The cause of intracerebral hemorrhage with particular increased risk in the elderly is intriguing. We think severe amyloid angiopathy is crucial in the pathogenesis, but only a few well-documented cases have been reported. Kase et al very recently drew attention to an excessive prolongation of APTT, not found in our series. However, it may well be that excessive anticoagulation together with severe amyloid angiopathy is the final common pathway. We recently observed one patient (Figure) with multiple intracranial hemorrhages from excessive warfarin anticoagulation alone. Fibrinolytic agents may be only one of the triggers in the pathogenesis of intracranial hemorrhages following acute myocardial infarction. It may be that any type of anticoagulation, which significantly prolongs bleeding time, will predispose patients to the catastrophic hemorrhage (hemorrhages in multiple sites and compartments, fluid levels) described.1-3

Eelco F.M. Wijdicks, MD
Clifford R. Jack, Jr, MD
Department of Neurology and Diagnostic Radiology
Mayo Clinic
Rochester, Minn

References

Extracranial Vertebral Artery Dissection Presenting as Subarachnoid Hemorrhage

To the Editor:

We were interested by the recent case report by Kaplan et al of extracranial (C3 to C7) vertebral artery dissection with subarachnoidal hemorrhage (SAH). The patient was said to be “the first patient with an extracranial vertebral artery pseudoaneurysm presenting with subarachnoid hemorrhage…. We are surprised that the authors did not discuss the possibility of an associated intracranial vertebral artery dissection.

Subarachnoid hemorrhage is present in more than half of the reported cases of intracranial vertebral artery dissection, which account for nearly 5% of lethal SAH. Furthermore, 20% of vertebral artery dissections involve both the extracranial and intracranial portions. In the case report by Kaplan et al, angiography was performed twice and said to be normal, but no specific information was provided on the intracranial circulation. Moreover, a normal angiogram would not rule out an intracranial vertebral artery dissection, which is notoriously difficult to diagnose, particularly in the presence of SAH.

We reported in this journal a case very similar to that of Kaplan et al, involving a 44-year-old woman who presented with SAH and blood in the third ventricle. Cerebral angiography disclosed a diffuse but moderate narrowing of the intracranial segment of the right vertebral artery and an aneurysm in its extracranial segment at the C1 level. The patient recovered completely without treatment, and control angiography performed 6 weeks later was normal. The interesting fact is that the diagnosis of intracranial dissection of the vertebral artery would have been impossible without the coexistence of the typical image of a dissected aneurysm on the extracranial segment.

We would therefore like to suggest that the most likely explanation for the occurrence of SAH in the case of Kaplan et al was, as in ours, an associated intracranial vertebral artery dissection.

We were also rather surprised by the therapeutic approach of this case. Admittedly, the proper management of vertebral artery dissection is still controversial. However, it is well established (from a number of recent series of vertebral artery dissections, which Kaplan et al do not refer to in their very surgically oriented review of the literature) that the prognosis of extracranial vertebral artery dissection is usually good and that in the vast majority of patients with stenosis the artery returns to normal in less than 3 months. The authors performed a balloon occlusion of the vertebral artery to “reduce the threat of hemorrhage from the pseudoaneurysm.” Rebleeds occur in 30% of patients with intracranial vertebral artery dissections initially presenting with SAH,4-12 but there is no evidence that extracranial dissecting aneurysms carry a risk of rebleeding. The natural history of such aneurysms, which is much better known for the carotid artery, is that they resolve or improve in almost 50% of cases, and when they persist, they don’t rupture.4,5,11 We therefore see no scientific evidence for practicing vertebral artery occlusion (or surgery) in such cases. Furthermore, one could also dispute the use of anticoagulants, even after vertebral artery balloon occlusion, in a patient presenting with SAH. Most authors recommend anticoagulation in patients with extracranial cervical artery dissections but consider that anticoagulation is contraindicated if the dissection extends intracranially or if the cerebrospinal fluid contains blood.4,7,12

In summary, the case reported by Kaplan et al does not prove that an isolated dissection of the extracranial segment of a vertebral artery is a cause of SAH. An intracranial dissection could have been associated, even in the presence of a normal angiogram. The existing literature on extracranial dissecting aneurysms of carotid and vertebral arteries does not suggest a risk of bleeding, and there is no scientific rationale for arterial occlusion (or surgery) in such cases.

Valérie Blouesse, MD
Marie-Germaine Bousset, MD
Hôpital Saint-Antoine
Jean-Louis Mas, MD
Hôpital Saint-Antoine
Paris, France
activate voltage-sensitive calcium channels (VSCC). In vitro experiments have established that calcium influx through VSCCs can lead to rapid transcriptional activation of immediate early genes (IEGs), a class of genes involved in signal transduction to the nucleus. Other stimuli, such as activation of the N-methyl-D-aspartate receptor, can also elicit IEG expression. Once induced, IEG mRNAs are shuttled to the cytoplasm and translated into proteins, eg, FOS or JUN. These proteins reenter the nucleus, bind to their target genes, and regulate their transcription.

Distinctive compensatory changes in neuronal gene expression appear to be mediated by the specific IEGs induced. A large number of these have been now identified, and a significant effect is now aimed at describing the specific IEGs induced over time in different ischemic models, with the goal of distinguishing IEGs that may lead to protection from those that may signal or induce cell death.

An and colleagues, by using a model of transient reversible focal ischemia, recently showed that jun B and c-fos mRNAs were induced by ischemia, and their relative concentrations were significantly higher at 60 minutes of reperfusion. The authors showed that the increase in IEG expression was associated with a fourfold to sixfold increase in the activity of the transcription factor AP-1, which may in turn induce the expression of late response genes such as those that lead to the production of growth factors. While it is clear that some IEGs may modify the postischemic cerebral environment in potentially protective ways, Smyne and colleagues showed in nonischemic models that c-fos will appear just after histological evidence of cell death. Using transient global ischemia in which a period of four-vehicle occlusion is subsequently followed by selective vulnerability of striatal and CA1 neurons, Wessel and colleagues showed that the CA1 region developed an early and late c-fos signal after ischemia. It should soon be possible to experimentally modify the regional concentrations of one or more of these mRNAs to test for the protective or destructive effect that each may mediate.

Heat-shock protein (HSP) is also likely to play a role in neuronal protection from ischemia. Since HSP mRNA does not contain an AP-1 site, its regulation is probably distinct from that of IEGs. Induction of HSP was shown to be protective in retinal cells. Using cell culture studies Lowenstein et al suggested that stress proteins may have a protective role in excitotoxicity. Kirino and his colleagues were able to induce tolerance to ischemia in the gerbil hippocampus and correlated it with the induction of HSP. This protein is known to rise regionally after ischemia and may thus possess neuroprotective properties that can be experimentally modified.

It is clear, then, that a brain region that has been exposed to an episode of transient ischemia can rapidly set in motion mechanisms that may lead to long-term alterations in its structural and functional protein composition. At least some of these changes may be neuroprotective, and others may carry cell death programs. The experimental challenge is to identify these factors and test the effect of modifying them on cell survival.

At the clinical level, the occurrence of a TIA identifies the patient as being at increased risk of developing a stroke, but TIs have never been studied from the perspective that they may increase the brain’s resistance to subsequent infarction. Patients who have a single TIA face a smaller (and a declining) effect of modifying them on cell survival.

It is now clear that in response to short-lasting stimuli at its surface the cell can activate genes that may lead to alterations in its protein composition. We have shown in animal studies in vivo that transient ischemia such as occurs during a TIA can reversibly activate voltage-sensitive calcium channels (VSCC). In vitro experiments have established that calcium influx through VSCCs can lead to rapid transcriptional activation of immediate early genes (IEGs), a class of genes involved in signal transduction to the nucleus. Other stimuli, such as activation of the N-methyl-D-aspartate receptor, can also elicit IEG expression. Once induced, IEG mRNAs are shuttled to the cytoplasm and translated into proteins, eg, FOS or JUN. These proteins reenter the nucleus, bind to their target genes, and regulate their transcription.

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Some investigators have shown that brief ischemic insults can under some circumstances increase the brain’s tolerance to a subsequent “significant” episode of ischemia. Kirino and his colleagues, using bilateral common carotid artery occlusion in the gerbil, showed that a 5-minute ischemic episode causes significant injury to the CA1 region of hippocampus. However, neuronal damage was reduced when the same 5-minute ischemic insult was preceded 1 to 4 days earlier by a 2-minute episode of ischemia. This protection was removed if the two ischemic episodes were spaced more closely. These data agree with the findings of Kitagawa et al and Kato et al, who showed that both the duration of the first ischemic insult and the interval between the two episodes are important determinants of the degree of protection. It is reasonable, then, to conclude that at least in animal experiments, transient episodes of ischemia that do not cause damage may under some circumstances be neuroprotective. These data suggest that short-lasting ischemic episodes probably upregulate enzymatic and other protein synthetic activities that can ultimately confer protection.

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V Biousse, M G Bousser and J L Mas

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