Case Description

A 47-year-old woman presented to her primary care physician (PCP) with severe left-sided headache localized in the retrobulbar and temporal region. The PCP suspected migraine and prescribed a nonsteroidal anti-inflammatory drug. But despite analgesic treatment, her headache continued, and she returned to her PCP 2 weeks later. At this visit, the PCP noticed new anisocoria with a miotic pupil on the left. Emergent magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) of neck and brain revealed no acute or subacute cerebral lesions but a narrowing and semicircular wall hematoma of the left internal carotid artery (ICA) up the petrous segment (Figure 1). The wall hematoma resulted in almost complete occlusion of the arterial lumen. Hereafter, she was transferred to our stroke center, where we confirmed diagnosis of ICA dissection with incomplete Horner syndrome.

Extracranial and intracranial duplex sonography revealed a resistance flow profile in the dissected ICA indicating distal occlusion. Collateral circulation through the left posterior communicating artery maintained the blood flow in the left anterior and middle cerebral artery. Six days later a repeated ultrasound showed improving blood flow with only local flow accelerations in the distal extracranial portion of the dissected ICA. The patient was treated with aspirin 300 mg daily for 2 weeks followed by a dose reduction to 100 mg daily. During hospitalization, she remained clinically stable and was discharged home after 8 days.

At follow-up visit 3 months later, the patient reported fatigue, difficulty concentrating at work, and persistent left-sided headache. In addition, she had observed an asymmetrical flushing and sweating of her face during a strong hike (Figure 2). The neurological examination was otherwise normal, except for the preexisting left-sided miosis. Blood flow in the left ICA further improved but was still accelerated distally. The patient was told to continue the antiplatelet treatment with aspirin 100 mg daily.

Discussion

We present a patient with a rare, nonischemic symptom of ICA dissection, which has been termed Harlequin sign.¹ Dissections of the carotid and vertebral artery are defined by the occurrence of an arterial wall hematoma. MRI with T1-weighted axial scan with fat-saturation technique is the preferred method to detect the mural hematoma in cervical artery dissection, but it can be missed within the first days after onset.²

About two thirds of patients with cervical artery dissection present with stroke or transient ischemic attack and headache or neckpain. Local symptoms (ie, Horner syndrome, cranial-nerve palsy, cervical root injury, and tinnitus) occur in about one third of all cases.³ These local symptoms are caused by an eccentric expansion of the mural hematoma, which leads to compression and stretching of nearby structures (sympathetic-nerve fibers, which proceed along the carotid artery, cranial-nerves, and cervical roots).² A typical local sign is Horner syndrome, which is defined by the occurrence of pupillary miosis and eyelid ptosis with or without facial anhidrosis. In ICA dissection, Horner syndrome is caused by local disruption of sympathetic fibers at the level of ICA. Another, only rarely observed local sign with the same underlying pathophysiology, is the Harlequin sign. Patients with Harlequin sign complain about asymmetrical facial flushing and sweating.

The sympathetic pathway consists of 3 neurons. The first-order neuron originates in the posterior hypothalamus, the second in the intermediolateral cell column at spinal cord level C8-T2, and the third in the superior cervical ganglion near the bifurcation of the common carotid artery.⁴ Third-order neurons carry 2 different types of sympathetic fibers: oculosympathetic and vaso-/sudomotor fibers. Oculosympathetic fibers ascend along the ICA and innervate the iris dilator muscle and the superior tarsal muscle. Oculosympathetic pathway injury results in ipsilateral Horner syndrome. The vaso-/sudomotor fibers separate at the level of carotid bifurcation.
Fibers innervating ipsilateral blood vessels and sweat glands of the medial forehead and nose travel along the ICA, whereas fibers for the remaining facial areas proceed along the external carotid artery. Therefore, postganglionic lesions along the ICA result in ipsilateral paleness and anhidrosis of the medial forehead and nose, whereas preganglionic lesions impair the ipsilateral half of the face. The Harlequin sign comprises both pre- and postganglionic injury of vaso-/sudomotor fibers.4

Harlequin sign is rarely observed in ICA dissection and is restricted to 2 case reports in literature only. Both patients had left-sided ICA dissection and reported contralateral, hemifacial flushing, and sweating during physical exertion a few weeks after diagnosis of ICA dissection. Photographs of both patients showed a pale ipsilateral forehead and nose.5,6 As in our case, Horner syndrome preceded the Harlequin sign by weeks in both patients. The recognition of Harlequin sign might have been delayed because patients had avoided physical exertion during earlier stages of ICA dissection. A secondary enlargement of the wall hematoma or a recurrent dissection as reasons of a delayed development of Harlequin’s sign cannot be excluded, but seem unlikely to us. Furthermore, it remains unclear why Horner syndrome is much more frequently observed than Harlequin sign in ICA dissection although oculosympathetic fibers have a close anatomic relationship to vaso- and sudomotor fibers. In some cases, Harlequin sign might have already been resolved completely when patients start physical exercises or they simply did not realize it, especially in case of mild severity.

Harlequin sign is not specific for ICA dissection. But in this case, the deficiency of vaso-/sudomotor fibers should be restricted to the ipsilateral medial forehead and nose. In published reports, several other causes of Harlequin sign have been reported with injury to the sympathetic pathway at different levels.4

Patients with cervical artery dissection should be treated with antiplatelets or anticoagulants to prevent future cerebrovascular ischemic events. At present, there is equipoise, whether antiplatelets or anticoagulants are more effective. The decision to use aspirin in our patient was based on pathophysiological consideration as proposed by the CADISP group in 2007.7 In our patient, the following criteria were arguments in favor of aspirin: (1) purely local, nonischemic symptoms; (2) no ischemic brain lesions on MRI scan, and (3) involvement of intracranial segments of the ICA as the latter might point toward higher risk of subarachnoid hemorrhage.7 Nevertheless, the available level of evidence for antithrombotic treatment decisions in cervical artery dissection is relatively low and currently has to be based on purely observational data. At least, 3 systematic meta-analyses across such observational, nonrandomized studies comparing both treatment approaches showed contradictory results.8–10 One meta-analysis revealed a trend in favor of anticoagulants in preventing the composite end point death or disability, whereas in turn symptomatic intracranial hemorrhages and major extracranial hemorrhages solely occurred in the anticoagulation group.8 Another reported no difference in risk of stroke and death between both treatment groups.9 A third analysis showed a superiority of antiplatelets in preventing the composite outcome of ischemic stroke, intracranial hemorrhage, or death.10 But authors of the latter admitted that when the meta-analysis was confined to studies of higher methodological quality, this benefit was not found. Thus, randomized-controlled studies (RCTs) are warranted. A
UK-based RCT (ie, Cervical Artery Dissection in Stroke Study [CADISS]) is under way.9 Because of the (expectedly) low frequency of clinical end points, the use of surrogate outcomes, for example, ischemic and hemorrhagic lesions on MRI, may be a reasonable alternative approach. Such RCT was indeed launched in September 2013 in Switzerland: The TREAT-CAD study aims at demonstrating noninferiority of aspirin as compared with vitamin K antagonists in ICA dissection patients with regard to a composite outcome of clinical or imaging end points of brain ischemia or bleeds, or death (Biomarkers and Antithrombotic Treatment in Cervical Artery Dissection, TREAT-CAD. NCT02046460. www.clinicaltrials.gov).

In the present case, we decided to continue the treatment with 100 mg of aspirin until morphological and blood flow changes in the dissected ICA will be completely resolved on MRI/A and neurosonography.

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### Disclosures
None.

### References

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Internal Carotid Artery Dissection and Asymmetrical Facial Flushing: The Harlequin Sign
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