Brief Communications

Patient with Cluster Headache and Harlequin Sign – Related or Not?

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Background.—The harlequin sign or syndrome is a rare cranial autonomic condition characterized by unilateral diminished flushing and sweating of the face (and sometimes arm), in response to heat or exercise. It results from autonomic, mainly sympathetic dysfunction. Although the idiopathic form is the most common, underlying structural abnormalities in the head, neck, and thorax need to be excluded.

Methods and Results.—Here, we describe the first case of the combination of primary cluster headache and the harlequin syndrome in a 49-year-old female patient. The patient presented with a first bout of cluster headache with persisting Horner syndrome and new harlequin sign after the bout. Additional neuroimaging did not reveal underlying pathologies. This report provides an overview of cases from the literature and then discusses the association between primary headaches and the harlequin syndrome. Relevant anatomy, diagnostic tools, and therapeutic options are all considered.

Conclusion.—This case reports a rare combination of cluster headache and harlequin sign that warrants further testing to exclude pathology in the brain, neck or mediastinum. It also illustrates the underlying anatomy and physiology of the autonomic nervous system.

Key words: cluster headache, migraine, autonomous nervous system, harlequin sign

INTRODUCTION

The harlequin sign or syndrome is a rare cranial autonomic condition that is characterized by a hemifacial redness and perspiration in response to heat or exercise. In some patients, 1 arm is affected as well.

These symptoms are almost always caused by a disorder in the functioning of the sympathetic nervous system. In the majority of cases, this disorder is idiopathic, without underlying structural abnormality. Secondary causes are rare but need to be excluded. Here, we report the case of a 49-year-old female patient who presented with primary cluster headache who, after the first bout, developed hemifacial redness and transpiration after jogging. We diagnosed her with harlequin syndrome. In addition, we give an overview of all 10 patients that have been described in the literature until now with the combination of a primary headache disorder and the harlequin syndrome, of whom only 1 had (non-concomitant) cluster headache.

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CASE REPORT

A 49-year-old woman presented with attacks of very severe, stabbing, pain behind the left eye with ipsilateral ptosis and miosis (Horner’s syndrome), conjunctival injection, lacrimation, and obstructive nasal complaints during 2 months. She also reported the urge to move during the attacks, which lasted for 2-3 hours each up to twice per day. The family history was negative for primary headache disorders. The neurological examination and an MR-scan of the brain were unremarkable and a diagnosis of the first bout of cluster headache was made. The patient was able to successfully abort the attacks using subcutaneous sumatriptan injections and oxygen inhalation therapy. After this first bout subsided, the Horner’s syndrome persisted. A few weeks later, she again reported that the right side of her face had turned red during jogging, while the left side retained its normal color (Fig. 1). At that time, she no longer had cluster attacks. She also no longer perspired on the left side of her face. Horner’s syndrome had not changed. Additional neuroimaging tests were performed (CT-angiography of the cerebral vessels and carotid arteries; X-ray of the chest) and showed no abnormalities. Specifically, there were no signs of a carotid artery dissection or a tumor in the trajectory of the vagal nerve/cervical sympathetic trunk. Pharmacological studies into pupillary signs were not performed since they had no additional diagnostic value in this case. The patient was reassured by the absence of underlying pathology and her symptoms decreased to some extent over a few months. One year later, she reported 1 new bout of cluster headache for which she successfully started verapamil as a prophylactic treatment in addition to her attack treatment. She did not require any symptomatic treatment for the harlequin sign. Altogether, this appears to be the clinical image of the harlequin syndrome, most probably in association with her cluster headache.

DISCUSSION

The Harlequin Syndrome.—The harlequin sign or syndrome is a rare, cranial, autonomic nervous system condition that is characterized by hemifacial redness and perspiration in response to heat or exercise. The syndrome was first described by James Lance in 1988 and was named after the resemblance that the faces of patients had with his son’s toy harlequin [personal communication PJ Goadsby]. Until that point, the harlequin syndrome

Fig. 1.—The patient’s face after jogging showing physiological right-sided flushing of the face and pathological left-sided absence of flushing, ptosis, and miosis.
was only used for vasomotor instability and/or ichthyosis congenita in children.

Typically, the blushing, red, and perspiring side of the face is most prominent for patients. Therefore, this side with symptoms was initially assumed to be the pathological side of the face. Later it was discovered that the non-blushing, anhidrotic side was pathologic and that it was mainly due to sympathetic dysfunction. Pharmacological studies into pupillary reactivity showed parasympathetic dysfunction in some patients as well. Nowadays, the harlequin syndrome is considered to be a condition within the spectrum of cranial autonomic disorders that also includes Holmer-Adie’s and Horner’s syndromes. In the literature, a total of approximately 90 cases of harlequin syndrome have been reported. The majority are primary or idiopathic. Only a few patients have an underlying (structural) pathology is found.

**Anatomy.**—Perspiration and blushing are both functions of the sympathetic nervous system, of which the vasomotor and sudomotor innervation originate from the hypothalamus (Fig. 1). From here myelinated axons project caudally to the ganglions within the sympathetic trunk: the centrum ciliopinale at the level of C8-Th1 (facial innervation) and at Th1-Th4 (innervation of the arm) (Fig. 2). Sympathetic dysfunction and the symptoms described above can result from a dissection of the carotid artery, an aneurysm of the cerebral vessels, or a (space-occupying) lesion in the brainstem, neck, apex of the lung or mediastinum (trajectory of the vagal nerve or sympathetic trunk). For exclusion of underlying causes, an MR scan of the brain/neck region, a doppler ultrasound of the carotid arteries, a CT-angiography of the neck and cerebral arteries, and/or an X-ray of the chest can be considered.

**Headache and the Harlequin Syndrome.**—Some patients with harlequin syndrome also report headaches, as was first described by Lance et al. Although rare, this co-morbidity enables us to hypothesize about the underlying pathophysiology. The literature has so far described a total number of 10 patients with both harlequin syndrome and a co-morbid primary headache disorder. Recently, an overview of the clinical characteristics of 9 out of these 10 patients has been presented. With the data from our case included, Table 1 gives an overview of all 10 patients.

Between migraine and harlequin syndrome, a pathological association does not seem likely. In the reported cases the patients had been free of attacks for years or the harlequin symptoms were not simultaneous with the migraine attack. This is underlined by 2 pharmacological observations: sumatriptan and dihydroergotamine did not have any effect on the harlequin syndrome (but were able to successfully treat migraine headache), and intravenous administration of...
Table 1.—Overview of patients with harlequin syndrome and co-morbid primary headache disorder (adapted from Fiana et al)  

| Patient | Sex | Age, year | Headache before HS | Headache localization | Frequency | Headache exertion | Diagnosis | Side | Sinuläna | MA | TTH† | MO | Migraine | Migraine‡ | Migraine | CH | Right |
|---------|-----|-----------|---------------------|----------------------|-----------|------------------|-----------|------|----------|-----|-------|----|---------|----------|---------|-----|-------|
| Fiana et al² | F | 49 | Left | Bilateral | 1-2/day | Yes | PEH | Left |
| Fiana et al³ | F | 41 | Left | Right | 1-2/month | Yes | PEH | Left |
| Fiana et al⁴ | F | 50 | Left | Left> Right | 4/month | Yes | MO | Left |
| Lance et al⁵ | M | 54 | Right | Right | 0,5/month | No | No | Left |
| Lance et al⁶ | F | 37 | Simultane | Simultane | — | — | No | Left |
| Drummond et al⁷ | F | 26 | Simultane | Simultane | — | — | No | Left |
| Corbett et al⁸ | F | 37 | Simultane | Simultane | — | — | No | Right |
| Fallon et al⁹ | F | 51 | Left | — | — | — | No | Right |
| Willaert et al³ | F | 43 | Left | Left | — | — | No | Right |
| Lehman et al⁵ | M | 60 | Left | Left | — | — | No | Right |

In total, 8/11 patients have migraine, 1/11 has post-traumatic headache (phenotypically tension-type headache). The patient described in this case report is the second patient with both cluster headache and harlequin syndrome. In 8 patients, harlequin syndrome developed after the onset of headache, in 3 patients this was approximately simultaneous. Headache during exercise was reported by 4/11 patients.

CH = cluster headache; F = female; HS = harlequin syndrome; M = male; MA = migraine with aura; MO = migraine without aura; PEH = primary exertional headache; TTH = tension type headache; — = not mentioned or specified in reference.

†Right-sided dull headache without accompanying symptoms since a car accident 22 years earlier.

‡Reported as “classic migraine”.

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of nitroglycerin (a validated experimental model for migraine attack provocation) was able to trigger a migraine attack but not the harlequin symptoms. Furthermore, one of the 2 patients in whom the migraine and the harlequin syndrome developed simultaneously had a severe ENT-infection and a tonsillectomy shortly before, which are a very likely cause. The association, therefore, can be considered incidental.

One cluster headache patient was described in the literature as experiencing his first bout at the age of 60 years. The harlequin symptoms, however, were not simultaneous with the cluster attacks and both had started after a complicated ipsilateral dental root procedure suggesting an iatrogenic cause. The patient in this case report is the second such case described, and the first one with primary cluster headache and the harlequin sign. Dysfunctioning of the (sympathetic) autonomic nervous system is a plausible explanation for both disorders. The harlequin syndrome in this case can be seen as due to the autonomic dysfunctioning in cluster headache. However, a shared, underlying (structural) cause cannot be excluded fully. Follow-up neuroimaging tests will be planned for our patient.

Therapy.—The treatment for harlequin syndrome depends primarily on the underlying cause. Structural lesions need to be addressed according to pathology. In the idiopathic form, a symptomatic treatment is seldom warranted, as the symptom severity seems to decrease over time. Patient reassurance is important, as symptoms can be quite striking and upsetting. Onabotulinum toxin injections and surgical sympathetic denervation on the non-pathological, contralateral side of the face and arm are treatment options when patients suffer socially from asymmetric hyperhidrosis and blushing.

CONCLUSION

The harlequin sign or syndrome is a rare, cranial, and autonomic disorder that is characterized by hemifacial redness and perspiration (sometimes including the arm as well) in response to heat or exercise. On pathology considerations, an association with cluster headache is plausible, but not with migraine. In most cases, harlequin syndrome is idiopathic. Underlying causes such as a dissection of a carotid artery, cerebral aneurysm of (space-occupying) lesion in the brainstem, neck, apex of the lung or mediastinum should be excluded using (follow-up) neuro-imaging. Treatment depends on the underlying cause if present. Idiopathic forms seldom need treatment.

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