG antibodies (VZV ASI ≥1.5) was detected on two occasions, while 11 subjects had a VZV ASI <1.5 in both samples, and the remaining 2 individuals had a VZV ASI ≥1.5 once only. In one subject, intrathecal synthesis of anti-VZV IgG antibodies was found for up to 2 years after zoster.

4. Discussion

Herein, we present results of a retrospective analysis to detect intrathecal synthesis of antiviral antibodies directed against VZV, measles virus, HSV-1 and HSV-2 in 180 HIV-positive subjects, 76% of whom had AIDS, from a single neurology clinic seen over an 18-year period. Zoster developed in 19% of our HIV-positive subjects, similar to the 13–21% incidence of zoster found in other HIV-positive populations [12–16].

Remarkably, we detected intrathecal synthesis of anti-VZV IgG in 28 (16%) of 180 HIV-positive subjects, 24 (86%) of whom had no history of herpes zoster. Intrathecal synthesis of anti-measles virus antibodies was found in 8%, anti-HSV-1 IgG in only one HIV-positive subject, and no anti-HSV-2 antibodies were found in our HIV-positive population. No

immediate explanation for the lack of subclinical reactivation of HSV-2 is apparent other than the fact that if HSV-2 reactivated subclinically, it did not occur in the CNS.

Our findings are most readily explained by subclinical reactivation of VZV in the absence of rash in ~15% of HIV-positive subjects. Furthermore, subclinical reactivation most likely was followed by persistent virus infection; if virus reactivation had been incomplete or abortive, antibody in CSF would be washed out within a couple of days. However, an earlier limited study of 23 HIV-positive individuals did not find clear differences in intrathecal IgG synthesis specific for VZV, HSV or cytomegalovirus [17]. On the other hand, intrathecal synthesis of antiviral antibodies is not restricted to HIV-positive individuals. In patients with multiple sclerosis (MS), for example, intrathecal synthesis of anti-measles virus antibodies in 78%, anti-rubella virus antibodies in 60%, anti-VZV antibodies in 55% and anti-HSV antibodies in 28% of patients was reported by Reiber et al [18]. Since none of these ubiquitous viruses persists in MS brain, and recombinant antibodies prepared from clonally-expanded CSF plasmablasts in MS CSF are not directed against VZV [19], measles virus (Owens, G.P, University of Colorado School of Medicine, personal communication) or Epstein-Barr virus [20], intrathecal synthesis of multiple antiviral antibodies in MS remains unexplained. Even if this poorly understood mechanism leading to intrathecal antiviral antibody synthesis against VZV, measles, and HSV were at play, it is difficult to explain why we detected such synthesis for anti-measles virus in only 8% of our HIV-positive subjects as compared to 78% of MS patients in the study by Reiber et. al. [18].

If many or even some of the ~15% of HIV-positive subjects found to intrathecally synthesize anti-VZV IgG antibodies in the absence of rash reflect subclinical reactivation, the estimated 33.4 million HIV-positive individuals worldwide (www.who.org; www.unaids.org) points to the possibility that millions of people with active VZV infection of the CNS, may be at risk for neurological disease. Given that VZV produces meningoencephalitis, cerebellitis, vasculopathy, myelitis and multiple ocular disorders, all in the absence of rash [5], clinicians must consider VZV as a potential cause of any neurological disorder in HIV-positive individuals. Finally, testing the CSF for VZV DNA as well as anti-VZV IgG and IgM antibody is essential to rule out VZV infection of the nervous system. In cases of VZV vasculopathy [21] and myelopathy [22], the CSF is often positive for anti-VZV antibody, but negative for VZV DNA. Even in zoster sine herpete in which the original cases were virologically verified by detection of VZV DNA in CSF [23], a recent case was negative for VZV DNA, but positive for anti-VZV IgG antibody [24].

Acknowledgments

This work was supported in part by Public Health Service grants AG006127 and AG032958 from the National Institutes of Health. The authors thank Marina Hoffman for editorial review and Cathy Allen for manuscript preparation.

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Table 1

Characteristics of 180 HIV+ individuals.

No. of males	151
Mean age (range in years)[a]	40 (22–71)
No. of females	29
Mean age (range in years)[a]	38 (18–60)
Mean age (range in years) of total series	40 (18–71)
Mean age (range in years) at HIV+ diagnosis	35 (10–63)
CDC categories	
A	14 (8%)
B	26 (14%)
C	113 (63%)
With AIDS	136 (76%)
No AIDS[b]	17 (9%)
Unknown[c]	27 (15%)
History of zoster	34 (19%)
Age (range in years) at zoster[d]	36 (20–53)

[a] No significant difference (p = 0.14) between males and females.

[b] Sufficient clinical and laboratory data to rule out AIDS.

[c] Insufficient clinical and laboratory data for diagnosis.

[d] Known in 21 of 34 individuals.

Table 2

Antiviral antibodies in serum and CSF of 190 HIV+ individuals [a]

Antiviral antibodies	Serum			CSF		
	No. positive (%)	No. negative (%)	ND[b] (%)	No. positive (%)	No. negative (%)	ND (%)
Anti-VZV IgG	174 (97)	6(3)	0	28 (16)	152 (84)	0
Anti-measles IgG	171 (95)	9(5)	0	15(8)	164 (91)	1 (0.6)
Anti-HSV-1 IgG	158 (88)	17(9)	5(3)	1 (0.6)	177(98)	2(1)
Anti-HSV-2 IgG	137 (76)	33 (21)	5(3)	0	178(99)	2(1)

[a] All CDC Categories of HIV positivity

[b] ND = Not determined because quantity insufficient for ELISA assay

Table 3

Intrathecal antiviral antibody synthesis in 180 HIV+ individuals.

Virus	Number positive	% positive
VZV[a]	28	16
Measles	15	8
HSV-1	1	0.6
HSV-2	0	0

[a]Represents all CDC clinical categories of HIV positivity.