Pathogenesis of the "sentinel headache" preceding berry aneurysm rupture

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Summary: Pathologic examination in a case of fatal intracerebral hemorrhage from a berry aneurysm showed that the "sentinel" or warning headache in this patient was due to the leakage of blood into the subarachnoid space through a previous small tear in the wall of her saccular aneurysm. Orbital pain, transient dysphasia, dizziness and, later, meningismus might have prompted the performing of a lumbar puncture to determine the presence of blood in the cerebrospinal fluid. This type of event is the likely pathogenetic mechanism for the premonitory headache that may precede a lethal rupture of a saccular aneurysm.

Résumé: *La pathogenèse de la "céphalée d'avertissement" qui précède la rupture d'un anévrysme sacciforme*

L'examen pathologique pratiqué dans un cas d'hémorragie intracérébrale à partir d'un anévrysme sacciforme a permis de montrer que la "céphalée sentinelle" (ou céphalée d'avertissement) observée chez ce malade était causée par l'épanchement de sang dans l'espace arachnoïdien à travers une minuscule lésion dans la paroi de son anévrysme. De la douleur orbitaire, une dysphasie passagère, de l'étourdissement et, par la suite, du méningisme peuvent avoir incité le clinicien à pratiquer une ponction lombaire pour établir la présence de sang dans le liquide céphalorachidien. C'est probablement dans ce genre de cas qu'on trouve le mécanisme pathogénétique de la céphalée prémonitoire qui peut précéder la rupture mortelle d'un anévrysme sacciforme.

In an attempt to identify the berry aneurysm that may rupture extensively before the catastrophic intracerebral event, clinicians have described a "sentinel" or warning headache.[1] Its etiology is considered by many to be the slow leakage of blood from the aneurysm sac into the subarachnoid space, since lumbar puncture frequently has shown fresh blood in the cerebrospinal fluid. However, other theories have been proposed, including the ill-defined concept of "spasm" due to stretching of the arterial wall by the enlarging sac. The case to be described provided the opportunity of pathologic examination of the changes underlying this clinical event.

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Case report

A 22-year-old woman previously in good health suddenly experienced pain over the left eye radiating to the occipital region on September 1, 1973. This was accompanied by dizziness, some dyspnea and difficulty in speaking. She was admitted to a hospital in Toronto, where she also noted some "trouble in straightening her legs". She was discharged without specific therapy and 5 days later was admitted to a London, Ont. hospital complaining of low back pain. Radiologic examination of her sacrum and coccyx disclosed nothing abnormal and she was released on analgesic medication.

Six weeks after the initial episode she opened the office where she worked at 8 am and was found unconscious 2 hours later by her employer. When she was seen in the emergency department of Victoria Hospital, London, Ont. at 11 am no pulses were detectable and her pupils were fixed and dilated. After a period of irreversible ventricular fibrillation she died, at 11.30 am.

FIG. 1—Ruptured saccular aneurysm, left middle cerebral artery. White thrombus fills much of the fundus.

Postmortem findings

Death was due to a massive fresh intracerebral hemorrhage from a ruptured saccular aneurysm at the trifurcation of the left middle cerebral artery. The hematoma had destroyed most of the left cerebral hemisphere and filled the entire ventricular system. Cerebral edema and tonsillar herniation were noted. A plug of firm, white material filled most of the fundus of the aneurysm (Fig. 1).

The wall of the sac, which showed the typical features of a saccular berry aneurysm, had ruptured extensively at the fundus. In addition, however, a much smaller aperture had been sealed by intraluminal thrombus (Fig. 2), which was well organized with active fibroblastic and neocapillary proliferation (Fig. 3). Superim-

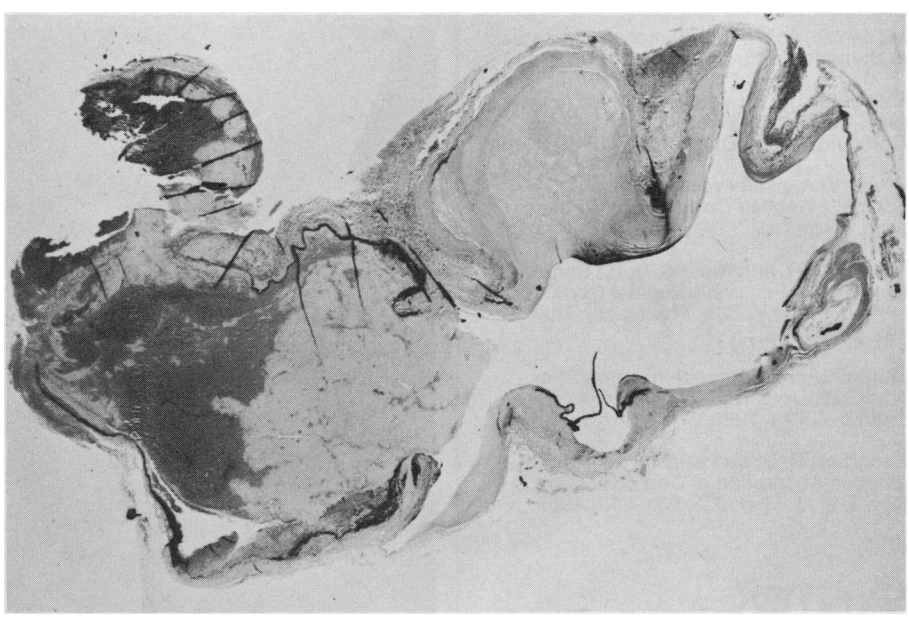

FIG. 2—Organized intraluminal thrombus in central portion of aneurysm; very fresh thrombus at left. Weigert's elastic stain. x6.

posed on the older thrombotic material was very fresh thrombus with lines of Zahn. In the adventitia immediately outside this site of previous rupture was a collection of both fresh erythrocytes and many macrophages laden with brownish pigment, confirmed by Perls's Prussian blue histochemical reaction to be iron-containing hemosiderin. Focal fibrosis was also seen in the perivascular leptomeninges adjacent to the aneurysm.

Sections of left frontal and temporal lobes, both within 1 cm of, and more than 4 cm distant from the aneurysm, exhibited an intense fibrosis of the leptomeninges (Fig. 4). Numerous perivascular cuffs of lymphocytes were seen and, again, hemosiderin-filled histiocytes were prominent in the fibrotic subarachnoid space. The superficial layers of the temporal cortex immediately below one such area had undergone a marked astrocytic hyperplasia (Fig. 4).

Discussion

In one study of 320 cases of unruptured aneurysm 165 patients had single, symptomatic aneurysms causing significant presenting complaints.[2] In the entire series of 3321 cases, significant symptoms were produced prior to rupture in 9.6%. Calvert's retrospective analysis, on the other hand, suggested that in 38.5% of his 200 cases of subarachnoid hemorrhage there was a definite antecedent history.[3] The most important premonitory clue in the history is the headache that arises suddenly *de novo,* or is obviously of a more intense character than any previously noted by the patient; this has been termed the "sentinel headache".

Most reports of this phenomenon offer no histopathologic proof for their pathogenetic hypotheses, although Hyland[4] did describe the postmortem findings in a 44-year-old woman who suffered sudden left hemiplegia 4 weeks after a severe occipital headache. She died of acute rupture of a second aneurysm 9 months later. At necropsy "old hemorrhage and gliosis" were observed around the ruptured sac of the first aneurysm, at the bifurcation of the right middle cerebral artery. There is no mention of the histologic findings.

Four histologic features in our case indicate that the headache 6 weeks prior to death must have been due to an actual tear in, and leakage of blood from the aneurysm:

1. The well organized thrombus that had sealed the site of previous rupture.
2. The old blood pigment in phagocytes both immediately adjacent to the sac and in the leptomeninges some distance away.
3. The collagenous fibrosis of the subarachnoid space.
4. The astrocytic reaction in subjacent cortex.

None of these changes could have occurred in the 3½ hours (or less) of the patient's last episode. All of them, on the other hand, are well known, later sequelae of previous subarachnoid bleeding from a leaking aneurysmal sac,[5,6] and require several days to occur. Furthermore, the "difficulty in straightening the legs" and the low back pain were almost certainly secondary to associated spinal subarachnoid hemorrhage, but because the cord was not available for examination this conclusion is not proved. It is not surprising that the terminal hemorrhage took place through a new site of rupture, since the well organized thrombus would have much greater structural stability than the attenuated aneurysm wall nearby.

The histopathologic features in this case provide firm evidence that the sentinel headache was due to actual rupture of the berry aneurysm with associated subarachnoid bleeding. Thrombotic occlusion of the earlier tear prevented fatal hemorrhaging initially. This pathophysiologic sequence may be common to all such patients.

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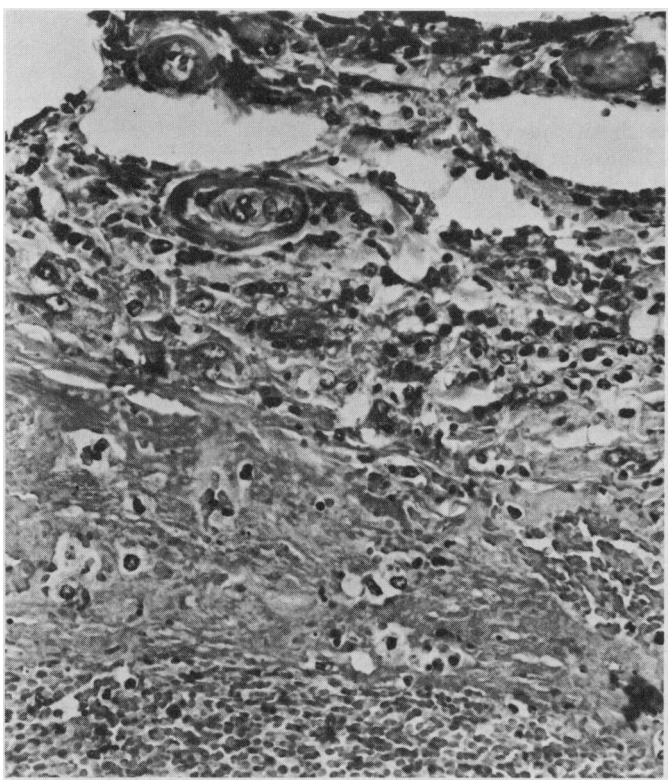

FIG. 3—Thrombus within aneurysm fundus. Actively proliferating fibroblasts and capillaries (upper half) indicate well established organization. Hematoxylin–eosin x230.

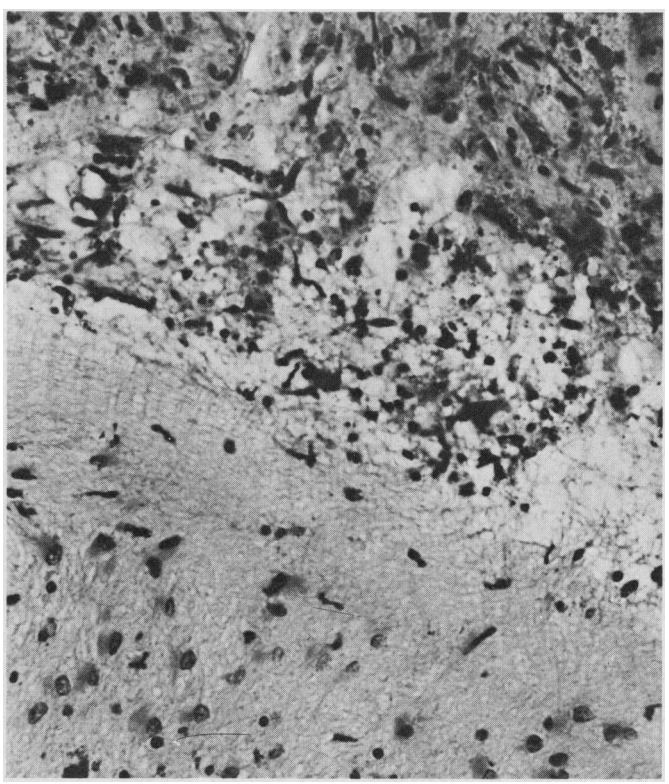

FIG. 4—Left temporal lobe. Dense leptomeningeal fibrosis (upper right) and astrocytic hyperplasia of cortex (lower left). Hematoxylin–eosin x230.