Published in final edited form as:

J Neurol Sci. 2014 April 15; 339(0): 32–34. doi:10.1016/j.jns.2014.01.044.

Varicella zoster virus (VZV) in cerebral arteries of subjects at high risk for VZV reactivation

Maria A. Nagel^a, Nelly Khmeleva^a, Alexander Choe^a, Jose Gutierrez^b, and Don Gilden^{a,c,*}

^aDepartment of Neurology, University of Colorado School of Medicine, Aurora, CO, USA

^bDepartment of Neurology, Columbia University Medical Center, New York, NY, USA

^cDepartment of Microbiology, University of Colorado School of Medicine, Aurora, CO, USA

Abstract

With a decline in varicella zoster virus (VZV)-specific cell-mediated immunity, VZV can reactivate, infect cerebral arteries and cause stroke. Previous studies of cerebral arteries from subjects without a history of transient ischemic attacks or stroke revealed no VZV DNA or antigen; however, VZV DNA and antigen were found in the cerebral arteries of a subject with diabetes, a known risk factor for VZV reactivation and zoster. The present study analyzed an additional 55 cerebral arteries from 18 subjects with co-morbidities that may increase risk of VZV reactivation: a history of alcohol abuse, tricyclic antidepressant intoxication, cocaine abuse, HIV or being over age 70. VZV antigen was detected in 24 (44%) cerebral arteries from 14 (78%) subjects.

Keywords

VZV; cerebral artery; subclinical reactivation; HIV; diabetes; drug abuse

1. Introduction

Varicella zoster virus (VZV) vasculopathy is caused by productive virus infection in cerebral arteries [1]. Although the exact incidence of VZV vasculopathy is unknown, it is not uncommon. In particular, there is a 30% increased risk of stroke within one year after zoster [2]. A recent study of 63 human cerebral arteries from 45 subjects with no history of transient ischemic attacks or stroke showed no VZV DNA in any arteries, and immunohistochemical analysis of single sections from formalin-fixed, paraffin-embedded arteries revealed no VZV antigen [3]. Importantly, a similar study detected both VZV DNA and antigen in the cerebral artery of a diabetic subject with no history of TIAs or stroke [4], which is not surprising since diabetic subjects are at greater risk for zoster [5]. Here, we examined cerebral arteries from additional subjects with potential co-morbidities that may increase the risk of VZV reactivation.

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*Corresponding author at: Department of Neurology, 12700 E. 19th Avenue, Mail Stop B182, Aurora, CO 80045, USA. Tel.: 1-303-724-4326; fax: 1-303-724-4329, don.gilden@ucdenver.edu.

Conflict of Interest Statement

All authors report no conflicts of interest.

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2. Methods

With written informed consent from donors before death and from next-of-kin after death, postmortem tissues from 18 subjects were obtained from the University of Miami Brain Endowment Bank as described [6]. Of the 18 subjects, 5 were HIV+ and 13 were HIV–. Fifty-five cerebral arteries were dissected from formalin-fixed brain. When available, clinical data were obtained from the donor registry, medical records and autopsy reports. Arteries were paraffin-embedded and cut transversely at 5- μ m thickness.

Based on tissue availability, 10–12 sections from arteries of HIV– subjects and 2 sections from arteries of HIV+ subjects were immunostained with rabbit anti-VZV antibody, rabbit anti-HSV antibody and normal rabbit serum as described [7]. When VZV antigen was detected, VZV-positive sections were scraped with a scalpel, pooled if more than one section was positive and placed into 200 μ l lysis buffer with proteinase K (DNeasy Blood and Tissue Kit; Qiagen; Germantown, MD), followed by DNA extraction per the manufacturer's protocol and quantitative PCR analysis as described [3]. Positive and negative controls were provided by amplification of serial dilutions of known quantities of VZV DNA and by omission of VZV DNA from the PCR, respectively.

3. Results

Immunohistochemical examination of 55 human intracerebral arteries from 18 subjects detected VZV antigen in 24/55 (44%) arteries from 14/18 (78%) subjects. The subjects whose arteries contained VZV had a history of alcohol abuse (1), tricyclic antidepressant (TCA) intoxication (1), cocaine abuse (4, 1 of whom was also HIV+), HIV+ (4, 1 of whom also had a history of cocaine abuse) or were over age 70 years (5, 1 of whom also had multiple myeloma) (Table). Figure 1 shows a representative artery from a VZV-positive subject with cocaine abuse. Most slides of VZV antigen-positive cerebral arteries did not have sufficient DNA for PCR analysis; however, those of subjects 5, 9, 13 and 18 had amplifiable DNA and VZV DNA was detected in all 4 subjects (not shown).

4. Discussion

Our present detection of VZV antigen in 24/55 (44%) cerebral arteries from 14/18 (78%) subjects with a history of alcohol and cocaine abuse, TCA intoxication, HIV positivity or age over 70 years contrasts with our previous negative results in detecting VZV antigen or VZV DNA in 63 cerebral arteries removed at autopsy from 45 subjects [3]. One possibility to account for the discrepancy is the examination here of 10–12 individual cerebral artery sections from the 13 HIV– subjects for VZV antigen staining, whereas only a single 5- μ m formalin-fixed, paraffin-embedded section of each cerebral artery was used previously. Note that staining for VZV in 20 sections of cerebral artery in two other studies revealed VZV antigen in the cerebral artery of a diabetic subject without a history of TIA or stroke [4] and in temporal arteries of 5 subjects who underwent biopsy for suspected giant cell arteritis [7].

A second possibility might rest in the different patient populations from which cerebral arteries were obtained since most subjects in the previous study (39/45) were <70 years of age and had less co-morbidities that may predispose to VZV reactivation. Herein, we found VZV antigen in cerebral arteries of 5 subjects over the age of 70 years, consistent with VZV reactivation most often in elderly individuals. Furthermore, our present detection of VZV in cerebral arteries of 4/5 HIV+ positive subjects (even when only 2 sections were examined) is consistent with the well-documented subclinical reactivation of VZV in these subjects [8].

While no immediate explanation is apparent for the detection of VZV antigen in the cerebral arteries of subjects with a history of cocaine or alcohol abuse or TCA intoxication, TCA [9]

as well as cocaine and alcohol are known to have immunosuppressive effects [10–14]. Larger studies to detect VZV in cerebral arteries are required to further delineate the frequency and significance of VZV infection in cerebral arteries [15,16].

Acknowledgments

This work was supported in part by Public Health Service grants NS067070, AG006127 and AG032958 from the National Institutes of Health. The authors thank Marina Hoffman for editorial assistance and Lori DePriest for word processing and formatting.

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Fig. 1. Varicella zoster virus (VZV) antigen in cerebral arteries

Note VZV antigen in a cadaveric cerebral artery 14 days after experimental infection with VZV (A, arrows, pink color) and in the cerebral artery stained with rabbit anti-VZV antibody (B, arrows, pink color), of a 37-year-old man (subject 5) with a history of cocaine abuse; no staining was seen with normal rabbit serum (C) or anti-HSV antibody (not shown). Magnification 600X.

Clinical features of subjects whose cerebral arteries were analyzed for the presence of VZV antigen, number of arteries analyzed and those that contained VZV antigen.

Table 1

Subject	Age	Sex	Clinical features	No. arteries analyzed	No. VZV+
1	40	M	alcohol abuse	2	1
2	33	M	cocaine and alcohol abuse	3	0
3	38	F	cocaine abuse	3	2
4	32	F	tricyclic drug intoxication	3	1
5	37	M	cocaine abuse	3	1
6	37	M	cocaine abuse	2	0
7	102	F	pneumonia	3	2
8	85	M	ischemic cardiomyopathy; COPD ^a	2	1
9	85	F	ischemic cardiomyopathy	3	2
10	82	F	ischemic cardiomyopathy; atrial fibrillation	3	0
11	73	F	multiple myeloma	4	3
12	89	F	pneumonia	2	1
13	42	M	cocaine abuse	7	3
14	46	M	HIV+	3	2
15	46	M	HIV+	2	1
16	49	F	HIV+	3	0
17	50	M	HIV+; cocaine abuse	3	2
18	36	M	HIV+	4	2

^a COPD, chronic obstructive pulmonary disease.