

Vertebral artery dissection and stroke following neck manipulation by Native American healer

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Stroke as a complication of cervical manipulation and dissection of the vertebral artery is rare but has been well described¹ and is most commonly associated with chiropractic manipulation of the neck using a technique often called "high velocity thrust."² Strokes from vertebral artery dissections have also been reported with cervical self-manipulation and other causes of neck trauma such as sports and roller coasters. The authors report on a patient with vertebral artery dissection and a stroke occurring after a Native American healing ceremony.

Case report. This previously healthy 32-year-old woman from the Pueblo of Zuni presented with the sudden onset of vertigo, left-sided ataxia, and vomiting. Six days before the onset of her symptoms, the patient underwent a healing ceremony with a native healer whom she referred to as a "bone setter" for complaints of nontraumatic left shoulder discomfort. During the ceremony, she underwent vigorous manipulation of her neck with a sudden thrusting of the head upward and to the right while her left shoulder was being held to the ground. She noted neck discomfort immediately afterward, which persisted. She awoke on day 6 vertiginous with left-sided ataxia. She had no identifiable risk factors for stroke or vertebral artery dissection and no family history of cerebrovascular disease.

She had normal mentation, cranial nerves, sensation, strength, and physiologic deep tendon reflexes with slow inaccurate responses on left finger-to-nose testing and on rapid alternating movements. Her gait was wide based, and she leaned to the left. The results of routine laboratory studies, a rapid plasma reagin test, and prothrombin time were normal.

MRI showed acute infarction in the midline left cerebellar hemisphere and vermis in the distribution of the left posterior inferior cerebellar artery (figure, A). MR angiography demonstrated likely occlusion of the left vertebral artery. On vertebral arteriography, severe narrowing of the left vertebral artery was identified beginning at the level of the C2 vertebral body and extending upward (see the figure, B). At the level of C1, collateral blood flow was seen entering the left vertebral artery from a small artery that arose from a branch of the thyrocervical trunk. No blood flow was seen in the left posterior inferior cerebellar artery (PICA).

A diagnosis was made of left vertebral artery dissection with a probable embolus originating from the distal vertebral artery stump and occluding the PICA. The patient improved and was discharged on warfarin anticoagulation therapy. At 6 months, she had a normal gait with minimal abnormalities on left finger-to-nose testing. Repeat MRI and MR angiography were unchanged.

The warfarin was discontinued without subsequent neurologic events for 1 year.

Discussion. This case illustrates the occurrence of PICA infarction and vertebral artery dissection as sequelae of vigorous cervical manipulation performed by a Native American healer during a healing ceremony. The patient's signs and symptoms were typical for a vertebral artery dissection. Neck pain develops in one-half of such patients, and headaches occur in two-thirds, often beginning within hours of the neck manipulation, although cerebral ischemic signs may be delayed for days to 2 weeks.¹ The outcome of the stroke depends on the size and severity of the initial infarction and the extent of collateral circulation. In our patient, a small collateral artery appeared to carry blood around the dissection (see the figure, B), which may have contributed to her good outcome. Overall, about 75% of patients make a good recovery, but some patients are permanently quadriplegic from a brainstem infarction, and approximately 5% die.¹

Most Native American healing ceremonies do not involve vigorous neck manipulations. Vigorous neck and head manipulation apparently can occur in healing ceremonies conducted by a "bone setter," however. Bone setters are one of 12 Zuni medicine fraternities.³ Tradition has it that a bone setter must be a survivor of a lightning bolt strike who then gains special powers to heal bones.^{4,5} These individuals apprentice with established bone setters for variable periods of time so as to learn traditional methods of healing diseases of bones and joints. Because Zuni healing ceremonies are rarely observed by physicians, it is not known how this neck manipulation compares with chiropractic manipulation.

Worldwide, many indigenous and ethnic groups, including Native Americans, have a long history of traditional medical healers called bone setters who treat bone and joint problems.^{6,7} Complications from their nonmedical approach to healing bones are recognized.^{6,7} It is not known how many bone setters practice vigorous cervical manipulation and thus are at risk of causing stroke from traumatic dissection of a vertebral artery.

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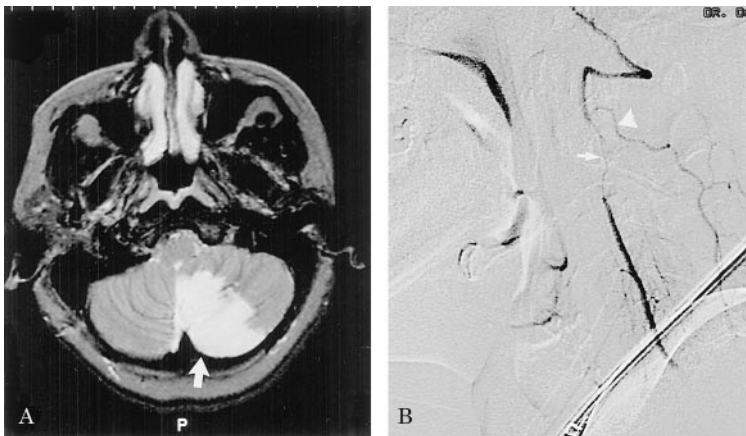


Figure. (A) Intermediate-weighted MRI scan 2 days after the onset of stroke showing a cerebellar stroke in the midline left cerebellar hemisphere and vermis in the territory of the left posterior cerebellar artery (arrow). (B) Left vertebral arteriogram with subtraction 2 days after the onset of stroke demonstrating severe narrowing of the artery beginning at the level of the C2 vertebral body and extending upward to the level of C1 (arrow). Note a collateral artery, likely a branch of the thyrocervical trunk, entering the vertebral artery above the level of the stenosis at about the level of the first cervical vertebra (arrowhead).

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Absence of elevated anti- α -synuclein and anti-EBV latent membrane protein antibodies in PD

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We recently demonstrated that commercially available monoclonal antibodies generated against the latent membrane protein 1 (LMP1) of Epstein–Barr virus (EBV) cross-react with the neuronal protein α -synuclein.¹ LMP1 is a virally encoded protein expressed during EBV latency. Up to 22% of healthy EBV-seropositive individuals generate a humoral immune response against this protein as part of a lifelong immune surveillance of EBV.^{2,3} Whether this cross-reaction has any biological relevance remains to be determined. There is growing evidence for a primary role of α -synuclein aggregation in the pathogenesis of PD.⁴ Insoluble α -synuclein filaments accumulate in brains of patients with PD. Recombinant α -synuclein protein can assemble in elongated filaments with ultrastructural features similar to those of Lewy body filaments observed in situ. In light of this as well as the fact that EBV latently infects approximately 90% of the human population worldwide and represents the target of a lifelong immune response, we were interested in exploring the possibility that molecular mimicry between EBV (and specifically the LMP1 protein) and α -synuclein could be involved in the pathogenesis or progression of PD.

Methods and results. In the first phase of the investigation, we performed EBV-specific ELISA on serum samples from 10 patients with PD and 10 age-matched controls. All 20 samples showed evidence of latent EBV infection with detectable titers of antibodies against viral capsid antigen (VCA)-p18 and the latent nuclear protein Epstein–Barr nuclear antigen (EBNA)-1. For the detection of anti-LMP1, purified LMP1 protein was coated onto ELISA plates, separated by sodium dodecyl sulfate–polyacrylamide gel electrophoresis, and transferred to nitrocellulose in a parallel immunoblot analysis. Both assays are highly reproducible and have been described previously.³ Only three samples (two controls and one PD) displayed detectable levels of antibodies against LMP1.

We then analyzed serum samples from 28 patients with PD and 19 control subjects for antibodies against α -synuclein using a two-step sandwich ELISA. Briefly, the ELISA was performed as described previously¹ with the following modifications. A reference standard was prepared using a monoclonal antibody to human α -synuclein (Zymed, San Francisco, CA) added to human plasma. Reference plasma and test samples were diluted at least 25-fold before application to the plate. A peroxidase-labeled antibody solution reactive to both human and murine IgG was used as the detecting antibody. The results were expressed as monoclonal antibody equivalents in micrograms per milliliter. All subjects showed low levels of serum anti-synuclein antibodies (0.055 to 0.276 μ g/mL), with the exception of three from each group who showed higher anti-synuclein antibody levels (0.301 to 0.795 μ g/mL). Notably, there was no difference in the mean anti-synuclein antibody reactivity between PD (0.178 μ g/mL) and control (0.216 μ g/mL) groups ($p = 0.37$).

In light of the negative results we obtained based on serum analysis and to address the possibility of CNS localization of an EBV infection and immune response, we applied the same sandwich ELISA to CSF samples from five PD cases and four controls. All samples showed extremely low to undetectable levels of anti-synuclein antibodies (0.006 to 0.015 μ g/mL). There was no difference in the mean values between PD and control samples ($p = 0.28$).

Finally, we used a highly sensitive PCR technique for the de-

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tection of EBV genome⁵ to address the possibility of local CNS infection. None of the PD or control CSF samples contained detectable EBV DNA sequences. In addition, none of 17 formalin-fixed and paraffin-embedded tissue sections, including four samples of PD midbrain, three samples of PD cortex, four samples of cortex from dementia with Lewy bodies, three samples of cortex from controls, and three samples of midbrain from controls, showed detectable EBV DNA sequences using either a single-copy EBNA-1 PCR or a BamH1-W repeat PCR with a sensitivity of 1 to 2 EBV genome-positive cells per assay. These PCR-negative samples became positive after spiking with EBV plasmid DNA, indicating absence of PCR inhibition and true EBV negativity of the samples. Moreover, all samples were positive using the same technique for the detection of β -globin DNA, indicating good DNA quality.

Discussion. The results of these studies do not provide evidence that an aberrant systemic immune response to latent EBV infection resulting in molecular mimicry between EBV LMP and α -synuclein has a role in the pathogenesis of PD. In addition, in our parallel analysis of a small group of CSF samples from PD patients and controls, we failed to reveal evidence for elevated immune reactivity to synuclein or LMP1 in PD generated exclusively within the CNS. Although the CSF results are consistent with the serum results, the sample size is small, and further studies of CSF in a larger cohort are needed to definitively exclude a discrepancy in anti-synuclein and anti-LMP1 antibody titers among PD and control subjects. Indeed, the mere presence of serum anti-synuclein antibodies (albeit at low levels) demonstrated in our studies is intriguing. Specifically, the possibility that low levels of circulating anti-synuclein autoantibodies may serve a protective role with respect to α -synuclein aggregation should be explored. This is particularly relevant in light of recent studies demonstrating that naturally occurring antibodies directed against β -amyloid exist in human CSF and plasma and that titers of these antibodies are reduced in AD.⁶ This finding is provocative in light of recent studies showing immune-mediated prevention and even reversal of Alzheimer-type changes secondary to immunization with the β -amyloid peptide in a mouse model of AD.⁷

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