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Spontaneous Thrombosis of Ruptured Intracranial Aneurysms During Treatment With Tranexamic Acid (AMCA)

Report of Three Cases

By

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With 8 Figures

Summary

Radiographically verified spontaneous disappearance of medium-sized arterial cerebral aneurysms is seldom reported, and only three times in connection with antifibrinolytic therapy (EACA). In our clinic repeat angiograms have shown non-filling of the aneurysms in three patients during treatment with tranexamic acid (AMCA) two, three, and four weeks respectively after primary bleeds. Initially, all three patients had severe radiological vasospasm associated with neurological deterioration. Follow-up angiograms have demonstrated partial reappearance of the aneurysm after one month in one patient and complete disappearance of the aneurysms in the other two patients after 9 and 22 months respectively. In two cases occlusion of cerebral arteries occurred. With regard to the higher risk of severe vasospasm and occlusion of cerebral arteries in our opinion it should not be a therapeutic goal to try to achieve a thrombosis of a ruptured aneurysm with antifibrinolytic drugs.

The reason for spontaneous aneurysm thrombosis during treatment with AMCA may be a local inhibition of plasminogen activators in and around the aneurysm wall. It may also be related to the sympathomimetic property of the drug, with vasospasm and a subsequent flow-reduction inside the aneurysm or a possible interaction with other drugs and substances.

Keywords: Spontaneous thrombosis; Intracranial aneurysm; Subarachnoid haemorrhage, Cerebral angiography; Vasospasm; Antifibrinolytic drugs.

Introduction

Spontaneous cure of an intracranial aneurysm was first reported by Hutchinson in 1875 [25]. His case was a giant aneurysm verified at autopsy. Since then there have been numerous reports of spontane-

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Table 1. *Reported Cases of Angiographically Demonstrated Spontaneous Thrombosis of Medium-Sized Cerebral Aneurysms*

Case No.	Author	Year	Age	Sex	Location of aneurysm	Size of aneurysm	Interval between angiograms	Comment
1	Marguth and Schiefer	1957	44 years	M	Internal carotid art.	"Pea"	15 years	Trigeminal tractotomy performed between angiograms
2	Höök and Norlén	1958	58 years	F	Middle cerebral art.	25 × 17 mm	6 weeks	
3	Lindgren	1958	43 years	F	Middle cerebral art.	"Pea"	3 years	Thrombosis of feeding artery
4	Hemmer and Umbach	1960	32 years	F	Middle cerebral art.	"Pea"	7 weeks	Thrombosis of feeding artery
5	Hemmer and Umbach	1960	37 years	M	Posterior cerebral art.	"Fingertip"	6 months	First angiography performed 9 weeks after SAH
6	Björkesten and Troupp	1962	36 years	M	Internal carotid art.	not specified (< 25 mm)	5 years	Thrombosis after craniotomy with unsuccessful clipping
7	Hollin and Gross	1965	36 years	F	Internal carotid art.	not specified (< 25 mm)	2 years	Thrombosis after craniotomy with inadequate clipping
8	Lodin	1966	62 years	M	Internal carotid art.	11 × 4 mm	2 years	
9	Lodin	1966	42 years	M	Sup. cerebellar art.	"Peppercorn"	3 months	
10	Devadiga *et al.*	1969	14 months	M	Internal carotid art.	not specified (< 25 mm)	2 years	Suspected carotid-cavernous fistula
11	Kowada *et al.*	1974	42 years	M	Middle cerebral art.	8 × 5 mm	3 months	Thrombosis seen at craniotomy
12	Spetzler *et al.*	1974	55 years	F	Frontopolar art.	6 mm	16 days	During treatment with EACA. Vasospasm. Reappearance of aneurysm after 23 days
13	Scott and Garrido	1977	19 years	F	Middle cerebral art.	not specified (< 25 mm)	7 days	During treatment with EACA. Vasospasm. Thrombosis of feeding artery
14	Edner *et al.*	1978	26 years	F	Anterior communicating art.	10 × 8 × 8 mm	13 days	During treatment with EACA. Vasospasm. Thrombosis of aneurysm after 14 months

Table 2. *Own Cases of Angiographically Demonstrated Spontaneous Thrombosis of Medium-Sized Cerebral Aneurysms*

Case No.	Age	Sex	Location of aneurysm	Original size of aneurysm	Interval between angiograms	Time to follow-up angiogram	Late CT scan	Comment
1	32 years	F	Left middle cerebral artery	8 × 4 × 5 mm	4 weeks	22 months	Decreased attenuation values left hemisphere enlarged ventricles	During treatment with AMCA Vasospasm, hypertension Occlusion and recanalization of feeding artery
2	36 years	M	Right pericallosal artery	15 × 5 × 4 mm	2 weeks	1 month	Decreased attenuation values right frontal lobe enlarged ventricles	During treatment with AMCA Vasospasm, hydrocephalus Reappearance and clipping of aneurysm
3	27 years	M	Left middle cerebral artery	10 × 9 × 8 mm	3 weeks	9 months	Decreased attenuation values left hemisphere enlarged ventricles	During treatment with AMCA Vasospasm, occlusion and recanalization of feeding artery

ous thrombosis of giant aneurysms and AV malformations. Radiographically verified disappearance of medium-sized ruptured saccular aneurysms have been reported in only 14 patients [3, 8, 9, 20, 22, 26, 29, 34, 36, 37, 52, 54] including three times in connection with antifibrinolytic therapy [9, 52, 54] (Table 1). In Umeå since 1969 we have treated approximately 100 patients with ruptured aneurysms with tranexamic acid (AMCA) in the preoperative period in order to prevent rebleeding. In three of these, repeat angiography has demonstrated non-filling of the aneurysm during AMCA treatment (Table 2).

Case Reports

Case 1: 32-year-old female with known hypertension since 1961. On 6 December 1972 she experienced sudden severe headache, and became unconscious with convulsions. After a few minutes she recovered consciousness, but was disorientated with severe headache and a stiff neck. Lumbar puncture showed blood in the CSF, and the patient was referred to Umeå University Hospital. During transportation she was given a tranexamic acid (AMCA) infusion of 1.5 g. On admission the same afternoon the patient was drowsy and aphasic with a slight right hemiparesis (Botterell III). Blood pressure was 160/100. Laboratory tests including coagulation factors were normal. Left carotid angiography performed about seven hours after bleeding showed a saccular aneurysm on the left middle cerebral artery with vasospasm, a left intracerebral expansive lesion, and prolonged circulation time in the left hemisphere (Figs. 1 a, b). The patient was given AMCA intravenously 6 g daily during the first week, 4 g daily from the second to fifth weeks, and 3 g daily during the sixth week. Bilateral carotid angiography on 18 December showed increased vasospasm with occlusion of parietal branches of the left middle cerebral artery. The aneurysm had the same size and shape. Repeat left carotid angiography on 2 January 1973 showed regression of spasm and markedly diminished size of the aneurysm. Treatment with AMCA continued for another two weeks. A final angiogram on 18 October 1974 showed no filling of the aneurysm but recanalization of the occluded arterial branches (Figs. 2 a, b). CT scan 20 January 1976 showed decreased attenuation values (infarction) in the left parietal region with enlargement of the ventricles (Fig. 3). The patient has no neurological deficit except for partial epilepsy.

Case 2: 35-year-old man who on 26 December 1976 developed sudden headache, and a few hours later became unconscious. On admission the following day he was still unconscious with increased tone and paresis in the right arm and leg (Botterell IV). Blood pressure was 140/90. The coagulation time was increased. Right carotid angiography showed a saccular aneurysm on the right pericallosal artery with a right frontal intracerebral haematoma (Fig. 4). Treatment with AMCA 6 g every 24 hours intravenously was started the same day. Repeat angiography on 10 January 1977 showed marked vasospasm with increased circulation time, right frontal expansive lesion, and contrast filling of the aneurysm, which was smaller. Repeat angiogram on 17 January 1977 showed vasospasm and a marked reduction in size of the aneurysm (Fig. 5). A right carotid angiogram on 28 January showed regression of spasm and a slight increase in the size of the aneurysm. On 2 February 1977 the patient was operated on, with clipping of the aneurysm neck, but the fundus of the aneurysm sac could not be identified during the operation. AMCA treatment was stopped on the same day. CT scan

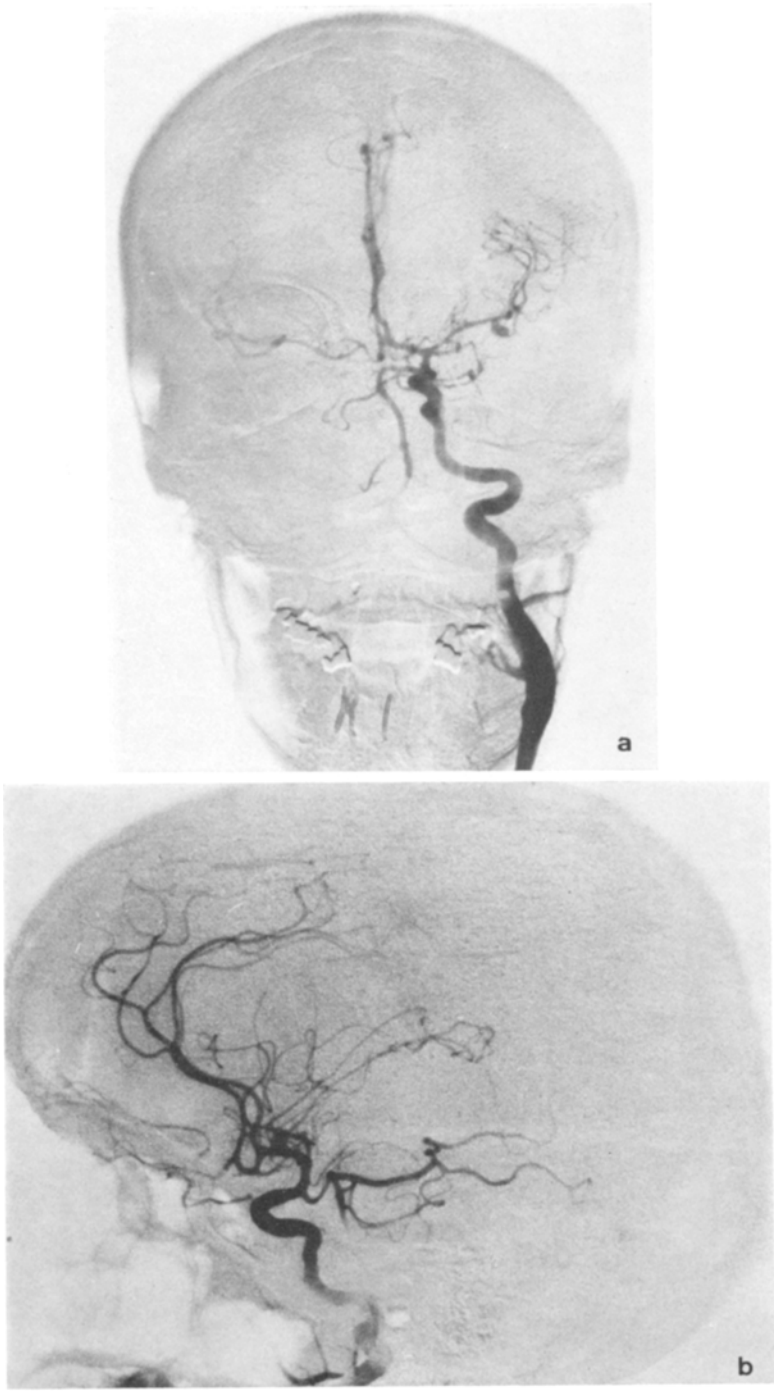

Fig. 1. Carotid angiography (case 1): Left middle cerebral artery aneurysm ($8 \times 4 \times 5$ mm), severe vasospasm and intracerebral temporal space-occupying lesion. a) A-P view, b) lateral view

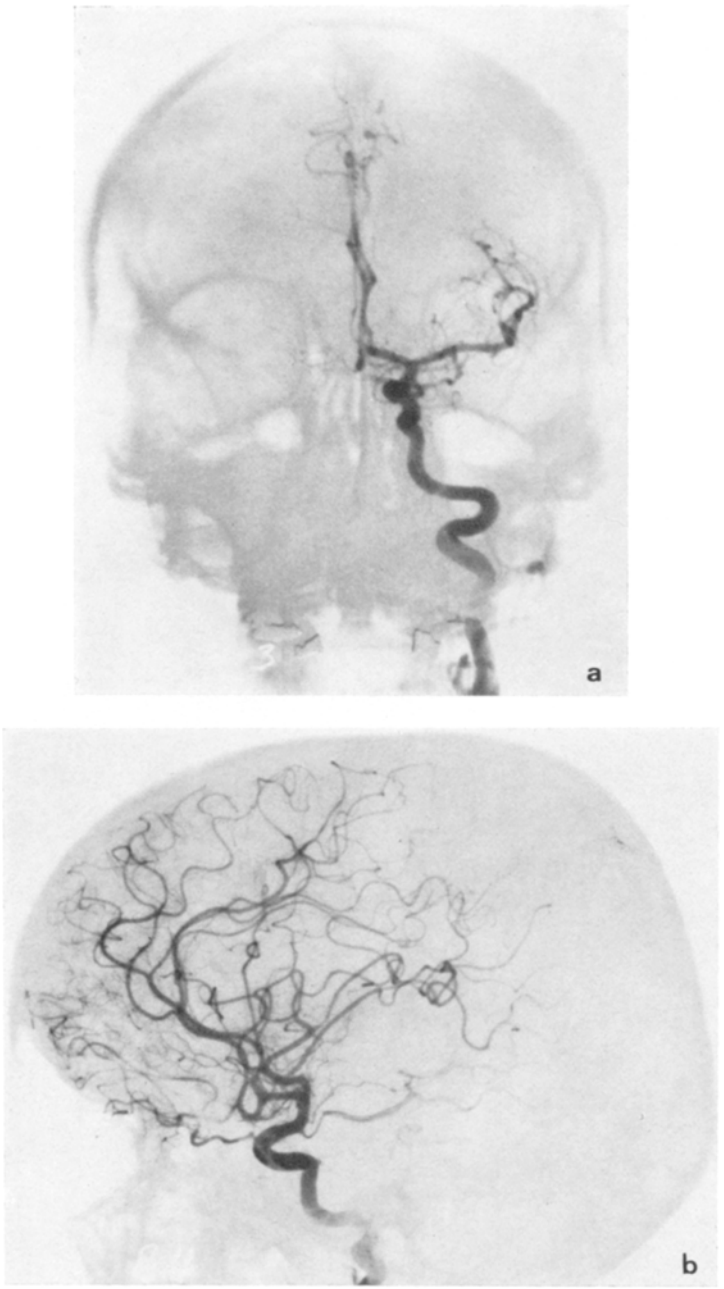

Fig. 2. Carotid angiography (case 1) 22 months later with no contrast filling of aneurysm. a) A-P view, b) lateral view

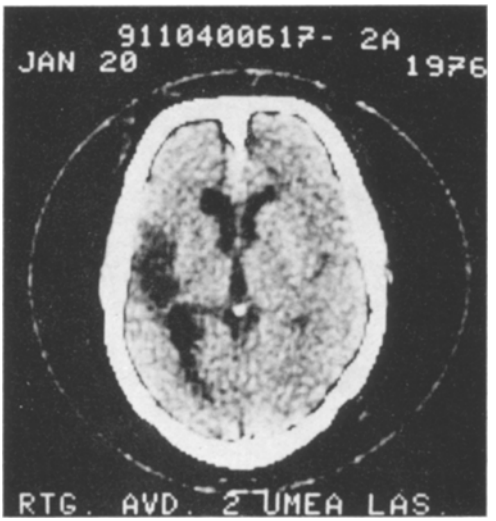

Fig. 3. CT scan (case 1) three years later showing left-sided porencephaly

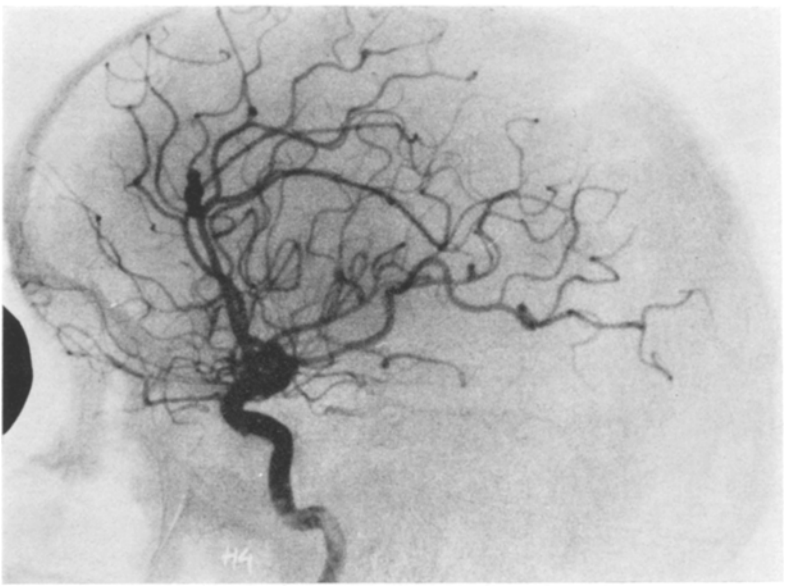

Fig. 4. Carotid angiography, lateral view (case 2): right pericallosal artery aneurysm (15 × 5 × 4 mm)

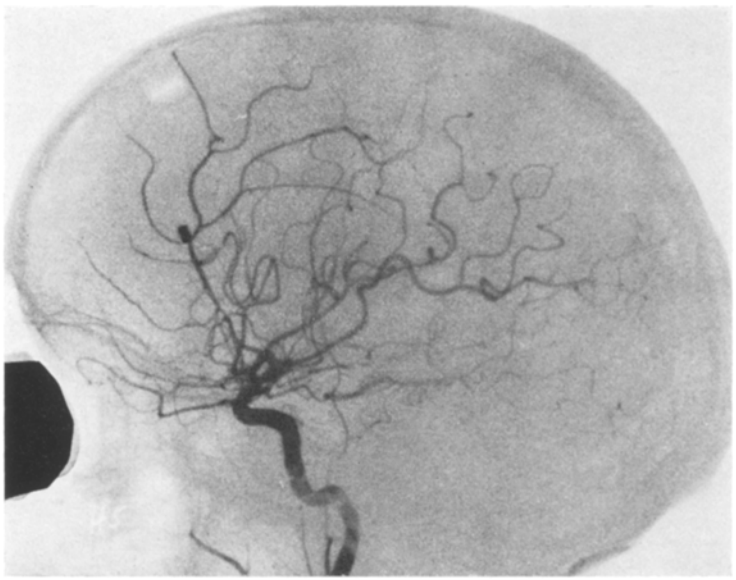

Fig. 5. Carotid angiography, lateral view (case 2), three weeks later with diminished size of aneurysm

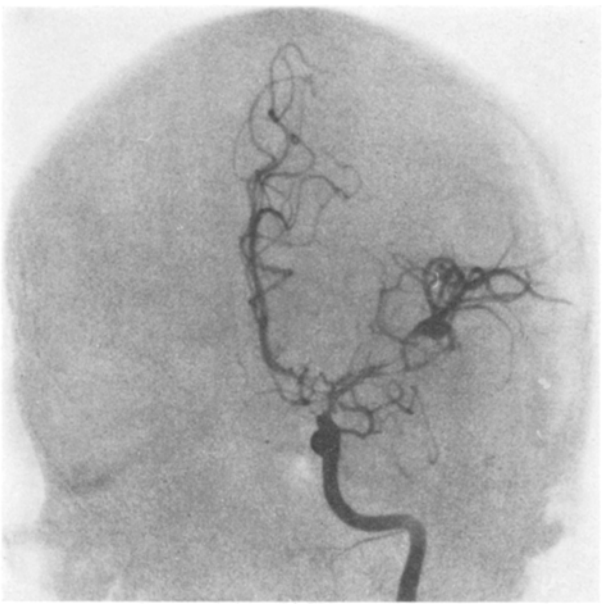

Fig. 6. Carotid angiography, A-P view (case 3): Left middle cerebral artery aneurysm (10 × 9 × 8 mm)

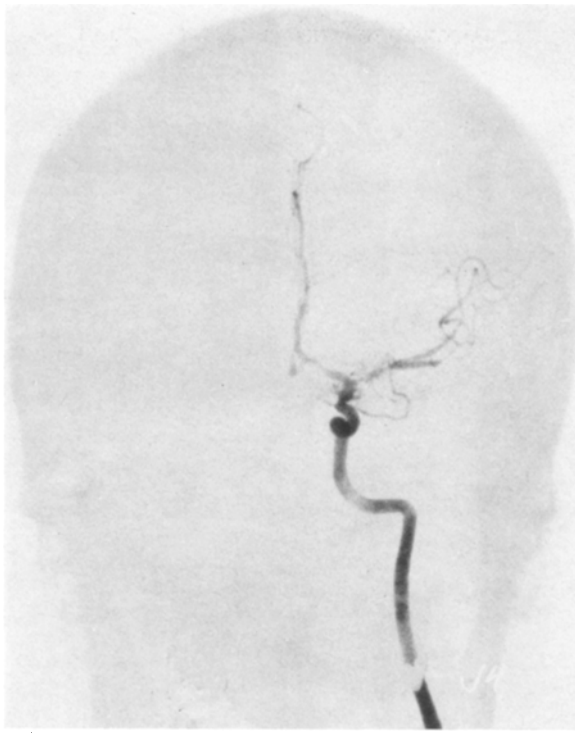

Fig. 7. Carotid angiography, A-P view (case 3), two weeks later with no contrast filling of aneurysm and occlusion of middle cerebral artery branch

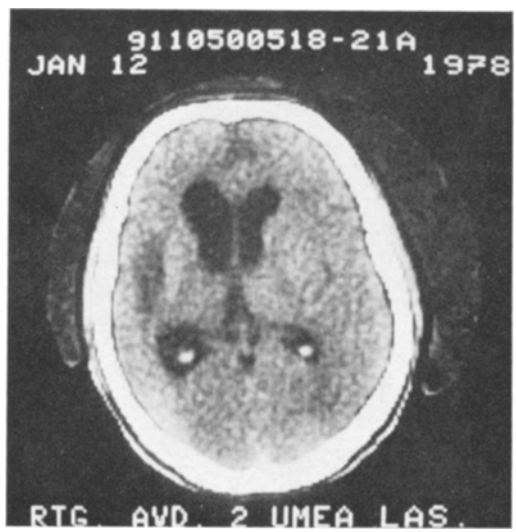

Fig. 8. CT scan (case 3) after nine months showing left parietal porencephaly

10 February, showed porencephaly in the right frontal lobe with ventricular enlargement. CSF hydrodynamic studies [10, 11] revealed increased CSF pressure, and on 24 February a ventriculo-peritoneal shunt was inserted. Follow-up examination shows minimal paresis of the right leg and impaired coordination.

Case 3: 27-year-old male who on 5 April 1977 became unconscious. On admission the same day he was stuporous (Botterell IV). Blood pressure was 140/90. Laboratory tests including coagulation studies were normal. Carotid angiography and CT scan showed a saccular aneurysm on the left middle cerebral artery and a small intracerebral haematoma in the left temporal lobe. Treatment with AMCA 6 g/24 hours intravenously was started on 6 April. Repeat left angiography on 13 April showed marked vasospasm with prolonged circulation time, a slight increase in the size of the aneurysm, and increased temporal expansive lesion (Fig. 6). A left angiogram on 26 April showed marked vasospasm, no filling of the aneurysm with contrast medium and occlusion of the feeding vessel, a branch of the middle cerebral artery (Fig. 7). There was also ventricular dilatation. Repeat angiographic examination on 16 May showed regression of vasospasm, but occlusion of the parietal artery branch and no contrast filling of the aneurysm. AMCA treatment was stopped on 17 May, and the patient was discharged from hospital with aphasia. A left carotid angiogram on 10 January 1978 showed no contrast filling of the aneurysm, but did show recanalization of the occluded arterial branch. CT scan showed hydrocephalus and infarction in the left parietal region (Fig. 8). CSF hydrodynamic studies were normal. The patient is doing well with no residual neurological deficit.

Discussion

Kågström [31] and Kågström and Palma [32] have expressed concern about increased incidence of cerebral ischaemic complications when an antifibrinolytic drug, and especially AMCA, is given. Sonntag and Stein [53] in their series of seven patients treated with EACA had three patients with cerebral arteriographic changes resembling arteritis or intravascular thrombosis and a deteriorating clinical course. Hood [23] commented that the angiographic findings in these patients cannot be differentiated from those of vasospasm. Fodstad *et al.* [12, 13] in a controlled trial found radiological vasospasm to be significantly more pronounced among patients with SAH treated with AMCA than in the control group. During antifibrinolytic treatment our three patients had radiological vasospasm associated with neurological deterioration. Weir *et al.* [59] have shown that radiological vasospasm has its onset about the third day after subarachnoid haemorrhage. One of our patients (no. 1) had severe vasospasm on the first angiogram seven hours after primary bleed (Figs. 1 a and b). AMCA was given intravenously only two hours after the bleeding episode, and could thus be responsible for the development of early spasm in this patient since it is known that both EACA and AMCA possess sympathomimetic properties and may theoretically induce vasospasm, possibly by acting via the adrenergic nerve terminals and thus depleting the stored catecholamines [1, 15, 17, 19, 35, 38, 44—46, 49, 56, 58].

There have been limited case reports about the occurrence of a thrombotic tendency and glomerular microthrombi during treatment with EACA [2, 5, 16, 40, 42]. Rydin and Lundberg [50] reported intracranial arterial thrombosis in two young women taking AMCA. Davies and Howell [7] reported the case of a woman who died from intracranial arterial thrombosis four months after taking AMCA. Our three patients who received AMCA showed a marked reduction in the sizes of their aneurysms during treatment after two, three, and four weeks respectively. In two of them (nos. 1 and 3) there was occlusion of parietal branches of the parent vessel (middle cerebral artery). In one patient (no. 2) the aneurysm partly reappeared after one month, and had to be clipped. Spetzler *et al.* [54] reported on a patient treated with EACA, whose aneurysm reappeared after 23 days, whereas Scott and Garrido [52] and Edner *et al.* [9] reported on single cases of aneurysm thrombosis during treatment with EACA that remained occluded after 11 weeks and 14 months respectively.

Spontaneous thrombosis of ruptured intracranial aneurysms has been estimated to occur in 9–13% of the patients in autopsy studies [6, 24]. Based upon repeated angiographic studies Edner *et al.* [9] suggested that only 1 or 2% of ruptured aneurysms will show spontaneous and complete thrombosis. We have seen spontaneous disappearance of ruptured aneurysms in 3% of our AMCA-treated patients who have undergone repeat angiography. All our patients showed subsequently porencephalic changes with enlarged ventricles on CT scan. However, only one patient required a shunt. Follow-up examination has shown residual epilepsy in patient no. 1, slight hemiparesis in patient no. 2, and complete recovery in patient no. 3.

Experimental evidence of vessel-wall changes in connection with administration of antifibrinolytic agents was first reported by Ooneda and co-workers in 1962 [47]. They treated 11 hypertensive rats with surgically constricted renal arteries with epsilon-amino-caproic acid (EACA) for seven weeks. Ten hypertensive rats were used for controls. The arterial lesions in the EACA-treated group were different from the controls showing fibrosis in the adventitia and cellular intimal thickening similar to productive endarteritis. Salmon [51] noticed an increased deposition of fibrin in the vessel walls of rats treated with EACA. Nordöy [43] produced thrombosis in experimental rats, and found that EACA 100 mg/kg body weight given orally every fourth hour for 24 hours doubled the incidence of thrombosis. Studer *et al.* [57] infused thrombin in rabbits and rats and found the removal of fibrin to be slowed by EACA. Other investigators [4, 60] found that rabbits given an atherogenic diet showed increased atherosclerosis when treated with EACA. Kwaan and Astrup [30] found that

rabbits treated with EACA alone developed medial aortic lesions, whereas Fritsch and co-workers [14] found no effect of EACA on the development of atheromatosis in rabbits. With AMCA Herschlein and Streichele [2] suggested that the drug had thrombotic effects in animals. In light- and electromicroscopy of arteries and other tissues from dogs treated with AMCA Steenblock and Celander [55] could not identify any fibrin deposits. Leandoer *et al.* [33] studied the effect of heparin and AMCA on coagulation and fibrinolysis in blood and lymph following massive haemorrhage in dogs. In the AMCA-treated animals thrombi or emboli were found in several vessels at autopsy. Kato and co-workers [27] found that AMCA promoted the development of atherosclerosis through its influence on the fibrin dissolution on and in the arterial wall. Åstedt and Liedholm [61] gave rats high doses of AMCA and found no effect of the drug on the fibrinolytic activity of the heart vessel walls. Mullan *et al.* [41] and Patterson and Harpel [48] demonstrated that antifibrinolytic agents help secure the permanency of an experimental arterial aneurysmal clot. Khilko and Shklyarova [28] injected EACA and fibrin directly into the carotid artery in 23 patients with saccular aneurysms and AV malformations. At the same time the carotid artery was constricted by means of a fascial cuff. In six of nine patients with internal carotid artery aneurysms thrombosis of the aneurysm was obtained. The authors mentioned nothing about morbidity and mortality.

If we add our three AMCA-treated cases to the three hitherto published EACA-treated cases whose ruptured aneurysms disappeared spontaneously, we may suspect that this phenomenon occurs more often when antifibrinolytic drugs are given. All six patients also had vasospasm, three of them had occlusion of the feeding artery, and in two patients the aneurysm partly reappeared. With regard to this it should not be a therapeutic goal to try to achieve thrombosis of a ruptured aneurysm with antifibrinolytic agents.

The explanation for the occurrence of such a thrombosis can only be speculative. Firstly, the damaged arterial vessel wall in patients with subarachnoid haemorrhage and vasospasm exhibits a "locus minoris resistentia" for irreversible changes and thrombus formation, and AMCA may enhance this for unknown reasons. It may also be due to a local inhibition of plasminogen activators in and around the aneurysm wall, although Hassler and Fodstad [18] could not find any decreased fibrinolytic activity in the aneurysmal wall in patients treated with AMCA. With regard to earlier experimental work [4, 27, 30, 43, 47, 51, 60] a direct toxic effect of antifibrinolytic agents on the arterial vessel wall must be taken into consideration. Theoretically at least, the vasoactive (sympathomimetic) effect

of AMCA with development of vasospasm and flow reduction inside the aneurysm could be of importance. Finally, there is a possibility of interaction with other drugs and substances with secondary vessel wall changes.

Controlled clinical trials have shown that tranexamic acid may be effective in preventing rebleeding in patients with ruptured aneurysms during the preoperative "waiting" period [12, 39]. However, unknown and possible adverse effects on the arterial vessel wall with subsequent flow reduction, thrombosis and cerebral ischaemia in patients with aneurysmal subarachnoid haemorrhage should be kept in mind when antifibrinolytic drugs are given.

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