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Early ischemic lesions following Subarachnoid Hemorrhage: common cold remedy as precipitating factor?

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Abstract

A 46-year-old woman presented with tetraplegia contrasting with a relatively preserved consciousness following aneurysmal subarachnoid hemorrhage (SAH). Multiple ischemic lesions were detected by magnetic resonance imaging (MRI), in the absence of vasospasm or signs of increased intracranial pressure. During the weeks before SAH, the patient had repeatedly used a nasal decongestant containing phenylephrine. After coiling of the aneurysm harboured by the right posterior cerebral artery, symptomatic vasospasm developed in the territory of the right middle cerebral artery and required aggressive therapy by intra-arterial infusion of milrinone followed by continuous intravenous administration. Follow-up MRI did not reveal new ischemic lesions. Echocardiography had demonstrated the presence of a patent foramen ovale. At 3 months follow-up, a major motor deficit persisted with akinetic mutism. The mechanisms of multiple early infarction following aneurysmal SAH are still debated, as vasospasm is usually not seen on the first imaging. Among precipitating factors of microvascular vasospasm, vasoactive substances like phenylephrine, may play a significant role.

Key words: Aneurysmal subarachnoid hemorrhage; early infarction; vasospasm; smoking; phenylephrine; patent foramen ovale.

Introduction

Delayed ischemic neurologic deficit (DIND) is mainly caused by vasospasm occurring from day 3 to day 14 following aneurysmal SAH (1). However, there is also evidence that multiple ischemic lesions can be detected very early in a significant number of patients, either by computed tomography (CT) or magnetic resonance imaging (MRI), either in the presence of an early vasospasm or even in the absence of any demonstrable vasospasm (2, 3). We discuss the possible role of precipitating factors in a patient with multiple early infarction following SAH.

Case report

A 46-year-old previously healthy woman was found alert at home (Glasgow Coma Score 10/15, E4V5M1, WFNS grade 4) but with tetraplegia. She was only able to give her name and age, and mainly complained from severe headache. She could not recall when the symptoms started, but according to the history collected from the relatives and neighbours, the maximal estimated delay should be 2 days. It is impossible to affirm that there was an initial loss of consciousness followed by a progressive recovery, but this scenario is likely. Arterial blood pressure was 136/60 mm Hg, and arterial oxygen saturation measured by pulse oxymetry (SpO_2) was normal. In the Emergency Room, neurological examination confirmed plegia of the lower limbs and left upper limb, but some movements were noted in the right upper limb (M3). There was no evidence for papilledema or retinal hemorrhages at admission fundoscopy. The admission brain CT with angiography revealed a diffuse subarachnoid hemorrhage (SAH) (Fisher group 3) and the presence of an intracranial aneurysm on the right communicating posterior artery. There was no evidence for vasospasm, ischemic lesions or brain oedema. As the clinical picture was not fully explained by the initial radiological findings, a brain magnetic resonance imaging (MRI) was performed and demonstrated multiple cortical ischemic lesions bilaterally in the territory of both anterior and middle cerebral arteries (Fig. 1). According to the relatives, the patient was a heavy smoker (> 50 cigarettes/day). During the weeks before SAH, she complained from common cold and

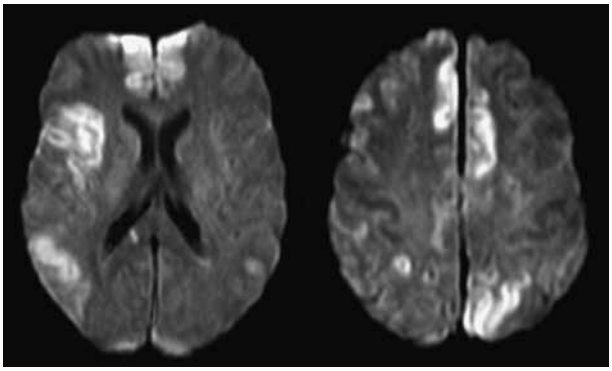

FIG. 1. — MRI, Axial Diffusion Weighted Imaging (DWI-SE-EPI, b1000): multiple acute and extended ischemic areas with high signal intensity in multiple arterial territories (bilateral anterior cerebral arteries and right middle cerebral artery).

extensively used for several weeks nasal sprays containing phenylephrine. There was no history of illicit drugs consumption.

The aneurysm was successfully treated by endovascular coiling. Treatment also included oral nimodipine and intravenous magnesium sulphate. Transoesophageal echocardiography revealed a patent foramen ovale (PFO) without thrombi formation, while sinus rhythm was recorded at electrocardiogram. By the second hospital day, bilateral vasospasm was suspected by transcranial Doppler (TCD) on both middle cerebral arteries (MCA), but the neurological condition was slightly improved (E4V4M4). Norepinephrine continuous infusion was started to increase mean arterial pressure. After 24 hours, neurological worsening (E2V2M4) was noted and as velocities on the right MCA had further increased at TCD, a new cerebral angiography confirmed the presence of a vasospasm in this territory. During the procedure, 10 mg of milrinone was infused intra-arterially over 30 min in the right MCA, and thereafter an intravenous perfusion was maintained at the dose of 0.5 μg/kg/min, together with high doses of norepinephrine (up to 150 μg/min). Consciousness improved after the procedure. Due to the persistence of extremely high velocities (up to 265 cm/sec) on the right MCA at TCD, the same treatment was continued until day 17, when TCD examination normalized. At discharge from the ICU (day 19), the patient had spontaneous movements in the upper limbs but akinetic mutism was well present and the condition remained unchanged at 3 months follow-up. Despite sustained vaspospasm, no new ischemic lesions were found on MRI at discharge.

Discussion

While the functional prognosis following aneurismal SAH is largely related to symptomatic vasospasm resulting in delayed ischemic lesions, it appears also that, as in the present case, early ischemia (usually within the first 24-72 hours) may be noted before any demonstrable vasospasm (4).

The exact incidence of early ischemia is also not precisely known, as some early or small ischemic lesions could not be detected by CT. In a large series of 487 patients with SAH, a total of 17 (3%) had acute infarction on CT performed within 3 days after SAH onset (5). A higher incidence was even suggested in a case series of 103 patients with SAH; 6 had cerebral infarction that was visible on CT by day 2, without vasospasm (3). The authors suggested that these patients had more physiological derangements on admission (acidemia, impaired oxygen delivery, hyperglycemia and abnormal brain perfusion). It can also be assumed that early ischemic lesions are underestimated by CT. Indeed, in a recent series using diffusion-weighted imaging (DWI) at MRI performed 10.9 ± 20.1 hours after SAH onset, the incidence of early infarction was 8% (6). No vasospasm was seen on the initial MRI. There was a clear predominance for the female gender, but smoking habits and drugs history were not detailed. Most of the patients were initially asymptomatic, but early DWI-detected infarction was associated with delayed angiographic vasospasm, delayed ischemic neurological deficit (DIND), CT or DWI-detected infarction and less favourable outcome.

The mechanisms of early ischemia are still poorly understood (7). Among the possible causes, microvascular vasospasm, microembolism or transient global ischemia are commonly cited.

In our patient, the latter mechanism appears unlikely as there was no evidence for a sustained increase in intracranial pressure with a global reduction in cerebral perfusion pressure.

Microembolism could be an alternative explanation for ischemic lesions in the absence of vasospasm. Microembolic signals may be detected by TCD in patients with SAH with and without vasospasm (8). The finding of a PFO in this patient does not necessarily support this hypothesis, as there are no literature data indicating that early infarction following SAH has any relationship with PFO.

Our final hypothesis is that microvascular vasospasm may have been directly triggered by the use of phenylephrine. Indeed, the potential role of vasoactive substances on ischemic lesions has been discussed at least in stroke and in reversible cerebral vasoconstriction syndrome (RCVS). It is now

accepted that sympathomimetics contained in over-the-count cold preparations (phelylpropanolamine or phenylpephrine) are associated with vasospasm and stroke, even at therapeutic doses (9). The RCVS is an entity clearly distinct from aneurysmal SAH, although some overlap may probably exist in the pathogenesis of vasospasm (10-12). In a series of 62 patients with RCVS, Ducros *et al*. found that exposure to various vasoactive substances was present in 60% of the cases; over-the-counter nasal decongestants represented 13% (12). Finally, cigarette smoking may also be listed among the risks factors to develop angiographic or symptomatic vasospasm after SAH (13-14).

In conclusion, the association of vasoactive substances like phenylephrine with ischemic lesions in stroke or RCVS suggests that a similar mechanism of an early drug-induced microvascular vasospasm may be at least partly involved in early ischemia following SAH.

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