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Recurrent Hyperperfusion Syndrome and Intracerebral Hemorrhage after Recanalization of the Extracranial Carotid ArteryMarkus Beitzke^a, Christian Enzinger^{a, b}, Kurt Niederkorn^a,
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The term cerebral hyperperfusion syndrome (HS) was coined by Sundt et al. [1] in 1981 to describe a rare complication of carotid endarterectomy (CEA) which may appear with severe unilateral headaches, seizures and focal symptoms related to cerebral edema or intracerebral hemorrhage (ICH) and is considered to result from a major increase in ipsilateral cerebral blood flow above the metabolic demands of the brain. Obvious risk factors include long-standing hypertension, high-grade stenosis, poor collateral blood flow and contralateral carotid occlusion [2–4]. Several mechanisms such as a paralysis of cerebral autoregulatory mechanisms, a break-down of the baroreceptor-reflex and an axon-like trigeminovascular reflex have been implicated in the pathophysiology of hyperperfusion and in the evolution of the cerebral HS [2]. Once it is associated with ICH, the prognosis tends to be poor [2, 4]. We here illustrate the obvious role of endothelial damage in the development of intracerebral bleeding with the imaging findings in a rare case of a recurrent cerebral HS.

Case Report

A 65-year-old hypertensive woman underwent CEA for an asymptomatic high-grade stenosis of the left internal carotid artery (ICA) in October 2001. On the second postoperative day, she developed clinical signs of a HS including throbbing unilateral headache, seizures and a right-sided hemiparesis. Brain CT revealed an ICH ipsilateral to the CEA. The patient recovered well.

Fig. 1. a Intra-arterial digital subtraction angiography confirms >80% left CCA stenosis (white arrow) and >50% left ICA stenosis (black arrow). **b** Postprocedural angiogram shows recanalization without local complications.

Thirteen months later, in November 2002, she was referred for treatment of a carotid restenosis. The patient had been asymptomatic since the first procedure. When assessed at our institution, the patient showed a residual mild, right hemiparesis. Doppler ultrasound revealed 80% stenosis of the left ICA and common carotid artery (CCA). There was also a high-grade left external carotid artery stenosis. The vessels of the posterior circulation appeared normal. Transcranial Doppler (TCD) studies revealed reduced left middle cerebral artery (MCA) flow velocities (VL; left MCA: VL_{systolic} 0.8 m/s, VL_{diastolic} 0.35 m/s; right MCA: VL_{systolic} 1.2 m/s, VL_{diastolic} 0.4 m/s). There was no evidence of any extra-intracranial collateral vascularization or cross-flow to the left ICA territory via the circle of Willis. Brain CT revealed a parenchymal defect after ICH in the left frontoparietal region. ⁹⁹Tc HMPAO-SPECT showed reduced radionuclide tracer uptake in the left ICA territory, which further decreased after acetazolamide challenge.

Selective intra-arterial angiography revealed >80% left CCA stenosis and >50% left ICA stenosis according to NASCET (fig. 1). The intracerebral angiogram was normal. Uneventful carotid artery stenting (CAS) was performed. On the first day after CAS, color Doppler ultrasound revealed normal VL in the region of the

Fig. 2. Brain MRI on the third day after CAS. **a** FLAIR sequences demonstrate edema of the left hemisphere with relative sparing of the cortical ribbon. **b** The diffusion-weighted image is largely unremarkable except for small cortical hyperintensities indicating areas of cytotoxic edema. **c** Corresponding apparent diffusion coefficient maps demonstrate relatively large areas of increased diffusion (high signal intensity) consistent with vasogenic edema. The foci of presumed secondary ischemic infarction show reduced diffusion (dark areas). **d** Gradient echo T₂*-weighted sequences without evidence of hemorrhage. **e** Postcontrast T₁-weighted sequences show multiple areas of intraparenchymal enhancement and vascular enhancement in the left MCA territory closely corresponding to the regions with vasogenic edema.

Fig. 3. a TCD before revascularization of the left carotid artery reveals a damped waveform of the left MCA in comparison to the right MCA (arrows) and reduced left systolic MCA VL, indicating hemodynamic significance of the extracranial carotid stenosis. **b** MRA on the third day after the intervention illustrates symmetrical flow signals of the proximal MCA (M1 segment). Narrowing of the vessels at the trifurcation of the left MCA probably indicating local arterial vasospasms (straight arrow) and enhanced flow signals of the left distal MCA branches in comparison with the right side (curved arrows) most likely indicating hyperperfusion.

left carotid bifurcation. The patient remained clinically stable for the next 48 h. Blood pressure (BP) varied between 160/80 and 140/80 mm Hg. Two days after the procedure, however, the patient developed focal seizure activity, severe unilateral headache ipsilateral to CAS and her right-sided hemiparesis worsened. Brain CT showed mild left hemispheric edema. TCD studies were unsuccessful due to incomppliance of the patient with failure to obtain an adequate acoustic window. Brain MRI on the third day after CAS confirmed edematous swelling of the left hemisphere (fig. 2) with evidence of increased diffusion on apparent diffusion coefficient maps consistent with vasogenic edema. The small areas of cytotoxic edema likely indicate secondary ischemia. Gradient echo T_2^* -weighted sequences revealed no evidence of hemorrhage. Postcontrast T_1 -weighted MRI showed multiple areas of

intraparenchymal enhancement in the frontal and deep white matter of the left hemisphere. Intracranial MRA indicated symmetrical flow signals in both proximal MCAs (fig. 3). Narrowing and subsequent prominence of the MCA branches at the trifurcation was felt to be consistent with vasospasm and possibly hyperperfusion. For the next 3 days the patient remained clinically stable. BP varied between 115/65 and 180/80 mm Hg (mean 130/70 mm Hg). Six days after CAS, the patient suddenly became unresponsive with right hemiplegia. Urgent brain CT revealed extensive intracerebral bleedings exactly at the same site as the areas of contrast enhancement on the MRI (fig. 4). The level of consciousness further deteriorated and the patient died 8 days after the procedure. A postmortem examination was not performed.

Fig. 4. a Brain CT on day 6 after revascularization shows extensive ICH extending into the ventricles. **b** The bleedings are primarily located in the regions of previous contrast enhancement on MRI.

Discussion

Several risk factors for the cerebral HS have been recognized. A history of cerebral HS should probably be added to this list as evidenced by our patient. Although clearly rare, such a scenario might become more frequent with an ever better technical feasibility of both CEA and CAS and the trend to extend these procedures to very high age groups. The present case of recurrent HS and ICH could not be attributed to a high-grade contralateral carotid stenosis or occlusion. However, there was evidence of poor collateral vascularization, and SPECT cerebral blood flow studies revealed chronic misery perfusion as well as exhausted cerebrovascular reactivity in the left ICA territory.

There are several lines of evidence which point towards the importance of endothelial damage in the evolution of cerebral HS in our patient. Firstly, an increase in the apparent diffusion coefficient of large parts of the left hemisphere is consistent with vasogenic edema [5, 6]. Secondly, focal breakdown of the integrity of the blood-brain barrier was indicated by contrast enhancement on MRI and preceded exactly the areas of subsequent extravasation of blood. Another observation concerning intraparenchymal contrast enhancement on MRI in a patient with post-endarterectomy HS preceding fatal ICH was also reported by Toh et al. [7] more recently, but these investigators did not provide evidence for the exact regional matching of these events.

It has been suggested that BP elevations are interlinked with hyperperfusion and BP reduction can control symptoms. However, even though BP elevation is the rule, cerebral HS may occur

in the setting of only modest hypertension [8]. Nevertheless, elevated BP may be the significant trigger for a pathogenetic cascade finally leading to endothelial injury. Endothelial damage, however, with subsequent release of potent vasoconstrictors mediating cerebral vasospasm [6, 9], subsequent activation of the coagulation cascade causing local thrombosis or subsequent vasogenic edema significantly increasing tissue pressure may eventually, in combination, cause impaired microcirculation which results in ischemic injury most likely indicated by small areas of cytotoxic edema in the present case. While our observation clearly indicates a leading role of endothelial damage in the final stages of the cerebral HS, we can only speculate on the causes for its start. Even there, endothelial cells could play an important role. More recent studies have shown a correlation between reactive oxygen species produced during CEA and the development of postoperative cerebral hyperperfusion, and it has been speculated that this association could be mediated by endothelial cell damage as well [10].

In conclusion, our observation indicates the need to include the history of a preceding cerebral HS in the risk-benefit considerations of endovascular therapy of a recurrent carotid stenosis. MRI using diffusion-weighted imaging can assist in the rapid diagnosis of vasogenic edema and may provide a warning for subsequent bleeding by intraparenchymal leakage of contrast material.

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Raising Awareness of Orolingual Angioedema as a Complication of Thrombolysis in Acute Stroke Patients

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Background

Orolingual angioedema (OA) has been increasingly acknowledged as a hitherto underestimated and potentially life-threatening complication of alteplase treatment [1–3] with unilateral painless swelling of the lips, tongue and face 30–120 min after intra-

venous alteplase application, often contralateral to the ischemic lesion. Usually mild and reversible within 24 h [1], in severe cases OA might extend bilaterally to the oropharynx.

Methods

Between January 2006 and June 2008, 2,287 patients with acute ischemic stroke were treated at the Comprehensive Stroke Center Mannheim. We reviewed all cases undergoing recombinant tissue plasminogen activator (rt-PA) thrombolysis, and identified patients presenting symptoms of OA.

Results

Of the 312 receiving intravenous thrombolysis, 8 (2.6%) suffered OA. Six of 8 patients were on angiotensin-converting-enzyme inhibitor (ACEi) medication. In 5 of 8 cases, OA was lateralized, with 2 cases being ipsilateral to the stroke. Bilateral swelling occurred in 3 cases (table 1). Ischemic stroke lesions were distributed as follows: 5 right middle cerebral artery, 1 left territorial middle cerebral artery, 1 bithalamic and 1 scattered in the posterior circulation. All but 2 cases (1 intubation, 1 death of unrelated pulmonary complications 3 weeks after onset) resolved over 2–36 h, without further complications.

Discussion

According to the few recent systematic reports, the risk of OA is estimated to be between 1–2 [1] and 5% [2], depending on the quality of monitoring for typical symptoms. A considerably higher relative risk of 13.6 is described for patients with premorbid ACEi medication [2]. A well-established hypothesis, concerning the pathomechanisms of OA, suggests a simultaneous activation of complement system and kinin cascades by plasmin, produced by alteplase-induced cleavage of plasminogen [3]. Activation of the complement cascade is considered to be direct, causing mast cell degranulation and histamine release with consequent vasodilatation [4]. As alteplase has low antigenicity in humans, IgE-mediated allergic reactions or activation of the complement system through antigen-antibody complexes are considered unlikely (found in only 1 case with unusually severe systemic signs of anaphylaxis [5]). Initiation of the kinin cascades results in raised levels of bradykinin which also leads to vasodilatation [6]. The higher occurrence in patients with ACEi might be explained by inhibition of plasma kininases, which are responsible for degrading bradykinin [3]. The lateralization is possibly triggered through acute changes in the vasomotor tone of the hemiparetic side caused by central dysfunction of the autonomic nervous system [1, 3]. In particular, lesions involving the insular cortex, but also the postcentral cortex, basal ganglia and the internal capsule, have been shown to be associated with contralateral autonomic imbalance [7].

Acute therapy of OA is still empirical. Most propose the intravenous use of antihistaminic drugs (H_1 and H_2 blockers) as well as corticosteroids [1, 3], although there is no data on the efficacy of this regime. The rapid progression of edema to the oropharynx may require immediate intubation or even cricothyroidotomy, making early consultation for anesthesia and monitoring in an ICU setting for at least 24 h necessary. In conclusion, a routine inspection of lips and oral cavity of stroke patients during and after thrombolysis is necessary, with special focus on those patients taking ACEi.