Experimental induction of cerebral aneurysms in monkeys

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Saccular cerebral aneurysms were successfully induced in two monkeys treated with ligation of the common carotid artery, experimental hypertension, and β-aminopropionitrile feeding. The cerebral aneurysms developed on the large arteries at the base of the brain, such as the anterior communicating artery and the internal carotid artery at the origin of the posterior communicating artery. Because of the similarity of the monkey to man as a species, the present results strongly suggest the significance of postnatal aggravating factors in the development of cerebral aneurysms in man.

KEY WORDS • cerebral aneurysm • hypertension • carotid ligation • β-aminopropionitrile • pathogenesis • monkey

Although intracranial arterial aneurysms are of considerable importance in cerebrovascular pathology and neurosurgery, many problems concerning their etiology, pathogenesis, and treatment are still unsolved. The difficulties in studying the problems are partly caused by the extreme rarity of the disease in animals and the lack of an appropriate animal model of the disease.16

As described previously, this laboratory has developed an experimental model for inducing cerebral aneurysms in rats by ligation of one or both of the common carotid arteries and the production of experimental hypertension with or without β-aminopropionitrile feeding. The induced aneurysms are located on the large arteries at the base of the brain. Some of them apparently originate from the apex of an arterial bifurcation. The macroscopic and microscopic findings are generally in accordance with those of spontaneous lesions in man. These results have been presented in review form in several journals.4,9,10

This study reports for the first time the successful induction of cerebral aneurysms in monkeys after treatment with ligation of the common carotid artery, production of hypertension, and β-aminopropionitrile feeding under the same concepts as pertained to the rat model. Successful induction of cerebral aneurysms in primates indicates the possibility of establishing a new animal model of the disease. This model offers numerous opportunities for investigation related to cerebral aneurysms and subarachnoid hemorrhage that cannot be obtained from clinical observations, autopsy materials, or previously developed animal models.

Materials and Methods

Female monkeys (Macaca fascicularis), each weighing 3 to 3.5 kg, were used in this study. The estimated age of these animals was around 5 years. Under general anesthesia (intramuscular ketamine, initial dose 20 mg/kg followed by 10 mg/kg every 30 minutes), a posterior branch of the right renal artery and the left common carotid artery were ligated. One week after the operation when the animals had regained their preoperative level of activity, a posterior branch of the right renal artery and the left common carotid artery were ligated. One week after the operation, one percent NaCl solution was given as drinking water. One week after the second operation, β-aminopropionitrile fumarate (a lathyrogenic agent2) was added to a standard laboratory diet in a concentration of 0.2%. Seven monkeys were prepared by these techniques. Follow-up angiography was performed regularly every 3 months.

Results

One year after the start of the experiment, follow-up angiography in one of the monkeys revealed a cerebral aneurysm on the internal carotid artery at the origin of...
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FIG. 2. Magnified view of the saccular cerebral aneurysm at the anterior communicating artery. It is clear that the aneurysm originated at the arterial bifurcation. The dome of the aneurysm was transparent, indicating a very thin aneurysmal wall.

FIG. 1. Multiple cerebral aneurysms in a monkey sacrificed 1 year after the start of the experiment. A saccular cerebral aneurysm developed at the bifurcation of the anterior cerebral and anterior communicating arteries (white arrow). Another aneurysm was found on the internal carotid artery at the origin of the posterior communicating artery on the opposite side from the carotid artery ligation (black arrow). Another small protrusion was found on the internal carotid artery at the origin of the anterior choroidal artery (arrow-head).

Discussion

Three cases of naturally occurring cerebral aneurysms have been reported in chimpanzees. Although there are a few other reports about the production of cerebral aneurysms in primates, those lesions were traumatic in origin or lacked macroscopic or histopathological description. In 1978, we first induced cerebral aneurysms in rats by the same method as in the monkeys presented in this report. In that study, aneurysms induced in rats were shown to be very similar to spontaneous lesions in man in respect to the location, macroscopic and microscopic findings, and natural course. Analysis of the experimental conditions revealed that hemodynamic stress, arterial hypertension, and a metabolic disorder of the connective tissue were of primary importance for the development of cerebral aneurysms. By studying early stages of aneurysmal...
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development, it was found that the initial change occurs not at the apex, but on the distal side of the major branch adjacent to the apex, at the intimal pad and the neighboring distal portion.\textsuperscript{12,13} It is very difficult to detect cerebral aneurysms in rats before sacrifice, however, because of the size of the animal. For further biochemical study of the metabolic process occurring near the apex of an arterial bifurcation, the specimen obtained from rats is too small to analyze.

Before the successful induction of cerebral aneurysms in monkeys in this study, we treated seven other monkeys with different methods for inducing arterial hypertension or with differing timing of treatments. In that group adequate hypertension was not achieved or the animals died shortly after the start of the experiment. Although the present study is still under way and we continue to study the other treated monkeys, we think that it is useful to report the first successful induction of cerebral aneurysms in monkeys, indicating the possible establishment of a new animal model that is very similar to human cases in many aspects. Because of the species similarity of the monkey to man, the present results strongly suggest the significance of postnatal aggravating factors in the development of cerebral aneurysms in man.

References


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