



Harlequin Syndrome: two new cases and a management proposal

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Abstract

The Harlequin syndrome is a rare autonomic disorder, characterized by unilateral diminished sweating and flushing of the face in response to heat or exercise. We present two new cases and evaluate the data of 83 patients described in the literature. We provide diagnostic and therapeutic guidelines.

Key words: Harlequin syndrome; facial flushing; autonomic neuropathy; etiology; guidelines.

Introduction

The Harlequin syndrome, first described by Lance *et al.* in 1988 represents an uncommon disorder of the sympathetic nervous system. It is characterized by unilateral diminished sweating and flushing of the facial skin in response to heat or exercise (Lance *et al.*, 1988).

We present two new patients with this remarkable syndrome and evaluate the data of the patients reported in the literature. We provide guidelines for clinical practice.

Patients and methods

CASE REPORTS

Patient 1 is a 59-year-old man who was referred for evaluation of a peculiar pattern of facial flushing. The symptoms had been present for six months. Relatives had noticed flushing and sweating on the right side of his face following physical exercise, while the left side remained dry and maintained its normal color. His medical history was uneventful except for a recent drainage of a maxillar sinus. He had a burden of 40 pack years of tobacco use. He did not use any medication.

On examination at rest no asymmetric facial flushing or sweating was noted. Blood pressure and heart

rate were normal. Neurological examination was normal. Signs of ptosis or miosis were absent.

As a Harlequin syndrome was suspected, autonomic pupillary function was assessed with pupillography and pharmacological testing as previously reported (Bremner *et al.*, 2006). The tests of sympathetic integrity included topical 4% cocaine and 1% phenylephrine. Moreover 0.1% pilocarpine was used to test for parasympathetic supersensitivity. The tests showed normal results.

The patient was asked to run on a treadmill. After 5 minutes of running at 13 km/h, progressive flushing and profuse sweating was seen on the right side of his face. These symptoms were absent on the left side of the face (Fig. 1). No asymmetric patterns were present on the upper limbs or chest. The clinical picture was compatible with the Harlequin syndrome.

Laboratory tests, including ESR, haemoglobin, leucocytes, glucose, sodium, potassium, creatinine and thyroid function, were normal.

Duplex ultrasonography of the carotid arteries was also normal. Computer tomography of the brain, cervical spine and thorax did not reveal any abnormality. MRI-/MRA-scans were contra-indicated because of intraocular metal splinter. The patient was reassured of the benign nature of his complaints. One year later the clinical picture was unchanged. The patient had accepted the peculiar phenomenology.

Patient 2 is a 43-year-old female that was referred with complaints of a progressive sense of coldness of the left arm. Her husband had also noticed profuse left sided facial flushing and sweating during physical exercise. Changes in ambient temperature did not influence this pattern. Her medical history was uneventful except for migraine and two recent episodes of left sided optic neuritis with spontaneous recovery within 6 weeks. Neurological evaluation,



FIG. 1. — Patient 1. Primary Harlequin syndrome. Unilateral facial flushing and sweating on the right side following exercise. Arms are not affected. *Printed with permission.*



FIG. 2. — Patient 2. Primary Harlequin syndrome. Left sided profuse sweating of face associated with right sided sweating of the arm. In contrast, the left arm demonstrated coolness during exercise. *Printed with permission.*

including cerebral MRI and cerebrospinal fluid examination, had not revealed any signs of multiple sclerosis.

On examination at rest no asymmetric flushing or sweating was noted. Blood pressure and heart rate were normal. Neurological examination including cranial nerves and pupil responses was normal. Signs of ptosis or miosis were absent.

After 10 minutes of running on a treadmill at 13 km/h, unilateral sweating and flushing was observed on the left side of her face. The right side of the face remained dry (Fig. 2). After 10 minutes the patient reported a cold sensation of the left arm. Simple palpation confirmed the difference in temperature in both arms. Digital blood pressures as measured using plethysmography of both hands were normal.

Autonomic pupillary function testing showed normal results. Blood tests, including ESR, hemoglobin, glucose, renal and thyroid function, did not reveal any abnormality.

Duplex ultrasonography of the carotid arteries was normal. Computer tomography of the brain, cervical spine and thorax did not reveal any abnormality. MRI-scanning of the brain was also normal. The clinical picture was compatible with a primary Harlequin syndrome and the patient was informed on all aspects of the associated phenomenology.

LITERATURE REVIEW

A literature search on the Harlequin syndrome/sign was performed in Medline/Pubmed/Google using the following terms: 'Harlequin', 'facial

flushing', 'neuropathy', 'autonomic', 'syndrome', 'anhidrosis'. All articles reported since the original paper by Lance in 1988 were reviewed. Data on demography, etiology, clinical features, therapy and prognosis were collected. The two patients reported in the present paper were also included in the review.

Results

The characteristics of 83 patients with the Harlequin sign or syndrome that are reported in the literature, are listed in table 1 (Lance *et al.*, 1988; Umeki *et al.*, 1990; Saito, 1990; Noda, 1991; Drummond *et al.*, 1993; Turco *et al.*, 1996; Ten Holter *et al.*, 1997; Morrison *et al.*, 1997; Montigiani *et al.*, 1998; Corbett *et al.*, 1999; Coleman *et al.*, 2002; Lombardi *et al.*, 2004; Carrol *et al.*, 2004; Wasner *et al.*, 2005; Fallon *et al.*, 2005; Kalapesi *et al.*, 2005; Moon *et al.*, 2005; Burlacu *et al.*, 2005; Crawley, 2006; Mashour *et al.*, 2006; Abe *et al.*, 2006; Tascilar *et al.*, 2007; Kil *et al.*, 2007; Duddy *et al.*, 2007; Darvall *et al.*, 2007; Kilincer *et al.*, 2007; Majunder *et al.*, 2007, Bremner *et al.*, 2008, Sarikay *et al.*, 2008). A distinction is made between primary and secondary, cases.

Females are affected considerably more often than males in Harlequin syndrome (66% versus 34%). In about a third of the individuals the site of flushing was not confined to the face but extended to arm and/or trunk. Nearly half of the patients showed additional autonomic features, particularly Horner syndrome.

Sixty patients had a primary, idiopathic, Harlequin syndrome. In these patients no underlying cause

Table 1

Characteristics of patients with the Harlequin syndrome and sign, reported in the medical literature since 1988

Patients with Harlequin syndrome	(n)	83	
Female / male		53 / 30	(66% / 34%)
Primary		60 (72%)	
Idiopathic			55 (66%)
Congenital			5 (6%)
Secondary		23 (28%)	
Organic lesion			13 (16%)
Iatrogenic cause			10 (12%)
Average age at diagnosis (yr) (range)		43 (0,5-74)	
Site of flushing			
Head		56 (67%)	
Head, arm and / or trunk		27 (33%)	
Side of facial flushing			
Right		40 (48%)	
Left		43 (52 %)	
Concomitant (partial) autonomic syndromes			
Generalized dysautonomia		5 (6%)	
Horner's Syndrome		33 (39%)	
Adie's Syndrome		6 (7%)	
Ross Syndrome		1 (1%)	
Organic lesions			
2 mediastinal neurinomas			
2 cervical syrinx			
1 intramedullary astrocytoma			
1 thoracic neurofibroma			
2 left apical lung cancer			
1 medullary infarction			
1 compression thyroid artery			
2 brachial plexopathies			
1 spontaneous dissection of cervical carotid artery			
Iatrogenic causes			
5 paravertebral thoracic blocks			
1 jugular vein catheterization			
3 resection of a neck mass			
1 thoracic sympathectomy			

could be identified. Five of them had a congenital Harlequin syndrome. They belong to infants with congenital Horner's syndrome who also exhibit contralateral facial flushing and ipsilateral anhidrosis (Saito 1990; Morrison *et al.*, 1997). All patients with primary Harlequin syndrome showed a benign course.

In thirteen patients the symptomatology was due to the secondary form of the syndrome. Neoplasms were the predominant cause. Three patients were operated on. The symptoms of two patients who had thoracic neurogenic tumors, disappeared post-operatively (Duddy *et al.*, 2007; Kilincer *et al.*, 2007). The patients who's facial flushing was due to an mediastinal neurinoma did not show any change after resection (Noda 1991).

Ten additional patients developed the syndrome following iatrogenic damage, predominately after

high thoracic paravertebral anaesthesia (Burlacu *et al.*, 2005; Crawley, 2006; Mashour *et al.*, 2006; Majunder *et al.*, 2007). The majority of symptoms subsided in less than 8 hours.

Discussion

The two patients presented in this paper are classic examples of the Harlequin syndrome as first described by Lance *et al* in 1988. They display a primary Harlequin syndrome, idiopathic in origin and associated with a benign natural course. In both patients no structural underlying lesion could be found. In the recent literature the terms Harlequin syndrome and Harlequin sign have been used interchangeably. However it is preferable to reserve the term Harlequin syndrome for patients that show the paroxysmal signs of hemifacial flushing and

sweating, without other neurological symptoms. The harlequin sign can be used to denote flushing and sweating in patients that also exhibit other associated autonomic signs or syndromes, such as Horner syndrome, Adie's syndrome and Ross syndrome. The characteristics of Adie syndrome are tonic pupil(s) and tendon areflexia. Symptoms of Ross syndrome include tonic pupils, tendon areflexia and patchy hypohidrosis.

As shown by the literature search, most cases of the Harlequin syndrome are primary in nature, and no underlying cause can be identified. The syndrome is most common in women and social embarrassment is the predominant factor in seeking medical advice. A third of the patients with facial flushing also have autonomic ocular signs such as miosis and ptosis, and in a minority of patients, the Harlequin sign is part of a more extensive autonomic disorder including, Horner's syndrome, Adie's syndrome and Ross syndrome. Congenital Harlequin syndrome can be considered as a primary Harlequin syndrome with Horner syndrome as obligatory concomitant syndrome.

Historically the side of the face with excessive flushing and sweating was initially perceived to be the pathological side. In a later phase, however, it was recognized that the sympathetic neural damage was on the non-flushing side. The excessive flushing and sweating on the healthy side of the face, can be understood as a compensatory overreaction to provide normal heat regulation in the face as a whole (Lance *et al.*, 1988; Drummond 1993), a phenomenon that is also seen after cervical sympathectomy (Guttmann 1940).

Understanding the symptoms of the Harlequin syndrome requires insight in the anatomical structure of the autonomic nervous system. The cervicothoracic sympathetic system, supplying vaso-, sudo-, and pupillomotor innervation, acts through a three-neuron pathway as illustrated in figure 2. In the Harlequin syndrome affecting the face the site of the neural sympathetic damage is considered to originate in the T2 or T3 neuron in its course between the stellate ganglion and superior cervical ganglion. However a lesion proximal to the stellate ganglion can also affect the sudo- and vasomotor innervation to the arm, neck, arm and trunk. As in Harlequin syndrome the extent of clinical signs varies, apparently damage may be very selective. The co-existence of Harlequin syndrome and Horner syndrome without other neurological deficits suggests pathological lesions of the superior cervical ganglion, whereas the combination of Harlequin syndrome and Adie's syndrome implicates a ganglionopathy affecting not merely the sympathetic superior cervical ganglion,

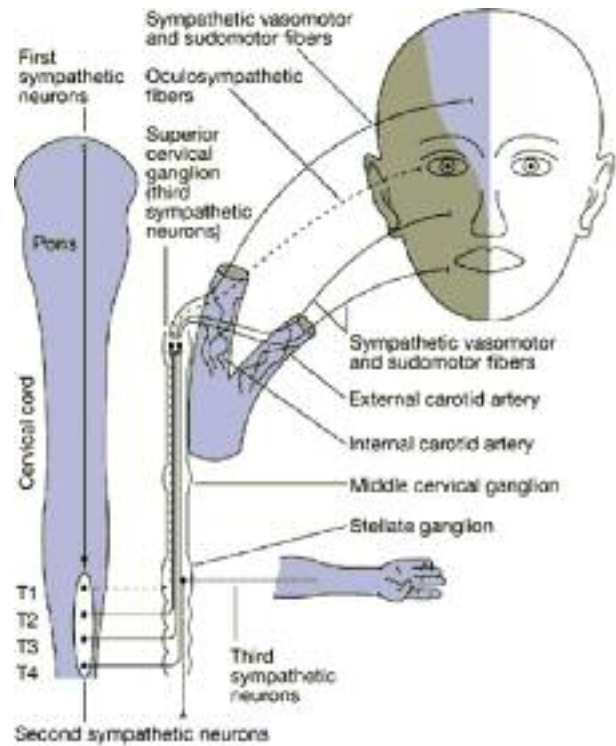


FIG. 3. — Schematic diagram showing the sympathetic fibers innervating the face and upper limb.

but also the parasympathetic ciliary and dorsal root ganglia.

The precise mechanism of axonal damage or degeneration in primary Harlequin syndrome is still unclear. Some suggested that an anterior radicular artery at the third thoracic segment occluded during strenuous exertion (Lance *et al.*, 1988) whereas others speculated that microvascular ischemia mediated by an autoimmune process or infectious agent might be responsible (Drummond *et al.*, 1993). Drummond *et al* described a case where a severe upper respiratory tract infection preceded a Harlequin syndrome (Drummond *et al.*, 1993). A similar mechanism may also have played a role in our first patient as he suffered from a severe maxillary sinusitis that necessitated decompressive drainage.

Several authors have described concomitant symptoms and diseases in conjunction with the Harlequin syndrome; headaches have been reported on frequently (Lance *et al.*, 1988; Drummond *et al.*, 1993). Accordingly migraine and cluster headache are known to be accompanied by autonomic disturbances (Drummond 1994). Lombardi *et al.* described 2 patients whose parasomnia was preceded by a Harlequin syndrome (Lombardi *et al.*, 2004) and Carroll *et al.* noted the Harlequin syndrome in a patient with multiple sclerosis (Carroll *et al.*, 2004).

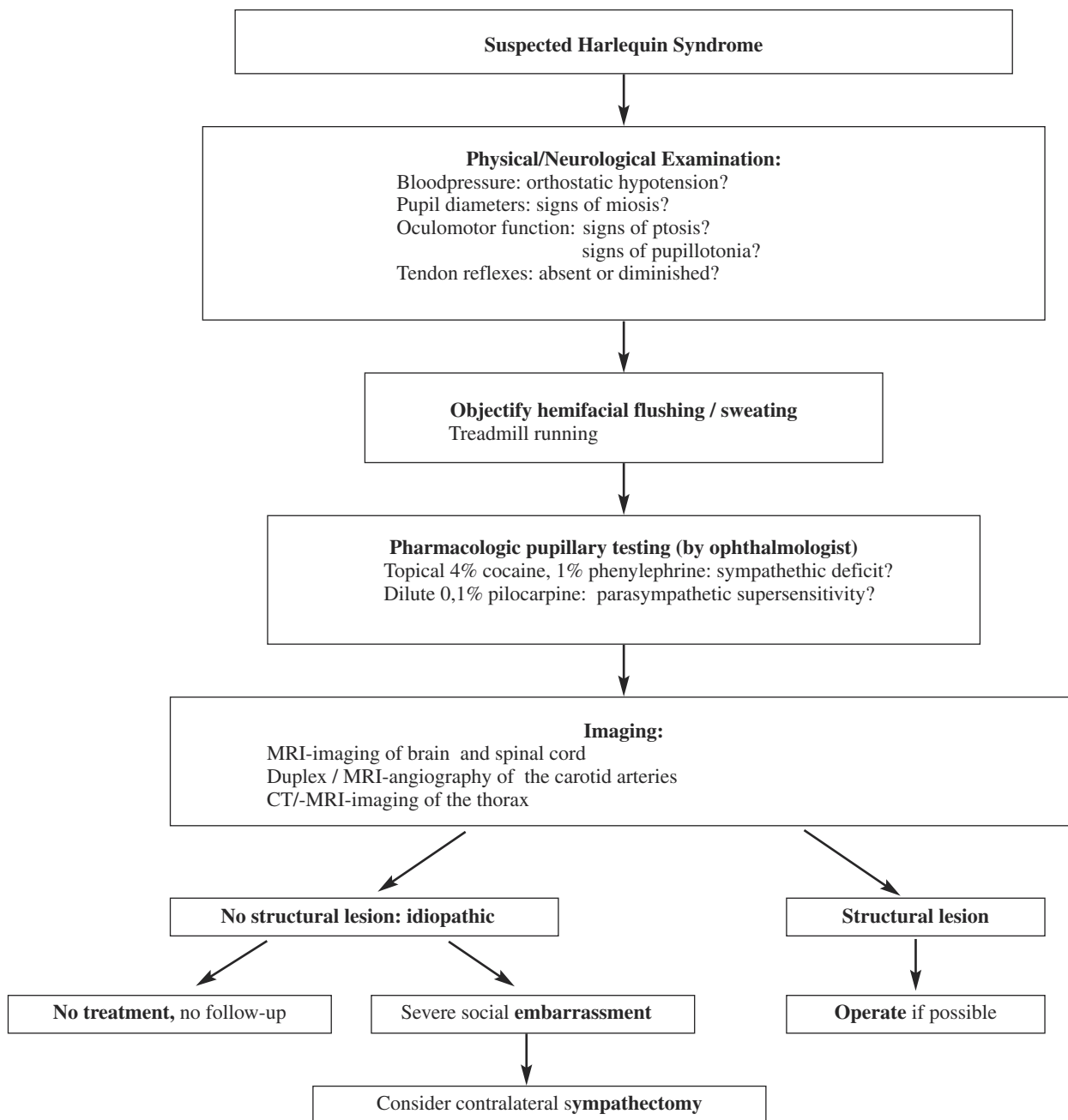
Our second patient had a history of optic neuritis. Although no cause was found for the optic neuritis and symptoms resolved without specific treatment, an immune mediated process similar to that in multiple sclerosis may have played a role. However, it must be emphasized that to date no direct causal relation has been established between any of these concomitant symptoms/diseases and the Harlequin syndrome. Therefore their presence may be pure co-

incidental. The precise etiology of the primary Harlequin syndrome or sign has still to be elucidated.

In about a sixth of the patients with Harlequin syndrome, the disorder is caused by an underlying disease or structural lesion. These patients display a secondary Harlequin syndrome. Most frequent are neurogenic tumors compressing the sympathetic trunk in the neck region (Tascilar *et al.*, 2007; Duddy *et al.*, 2007; Kilincer *et al.*, 2007). Pancoast's

Table 2

Diagnostic and therapeutic flowchart in patients with Harlequin syndrome



syndrome due to spinal invasion by an apical lung tumor (Burlacu *et al.*, 2005; Bremner *et al.*, 2008), medullar infarction (Lance *et al.*, 1988), sympathetic chain compression by an elongated inferior thyroid artery (Wasner *et al.*, 2005), brachial plexopathies (Bremner *et al.*, 2008) and dissection of the cervical carotid artery (Sarika *et al.*, 2008) are other identified causes. If the underlying lesion is amenable to surgical resection, one must note that symptoms do not always disappear postoperatively (Tascilar *et al.*, 2007).

The iatrogenic Harlequin syndrome has been reported with higher frequency recently. Ten such cases have been reported: one following internal jugular vein catheterization (Coleman *et al.*, 2002), five following paravertebral thoracic anesthetic blocks (Burlacu *et al.*, 2005; Crawley, 2006; Mashour *et al.*, 2006; Majumder *et al.*, 2007), three after a surgical resection of neck mass (Turco *et al.*, 1996; Kil *et al.*, 2007; Darvall *et al.*, 2007), and one after thoracic sympathectomy (Bremner *et al.*, 2008). In all cases with exception of the sympathectomy symptoms appeared temporary resolving within a few hours. Pharmacological blockade of the neural transmission, neuropraxia and surgical trauma of the autonomic nervous system were thought to be responsible.

The harlequin sign in an infant should alert the physician to the possibility of a congenital Harlequin syndrome (Saito, 1990; Morrison *et al.*, 1997; Abe *et al.*, 2006). In fact, congenital essential Harlequin is a primary Harlequin with Horner syndrome as an obligatory concomitant syndrome existing since birth. Of course, the diagnosis congenital essential can only be made after excluding structural lesions/iatrogenic causes.

When considering the optimal management strategy, a distinction should be made between primary and secondary forms of the Harlequin syndrome as the latter may require surgery or medical treatment. A wait-and-see approach is the only option when a cause can not be identified. The primary cases reported in literature usually show a benign character. Spontaneous regression or progression of symptoms is unusual. However, progressive disease with contralateral segmental hypohidrosis of limbs and body or with Horner's syndrome, has occasionally been documented.

A diagnostic and therapeutic algorithm is outlined in table 2 including the essential diagnostic non invasive tests. The focus of medical history should be on possible related factors as prior history of malignancy, and recent surgery or anesthesia related problems. Clinical and neurological examinations, as well as provocation tests are basic requirements

to objectify the extent of the autonomic dysfunction. Imaging techniques including CT/MRI of the brain, spinal cord as well as the carotid arteries and the lung apex must be performed to exclude a structural underlying lesion.

If a Harlequin syndrome can not be explained by an organic cause, the patient's concerns should be relieved by explaining the benign nature of the condition. Generally, there is no medical need for any follow-up visit. If social embarrassment impairs the patient's quality of life, a contralateral sympathectomy may be considered, although compensatory flushing and sweating of other parts of the body may occur.

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