Comparative Medicine
Copyright 2012
by the American Association for Laboratory Animal Science

Vol 62, No 4
August 2012
Pages 322–329

Case Report

Cerebrovascular Accident (Stroke) in Captive, Group-Housed, Female Chimpanzees

Sherrie M Jean,[1,*] Todd M Preuss,[2,4] Prachi Sharma,[3] Daniel C Anderson,[3] James M Provenzale,[5-8] Elizabeth Strobert,[1] Stephen R Ross,[9] and Fawn C Stroud[1]

Over a 5-y period, 3 chimpanzees at our institution experienced cerebrovascular accidents (strokes). In light of the increasing population of aged captive chimpanzees and lack of literature documenting the prevalence and effectiveness of various treatments for stroke in chimpanzees, we performed a retrospective review of the medical records and necropsy reports from our institution. A survey was sent to other facilities housing chimpanzees that participate in the Chimpanzee Species Survival Plan to inquire about their experience with diagnosing and treating stroke. This case report describes the presentation, clinical signs, and diagnosis of stroke in 3 recent cases and in historical cases at our institution. Predisposing factors, diagnosis, and treatment options of cerebral vascular accident in the captive chimpanzee population are discussed also.

Abbreviation: CVA, cerebrovascular accident.

Cerebrovascular accident (CVA; stroke) is a disturbance in brain function due to insufficient or complete loss of blood supply to an area of the brain. The lesion and clinical signs depend on the severity and location of the blockage. The 2 main categories of stroke—ischemic and hemorrhagic—both result in a loss of blood flow to an associated area of the brain. Ischemic strokes are due to either insufficient or direct loss of blood flow to the affected area of the brain from either temporary or permanent arterial occlusion of vessels supplying that area. Hemorrhagic strokes occur from rupture of a blood vessel and subsequent leakage of blood intracranially or into the subarachnoid space which results in clotting and decreased blood flow within that vessel and compression of the brain.[8,14,16,19] Loss of blood supply to a part of the brain, which can occur with ischemic or hemorrhagic stroke, initiates an ischemic cascade. The ischemic cascade is the result of secondary lack of oxygen and glucose; this lack consequently changes the intracellular metabolism from aerobic to anaerobic. This process ultimately leads to cell death and resultant disruption of cell membranes, thereby releasing toxins into the surrounding area and leading to increased cell death. This process results in a centrifugal progression of irreversible tissue damage and cell death.[1,11]

Brain tissue ceases to function when deprived of oxygen for more than 60 to 90 s, and irreversible tissue necrosis and brain damage can occur after a few hours. Ischemic strokes can result in varying degrees of damage to the tissue; consequently, clinical signs depend upon the amount of collateral circulation supplying the affected region of the brain. Part of the tissue may die immediately, whereas other parts may be injured only temporarily and ultimately recover.[8] Clinical signs that are typical of stroke victims consist of abnormal sensations, hemiparesis (that is, paralysis in one arm or leg or on one side of the body), aphasia, ataxia, and urinary incontinence. Severe strokes can result in stupor or coma. The defect in the brain usually is manifested as clinical signs on the opposite side of the body, depending on the part of brain that is affected.[8,9] Diagnosis typically is based initially on clinical signs and confirmed with imaging techniques such as CT and MRI, or the lesion is noted at necropsy.[6,16]

Whereas strokes are common in humans, only one report to date has discussed and documented spontaneous stroke in a chimpanzee.[6] In 2004, a 29-y-old male chimpanzee at a zoo experienced an ischemic stroke that most likely was due to occlusion of the middle cerebral artery.[2,6] The area of the brain supplied by the middle cerebral artery is the area most often affected in ischemic stroke in humans.[2,10] Although stroke has not been thoroughly researched in chimpanzees, studies in other species of nonhuman primates suggest that the predisposing factors and pathology are similar to those in humans.[3,18,20]

This case report describes the presentation, clinical signs, and diagnosis of CVA that occurred in 3 chimpanzees over a 5-y period at our institution and in an additional 3 animals identified during a retrospective review of the health records from the last 30 y. We also discuss predisposing factors, diagnosis, treatment options, and statistics of CVA in the captive chimpanzee population.

Received: 01 Nov 2011. Revision requested: 23 Nov 2011. Accepted: 04 Feb 2012.
[1]Department of Animal Resources, [2]Division of Neuropharmacology and Neurologic Diseases, and [3]Division of Pathology, Yerkes National Primate Research Center, Departments of [4]Pathology and Laboratory Medicine, [5]Radiology and Imaging Sciences, [6]Oncology, and [7]Biomedical Engineering, School of Medicine, Emory University, Atlanta, Georgia; [8]Department of Radiology, Duke University Medical Center, Durham, North Carolina; [9]Lester E Fisher Center for the Study and Conservation of Apes, Lincoln Park Zoo, Chicago, Illinois.
[*]Corresponding author. Email: sherriej@med.usc.edu

Case History

Within a 5-y period, 3 female chimpanzees died of CVA. The first was a 41-y-old, 61-kg female common chimpanzee (*Pan troglodytes*) that was socially housed at the Yerkes National Primate Research Center (Atlanta, GA); the chimpanzee was noticed on routine observation to be acutely lethargic, reluctant to move, and unstable on her feet. Further observations revealed right-sided hemiparesis, drooping of the right lower lip, and abrasions of the right buccal mucosa. The only significant abnormalities noted in her clinical history were obesity and a nonprogressing grade II systolic heart murmur. On physical examination, her temperature, pulse, respiratory rate, CBC, serum chemistry, blood and fecal cultures, and thoracic and abdominal radiographs were all within normal limits. An MRI performed the same day revealed a severe and extensive ischemic lesion in the left hemisphere, involving the temporal, parietal, and occipital lobes and suggesting occlusion of the left middle cerebral artery.[22] A detailed account of the microscopic neuropathologic findings in this case has been published elsewhere.[22] Clinical signs observed in combination with the lesion seen on MRI were consistent with ischemic CVA. Due to the severity of clinical signs and the size of the lesion observed on MRI, her prognosis for recovery was poor to grave. Therefore the chimpanzee was euthanized that day, and a necropsy was performed. Grossly, a large cavitation in the left cerebrum extended from the frontal temporal area to the occipital lobe. Histologically, the large focus of cavitation in the cerebrum had extensive necrosis intermixed with hemorrhage and occasional infiltrates of gitter cells.

A second female chimpanzee (age, 34 y; weight, 69 kg) was observed to have fallen from a climbing structure; in the days after the fall, she was anorexic and abnormally lethargic. She appeared ataxic and occasionally stumbled. The abnormalities seemed to be more prominent on her left side. On physical examination, the chimpanzee was only mildly responsive to stimulation and was reluctant to move. This animal had a documented 7-y history of lameness due to progressive arthritis. At the time of examination there was no evidence of trauma or swelling in the legs or arms. She was placed on pain medication (acetaminophen and oxycodone) prophylactically in the event that the pain was associated with arthritis despite the absence of trauma or swelling, but her condition did not improve. The lack of response to treatment, severity of the clinical signs, and unilateral presentation of the ataxia led us to believe that she most likely had had a stroke. An MRI was performed 4 d after the initial presentation, and a CVA in the pons and medulla was noted (Figure 1). Due to a poor prognosis for rehabilitation or recovery, she was euthanized.

Grossly, extensive subarachnoid hemorrhage around the brain stem (Figure 2 A) and multifocal hemorrhage in the pons (Figure 2 B) were present. Microscopic findings in the pons parenchyma included a focal extensive infarct (Figure 2 C) and multifocal hemorrhage around small blood vessels (Figure 2 D). Due to the subarachnoid hemorrhage, aneurysm was considered as a differential diagnosis. No gross or histologic evidence of aneurysm was observed, but because the brain could not be serially sectioned at necropsy or after fixation, a ruptured aneurysm could not be ruled out. Instead, the final diagnosis was determined to be hemorrhagic CVA.

The third animal was a 40-y-old, 51-kg female chimpanzee that was splenectomized at the age of 17 y and tested positive for hepatitis C at the age of 21 y. At 24 y, she was inoculated with malaria (*Plasmodium ovale*) and was treated a month later with chloroquine phosphate. The most recent test for hepatitis C was performed when she was 37 y old and was positive. At 5 mo past her 40th birthday, she was noticed to be acutely lethargic and had a thick mucoid nasal discharge. Physical examination revealed a mild cough, a slight head tilt to the right, and bilateral nystagmus during recovery. She began to receive antibiotics to treat for possible respiratory infection. Three days after the initial presentation, she was noticed to have generalized ataxia and paresis, right-sided facial paralysis, and a head tilt to the right and was unable to chew or swallow. MRI performed under general anesthesia showed an extensive infarct involving the right side of the pons, right middle cerebellar peduncle, and inferior aspect of the right cerebellar hemisphere; these findings were consistent with infarction of the territory subserved by the right posterior inferior cerebellar artery. Due to the dense clinical deficit, prognosis for recovery or rehabilitation was poor, and the animal was euthanized. The time from presentation to euthanasia was 1 wk.

Lesions primarily involved the superior pons and an extensive, adjacent anterolateral portion of the cerebellar hemisphere. Brain sectioning revealed a superficial (0.5 cm × 0.25 cm) focus of necrosis with hemorrhage in the brainstem, another focus of necrosis (diameter, 0.5 cm) on the right side of the cerebellum (Figures 3 and 4), and a distinct region of necrosis in the superior pons. Smaller, hemorrhagic foci were present in the medulla and pons, inferior and superior to the large zone of necrosis in the pons. The location of the lesions was consistent with the clinical signs noted before euthanasia. Other findings included severe focally extensive purulent bronchopneumonia, chronic multifocal lymphoplasmacytic interstitial pneumonia with vasculitis, multifocal myocardial fibrosis with mineralization, aortic mineralization, and atherosclerosis within the aortic arch.

A retrospective analysis of chimpanzee necropsies at the Yerkes Primate Center since 1966 revealed 3 other female chimpanzees with strokes. Advanced diagnostic imaging (CT and MRI) was either not available or not performed at the time of presentation for these animals. Diagnosis was made based on a combination of clinical signs, gross necropsy examination, and histopathologic evaluation.

This first historical case (animal 4) was a 33-y-old, 57-kg, female chimpanzee that died in 1977 with a clinical history consistent with CVA. The animal was noted to have lost most of the function in her left arm and leg. She was alert, responsive, and in good body condition at the time of diagnosis. Over the course of 1 mo, her condition did not improve and, in light of her poor prognosis, she was euthanized. Necropsy revealed calcification of the basilar artery and severe atherosclerotic lesions in the epicardium, myocardium, aorta, basilar artery, and vertebral vessels at the base of the brain. On the basis of the clinical signs and necropsy findings, ischemic CVA was suspected.

The second historical case (animal 5) was a 55-y-old, 40.8-kg, female chimpanzee that died in 1996. She was noticed to have right-sided hemiparesis. Clinical evaluation revealed that she most likely had experienced a stroke, but because her clinical signs were mild and did not impair her activity, she initially remained in her group. Three months later, she appeared to have experienced another CVA that resulted in worsening of her clinical signs. In light of side effects and the prominent clinical signs, the prognosis for her recovery and return to the group was poor, and she was euthanized. Necropsy examination of the brain

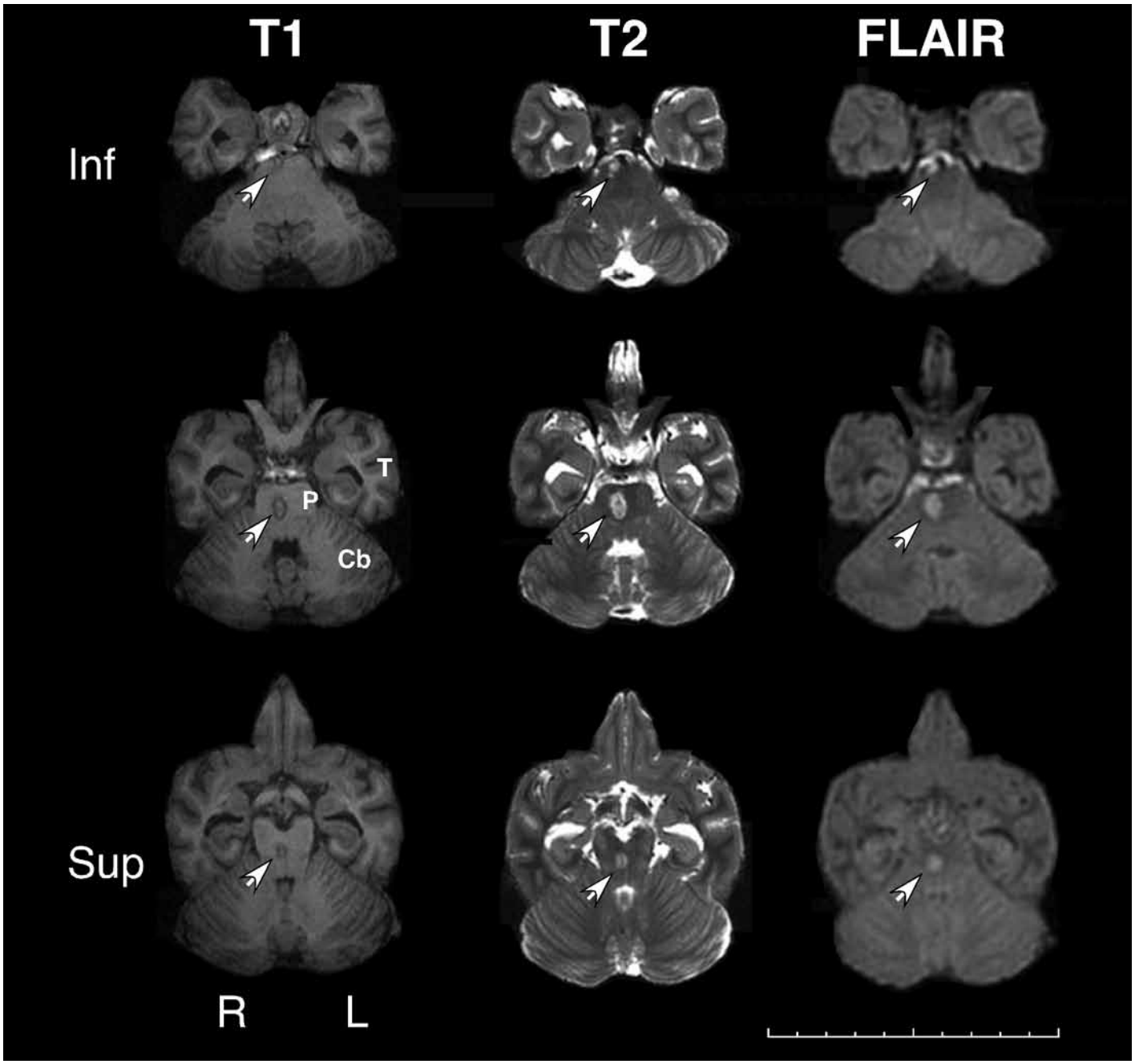

Figure 1. The brain region involved in stroke in chimpanzee 2, demonstrated through matching axial MRI sections, arranged from inferior (Inf) to superior (Sup), generated by using T1-weighted, T2-weighted, and FLAIR sequences. In all 3 imaging modalities, a lesion is evident in the right hemisphere that extends from the medulla rostrally through the pons. Images are shown in the radiologic convention, with the animal's left side on the reader's right. Cb, cerebellum; P, pons; T, temporal lobe. Bar is divided into 1-cm increments.

revealed an ischemic CVA evidenced by a subacute infarction in the left base of the pons. Moderate atherosclerosis involving the posterior cerebral, basilar, and vertebral arteries as well as the vessels in the basal ganglia also was present. The lesions observed at necropsy were consistent with the clinical signs observed prior to euthanasia.

Animal 6 was a 48-y-old, 53-kg, female chimpanzee that was found to be semicomatose one morning (1971). Nystagmus was present in both eyes, the right pupil was fixed and dilated, and it appeared as though the animal could not open the corresponding eyelid. The right side of her face was slightly distorted, with frequent twitching. Her condition progressively declined throughout the day, and she suffered a cardiac arrest 12 h after initial presentation. Findings at necropsy indicated hemorrhagic CVA. Notable findings were congested cerebral vessels and extensive superficial hemorrhage over the brain stem; a massive blood clot in the ventricles; and numerous prominent yellow-white streaks and plaques in the intima of the aortic arch, consistent with

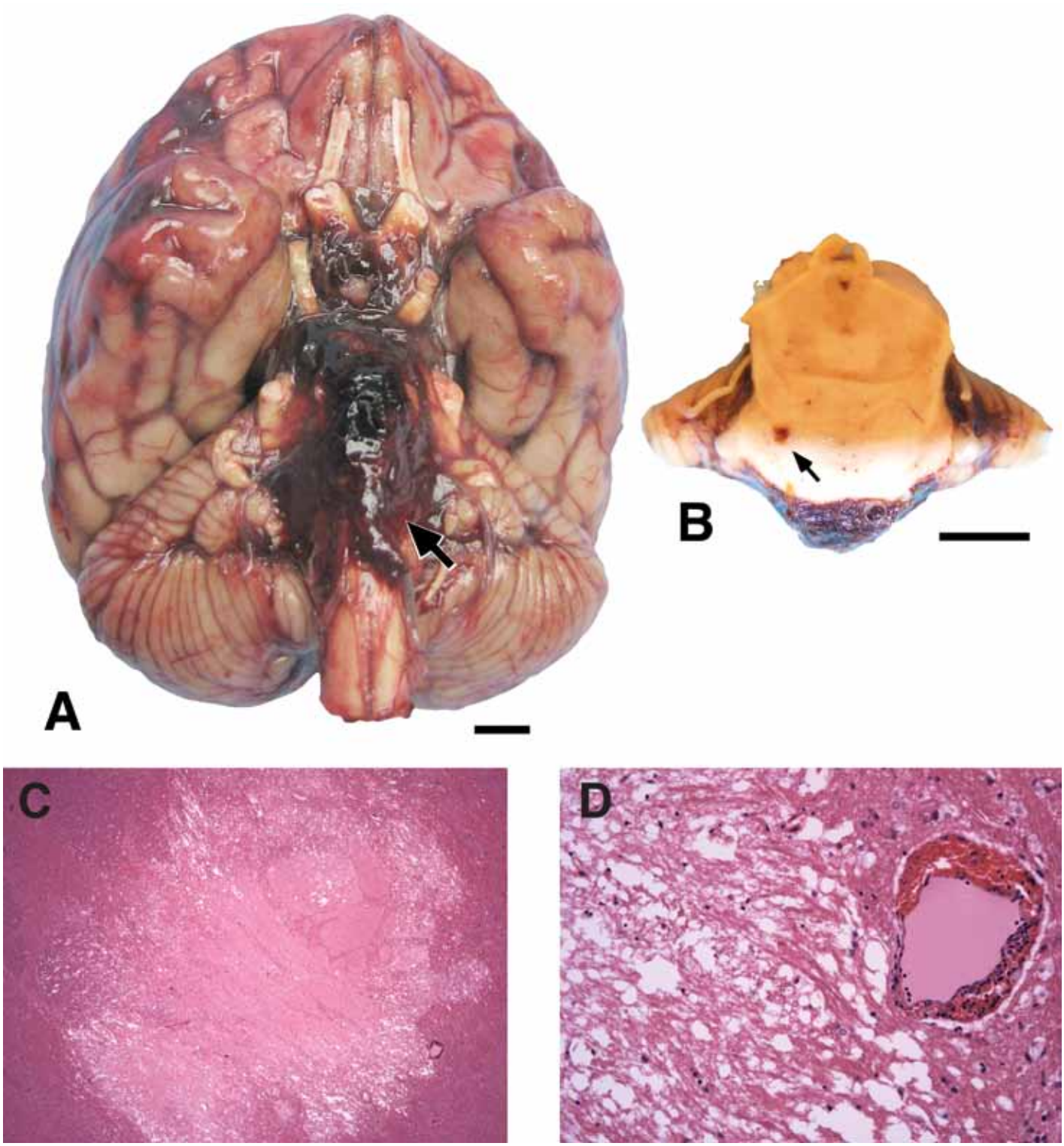

Figure 2. Necropsy photos of chimpanzee 2. (A) Basal view of the brain, showing extensive subarachnoid hemorrhage (arrow) below the pons and midbrain. (B) An example of multifocal hemorrhage in the pons (arrow). Bar, 1 cm. (C) Focal extensive infarction in the pons parenchyma (boundaries are denoted by arrows). (D) High-magnification view of the periphery of the infarct in the pons parenchyma also showing an example of the hemorrhage around small blood vessels (arrow). Hematoxylin and eosin stain; magnification: 20× (C), 200× (D).

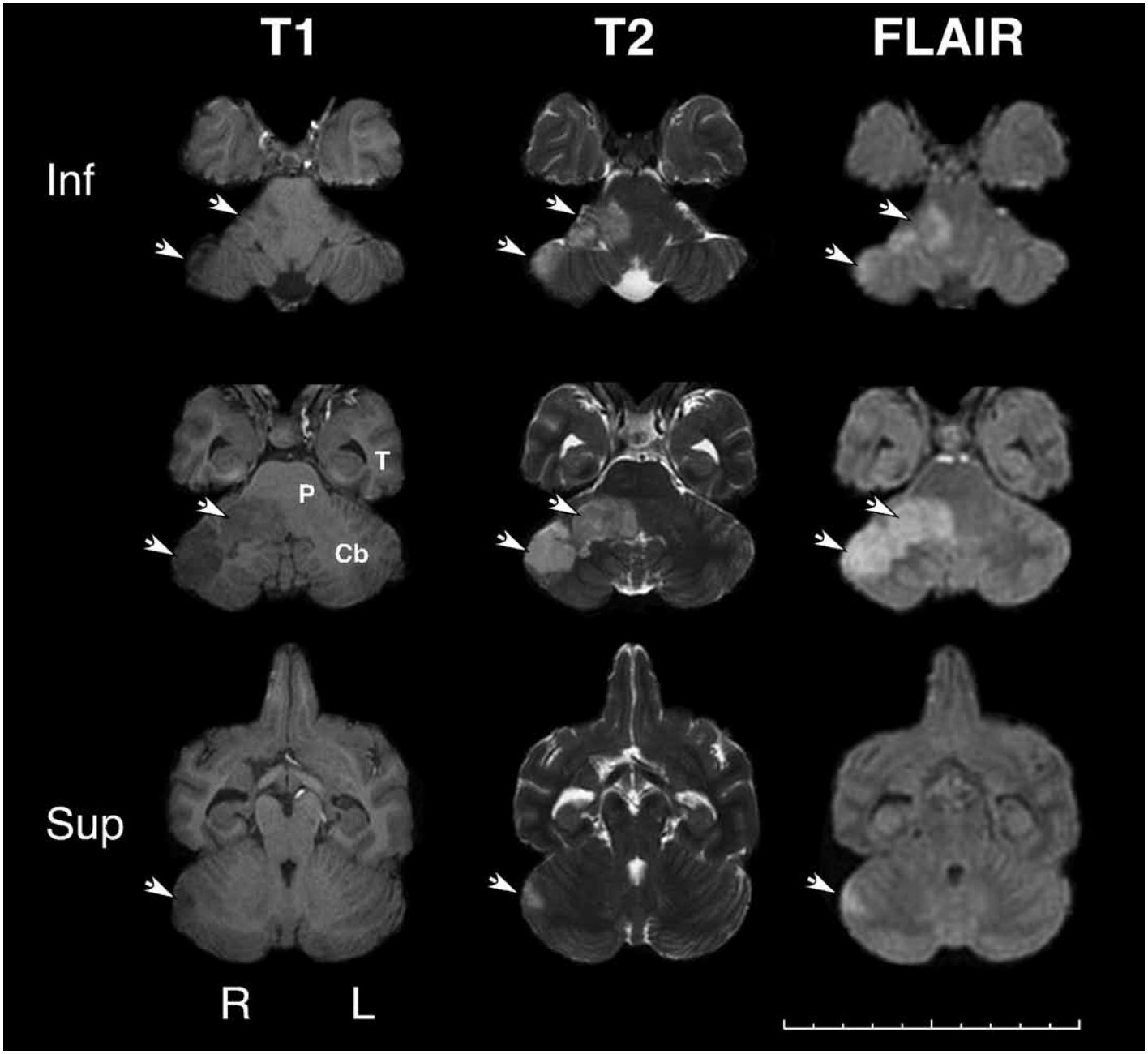

Figure 3. The brain region involved in stroke in chimpanzee 3 demonstrated through matching axial MRI sections, arranged inferior (Inf) to superior (Sup), generated by using T1-weighted, T2-weighted, and FLAIR sequences. The middle row of images shows the center of the affected region; the upper and lower rows show the stroke near its inferior and superior limits. The small arrows indicate the lesion, which in this case involves the right cerebellar hemisphere and adjacent part of the brainstem. Images are shown in the radiologic convention, with the animal's left side on the reader's right. Cb, cerebellum; P, pons; T, temporal lobe. Bar is divided into 1-cm increments.

atherosclerosis. Histologic evaluation revealed markedly thickened walls, primarily due to fibrous thickening of the intima, in all vessels examined. The brain was edematous, and most blood vessels in the brain were thickened, with a few containing small calcified areas.

Discussion

Although we cannot predict a change in the incidence of stroke in our colony or in the general population of captive chimpanzees, we do know that successful recovery from stroke depends on early diagnosis and treatment. Early diagnosis, treatment, and rehabilitation after middle cerebral artery infarction in a chimpanzee at a zoo[6] led to successful return of full gross motor function, with prolonged anticoagulation therapy with aspirin and a 45-d tapered course of prednisone. However, the lesions in 5 of the 6 chimpanzees we present here were too severe to be treated by pursuing a long-term treatment. The remaining chimpanzee's first stroke was mild enough that she was able to remain in the

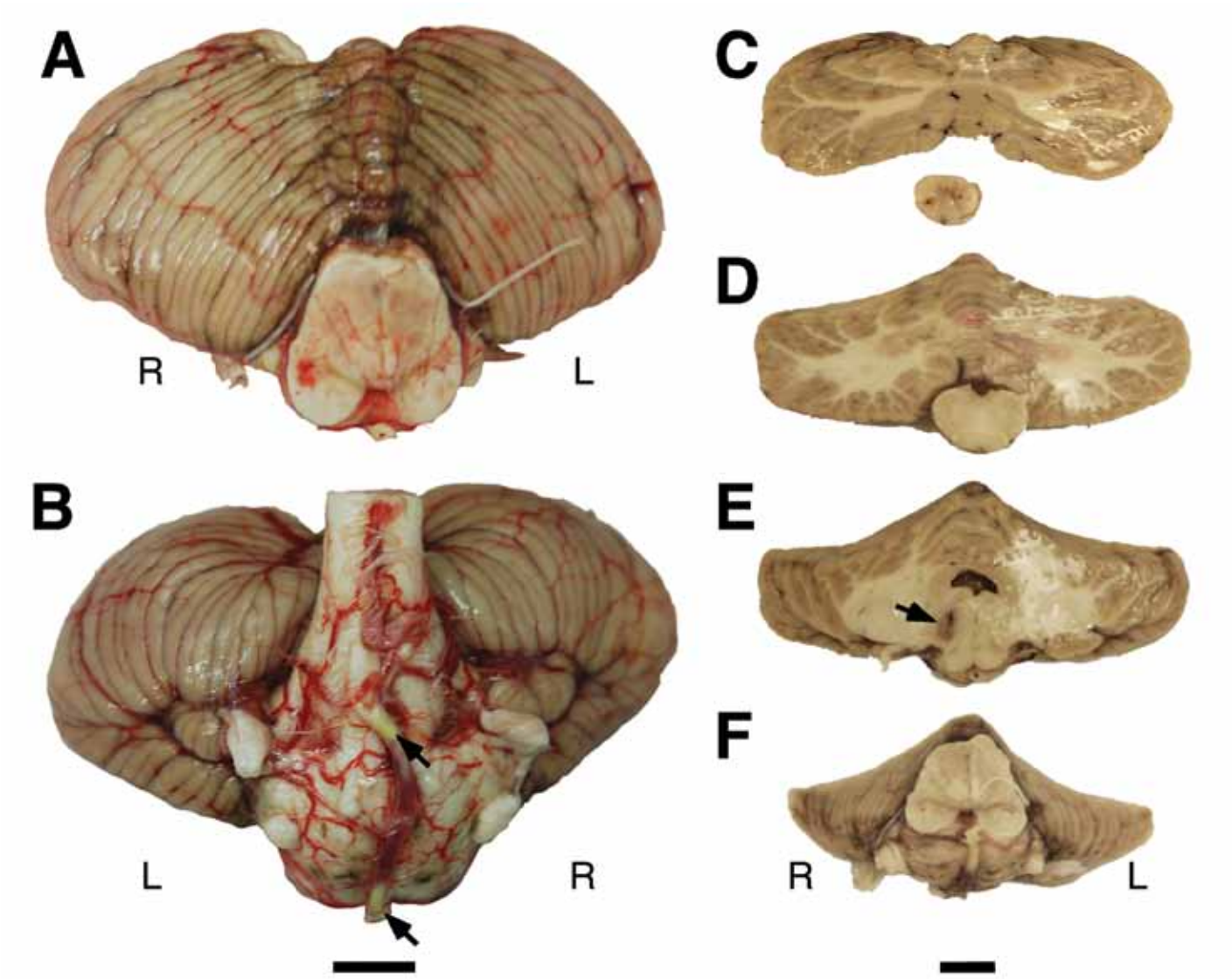

Figure 4. Necropsy photos of chimpanzee 3. (A) Superior and (B) inferior views of the cerebellum and brainstem. (A) The right cerebellar hemisphere is pale compared with the left hemisphere. (B) The basilar artery has yellowish discoloration (arrows). (C through F) A series of sections taken orthogonal to the axis of the brainstem. A lesion is clearly visible in the pons in E (arrow). Bar, 1 cm.

group for 3 mo, but the total damage sustained after the second CVA did not allow for the same outcome.

To assess whether cases of stroke in chimpanzees are underreported, we sent a survey to 43 persons representing 38 zoos (all of which participate in the Chimpanzee Species Survival Plan), 4 research facilities, and one sanctuary. We received 27 responses, and 6 facilities reported 5 additional cases of stroke in captive chimpanzees, including that described in the previous report.[6] Among the 6 additional cases (which occurred between 1971 and 2010), 5 involved female chimps, all animals were 25 to 40 y old, and all had accompanying clinical signs that led to diagnosis of stroke. CT and MRI were performed on 3 of 6 these animals, and results were consistent with the lesions observed at necropsy. The other 3 animals did not undergo advanced imaging analysis, but their lesions were confirmed at necropsy. Four of the 6 chimpanzees died or were euthanized as a result of the stroke or of complications resulting from the stroke. The remaining 2 animals were rehabilitated and returned to their social groups.

The clinical signs of stroke depend on the location and severity of the lesion.[9] Clinical signs can worsen during the first 2 to 3 d after the event, due to swelling from edema in the brain. Increased intracranial pressure can cause further functional impairment even if the original lesion does not enlarge. Symptoms lessen in a few days as the fluid is resorbed and pressure decreases.[3] The most commonly reported clinical signs in humans include unilateral muscle weakness, unilateral drooping of the face, incoordination, difficulty swallowing, numbness or tingling, and changes in mood or personality.[9] Diagnosis of numbness and tingling is difficult in chimpanzees, but the other clinical signs observed in them have been consistent with those reported in humans.

Studies have shown that some of the predisposing factors for stroke in humans are advanced age, hypertension, atrial fibrillation,

increased blood lipids, diabetes mellitus, blood disorders, and other heart-related problems.[7] Although the chimpanzees we describe here did not have atrial fibrillation, diabetes, or any blood disorders, they were all overweight, and chimpanzees 1 and 5 had histories of grade II and I systolic heart murmurs, respectively. Female chimpanzees appear to be predisposed to stroke, in that the cases we present here and those elicited through the survey were predominantly female. We do not have an explanation for this observation, but it warrants further research. Chimpanzees in captivity have been reported to live a maximum life span of 59 y for female chimps and 45 y for male chimps, with median life expectancies of 25.5 and 17 y, respectively.[5,13] According to these data, the CVA cases reported here occurred in middle-aged to older animals.

Hypercholesterolemia, diabetes, obesity, hypertension, and sedentary lifestyle are all risk factors for atherosclerosis.[25] Most of the animals we described were considered to be overweight to varying degrees. All of the 6 chimpanzees from our institution had some atherosclerosis, although it was determined to be clinically insignificant and not a factor in the etiology of the CVA. Serum cholesterol levels in these animals were compared with previously published serum cholesterol reference ranges.[12,15] Both sources were relatively consistent, documenting mean blood cholesterol levels of approximately 190 to 300 mg/dL for female chimpanzees older than 20 y[15] and of 175 to 315 mg/dL for female chimpanzees 30 to 60 y old.[12] Three of the 6 female chimps from our institution had cholesterol levels of 250 mg/dL or greater during the year preceding the CVA; these levels fall within the reference range for normal. One female chimpanzee yielded a cholesterol level of 429 mg/dL shortly before her CVA. Because blood cholesterol levels were not measured throughout the lives of the chimpanzees, we cannot draw any conclusions or correlations regarding whether persistently elevated or high normal cholesterol levels were related to stroke in these animals.

In humans, one of the most common etiologies of intracranial hemorrhage (and subsequently hemorrhagic stroke) is chronic hypertension, which results in degenerative changes in the vessel wall and eventual rupture and hemorrhage.[21] Hypertension-associated intracranial hemorrhage often occurs in the basal ganglia, thalamus, pons, and cerebellum and results from the rupture of arterioles that originate from the larger vessels of the proximal circle of Willis.[9] Because numerical values for blood pressure were not recorded consistently in the medical records of the chimpanzees at our institution, we were unable to make any evaluations or correlations regarding the role of hypertension in the development of stroke in these animals.

Diagnosis of CVA in humans usually is based on symptoms and the results of physical examination, imaging, and blood tests. Most ischemic strokes begin suddenly, develop rapidly, and cause death of brain tissue within minutes to hours; symptoms present acutely and are often most severe a few minutes after onset.[8,9] Animals suspected of having a stroke should receive a physical exam with a thorough neurologic exam. If the animal is stable, other tests are useful in diagnosing stroke, identifying its etiology, and ruling out other causes. Echocardiography can identify abnormal heart rhythms, which can predispose a patient to stroke, and is advantageous in visualizing thrombi, pumping or structural abnormalities, and valve disorders, all of which also can predispose to stroke. Diagnostic blood work can identify anemia, polycythemia, blood clotting disorders, vasculitis, infections, and hypercholesterolemia.[9] An angiogram of the cerebral vasculature can be performed to identify an aneurysm or arteriovenous malformation, which may increase the risk of hemorrhagic stroke.[16] The most advantageous of the diagnostic tests that can be done in suspected cases of stroke are advanced diagnostic imaging such as CT or MRI. CT helps to distinguish ischemic stroke from other pathologies, such as hemorrhagic stroke, brain tumor, intracranial abscess, and other structural abnormalities.[9,16,22] MRI is particularly useful because it can detect ischemic strokes within minutes of their start.[9,17,24] These tests should be performed as soon as possible to have the most benefit in managing the animal's outcome and rehabilitation.

The treatment of stroke is most beneficial if therapy is started as soon as possible after a CVA is diagnosed.[2,4,9,10] The course of therapy depends on the type of stroke. It is imperative that the type of stroke—ischemic compared with hemorrhagic—is diagnosed prior to initiating therapy. Antiplatelet and anticoagulant drugs are used in the treatment of ischemic strokes but are contraindicated and could be deadly if administered to a patient suffering from a hemorrhagic stroke. Short-term therapy for ischemic strokes is aimed at noninvasive or invasive recanalization of the blocked vessel.[9] Thrombolytic drugs are used to dissolve the clot or unblock the artery. Antiplatelet medications (for example, aspirin, heparin, warfarin) can be beneficial in discouraging further clot formation.[9] In addition, direct surgical removal of the thrombus can restore circulation to the area affected.[9] Angioplasty and vascular stenting have been used in humans but have not yet been described in chimpanzees.

Immediate therapy for hemorrhagic stroke is aimed at identifying the damaged vessel, stopping the hemorrhage, and potentially removing the clotted blood from the area. Once the hemorrhage is controlled, the tissue still needs time to reabsorb the fluid and cells; meanwhile, edema and swelling of the brain can cause patients to worsen clinically even though the lesion remains the same in size. The pressure from those processes can cause additional damage and varying additional clinical signs, depending on the area of the brain compressed even though the original insult has resolved. Long-term therapy is focused on rehabilitation of motor function to the areas of the body that are deficient because of damage to the corresponding area of the brain. Some lesions are so severe that brain function to that area is lost permanently. Other lesions are less severe, and the patient may regain partial or complete function over time as the swelling decreases and the brain heals and repairs itself.

Rehabilitation has only been documented once in a chimpanzee, with a favorable outcome.[6] Respondents to our survey reported that 5 of the 6 chimpanzees were treated; the remaining animal was not treated because it did not regain consciousness after anesthesia for examination. Three of the 6 animals were treated with thrombolytics but ultimately were euthanized because of the severity of their lesions. One of the 6 animals received fluids, antibiotics, oral aspirin, and twice-weekly physical therapy for months. The animal's clinical signs improved markedly over 6 to 8 mo and continued to improve slightly for an additional 4 to 6 mo. The animal regained some function of the affected arm and was able to compensate for the handicap when returned to its group. The final animal (previously reported[6]) was treated with aspirin to inhibit clot formation and with prednisone to decrease swelling and inflammation. Although successful treatment was achieved in only 2 animals in this review, as in humans the key

to successful treatment is early diagnosis and treatment. In light of the aging population of captive chimpanzees, the potential increased risk of CVA in this age group compared with humans, and the severity of the outcome of a CVA, veterinarians should recognize, diagnose, and institute treatment as early as possible to increase the likelihood of a successful outcome.

Acknowledgments

We acknowledge the invaluable contributions of Dr Jack Fountain, who provided neuroradiology consult. We thank Dr Xiaodong Zhang for directing the MRI scans. This work was supported by NIH–NIA grant P01AG026423 and the Yerkes base grant 2P51RR000165-51.

References

1. **Auriel E, Bornstein NM.** 2010. Neuroprotection in acute ischemic stroke—current status. J Cell Mol Med **14:**2200–2202.
2. **Barnett H.** 1992. Stroke: pathophysiology, diagnosis, and management. London (UK): Churchill Livingstone.
3. **D'Arceuil HE, Duggan M, He J, Pryor J, de Crespigny A.** 2006. Middle cerebral artery occlusion in *Macaca fascicularis*: acute and chronic stroke evolution. J Med Primatol **35:**78–86.
4. **deVeber GA.** 2010. Delays in the timely diagnosis of stroke in children. Nat Rev Neurol **6:**64–66.
5. **Dyke B, Gage TB, Alford PL, Swenson B, Williams-Blangero S.** 1995. Model life table for captive chimpanzees. Am J Primatol **37:**25–37.
6. **Fish PH, Carpenter JW, Kraft S.** 2004. Diagnosis and treatment of a cerebral infarct in a chimpanzee (*Pan troglodytes*). J Zoo Wildl Med **35:**203–207.
7. **Fonarow GC, Reeves MJ, Zhao X, Olson DM, Smith EE, Saver JL, Schwamm LH.** 2010. Age-related differences in characteristics, performance measures, treatment trends, and outcomes in patients with ischemic stroke. Circulation **121:**879–891.
8. **Garcia JH.** 1975. The neuropathology of stroke. Hum Pathol **6:**583–598.
9. **Gorelick PB, Ruland S.** 2010. Diagnosis and management of acute ischemic stroke. Dis Mon **56:**72–100.
10. **Guyton AC, Hall JE.** 2000. Textbook of medical physiology. Philadelphia (PA): WB Saunders.
11. **Heiss WD.** 2010. The concept of the penumbra: can it be translated to stroke management. Int J Stroke **5:**290–295.
12. **Herndon JG, Tigges J.** 2001. Hematologic and blood biochemical variables of captive chimpanzees: cross-sectional and longitudinal analyses. Comp Med **51:**60–69.
13. **Herndon JG, Tigges J, Anderson DC, Klumpp SA, McClure HM.** 1999. Brain weight throughout the life span of the chimpanzee. J Comp Neurol **409:**567–572.
14. **Jin R, Yang G, Li G.** 2010. Inflammatory mechanisms in ischemic stroke: role of inflammatory cells. J Leukoc Biol **87:**779–789.
15. **Lee DR, Doane, CJ**. 2003. APV Primate Formulary. [Cited May 2012]. Available at: http://www.primatevets.org/education
16. **Liebeskind DS.** 2009. Imaging the future of stroke. I. Ischemia. Ann Neurol **66:**574–590.
17. **Liu Y, D'Arceuil HE, Westmoreland S, He J, Duggan M, Gonzalez RG, Pryor J, de Crespigny AJ.** 2007. Serial diffusion tensor MRI after transient and permanent cerebral ischemia in nonhuman primates. Stroke **38:**138–145.
18. **Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VL, Rosamond W, Sacco R, Sorlie P, Thom T, Wasserthiel-Smoller S, Wong ND, Wylie-Rosett J, American Heart Association Statistics Committee and Stroke Statistics Subcommittee.** 2010. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. Circulation **121:**e46–e215.
19. **Murphy SJ, McCullough LD, Smith JM.** 2004. Stroke in the female: role of biological sex and estrogen. ILAR J **45:**147–159.
20. **Prusty S, Kemper T, Moss MB, Hollander W.** 1988. Occurrence of stroke in a nonhuman primate model of cerebrovascular disease. Stroke **19:**84–90.
21. **Plesea IE, Camenita A, Georgescu CC, Enache SD, Zaharia B, Georgescu CV, Tenovici M.** 2005. Study of cerebral vascular structures in hypertensive intracerebral haemorrhage. Rom J Morphol Embryol **46:**249–256.
22. **Rosen RF, Farberg AS, Gearing M, Dooyema J, Long PM, Anderson DC, Davis-Turak J, Coppola G, Geschwind DH, Pare JF, Duong TQ, Hopkins WD, Preuss TM, Walker LC.** 2008. Tauopathy with paired helical filaments in an aged chimpanzee. J Comp Neurol **509:**259–270.
23. **Saini M, Butcher K.** 2009. Advanced imaging in acute stroke management—part I: computed tomographic. Neurol India **57:**541–549.
24. **Saini M, Butcher K.** 2009. Advanced imaging in acute stroke management—part II: magnetic resonance imaging. Neurol India **57:**550–558.
25. **Varki N, Anderson D, Herndon JG, Pham T, Gregg CJ, Cheriyan M, Murphy J, Strobert E, Fritz J, Else JG, Varki A.** 2009. Heart disease is common in humans and chimpanzees but is caused by different pathological processes. Evol Appl **2:**101–112.