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Recognition of a patient with neck autonomic dysfunction: findings from a rare case report of harlequin syndrome in direct access physiotherapy

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ABSTRACT

Background: Harlequin syndrome is a rare autonomic condition consisting of unilateral facial flushing and sweating induced by heat, emotion or physical activity. The affected side presents anhidrosis and midline facial pallor due to denervation of the sympathetic fibers.

Case Description: This case describes a patient who reported right-side redness of the face associated with hyperhidrosis during physical activity. She had two previous major motor vehicle accidents. The patient demonstrated difficulties in the visual accommodation of the left eye, but cranial nerve assessment was unremarkable; the patient was then referred to an ophthalmologist, who excluded any autonomic dysfunction as the primary cause of convergence and visual acuity.

Outcomes: A left-sided sympathetic dysfunction with Harlequin sign diagnosis was made followed by a progressive compensatory adaptation of the right face. The patient was educated and reassured about the benign nature of her problem.

Discussion: Knowledge of the autonomic nervous system is still limited in clinical practice. Although challenging, physiotherapists should develop the knowledge and ability needed to perform appropriate assessment of autonomic dysfunctions.

Conclusion: A dispositional reasoning model should be considered in differential diagnosis.

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Introduction

Harlequin syndrome (HS) is a rare autonomic condition (<100 cases reported in the literature) consisting of unilateral facial flushing and sweating induced by heat, emotion, or physical activity [1–3]. This condition is caused by a unilateral dysfunction of the sympathetic system: the affected side fails to flush and sweat (namely, anhidrosis) because of a denervation of the sympathetic fibers [4]. Paradoxically, patients may progressively present a compensatory flushing and sweating on the unaffected sympathetic innervated side of the face, which is commonly confused as the affected one. Depending on the anatomical location of the compromise, the arms and trunk may also be affected [1–5].

The unilateral anhidrosis and reduced/absent facial flushing is caused by lesions along the pathway connecting the hypothalamus, intermediolateral column of the spinal cord, cervical sympathetic ganglia, and postganglionic sympathetic fibers. Most of the sudomotor and vasomotor fibers innervating the face exit the spinal cord at the T2 to T3 level and continue along both the internal and external carotid arteries to reach the facial region. Injury along this pathway leads to a loss of sympathetically mediated vasodilatation [5]. Unilateral sweating can occur in many other syndromes such as Holmes-Adie, Ross, and Horner syndrome [6]: in these disorders, hemifacial anhidrosis and loss of flushing have also been reported in association with ocular sympathetic deficit (namely, Horner's syndrome) or with tonic pupils (namely, Ross syndrome). Notably, most ocular sympathetic fibers leave the spinal cord at the first thoracic root; that is, clinicians must be aware that a localized lesion would determine a dissociation between ocular and vasomotor manifestation [7] for differential diagnosis purposes.

Although the cause of HS is often difficult to determine, most cases are thought to occur when these sympathetic fibers are injured. That is, individual cases of HS have been reported in association with dissection of the carotid artery [8], toxic goiter [9], tumors [10–12], syringomyelia [6], multiple sclerosis [13], birth canal trauma [14], iatrogenic effects of

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invasive procedures, and traumatic musculoskeletal conditions [15–18]. The diagnosis is made by excluding other conditions associated with HS by interpreting a series of tests including blood pressure, heart rate, temperature [5], neurological and ophthalmological exam [1,5,19,20], cranial nerve assessment [19,20], and autonomic tests such as skin perfusion measurement with laser Doppler flowmetry, iodine-starch test, and tilt-table testing [5]. The management depends on the causes of the lesion and consists of removing the source of sympathetic fibers compression; however, when the disorder is not interfering with a person's daily living, treatment may not be required. That is, HS may result in severe secondary psychological consequences (e.g. social embarrassment), impacting on patients' quality of life [3], and must be addressed when treating these patients [19]. Previous studies already suggested a relationship between whiplash and autonomic dysfunctions such as Raynaud phenomena [21]. To the best of the authors' knowledge, our case is the first to report a relationship between whiplash and HS. Direct access physiotherapists should possess the ability to appropriately triage those pathological conditions outside the scope of practice [20,22–25]. Therefore, the purpose of our case report is to increase clinicians' awareness of the clinical manifestation of HS and to emphasize the importance of evaluating the autonomic nervous system (ANS).

Methods

This case report follows the CARE checklist [26]. The clinical examination and reasoning process of this case were informed by Mourad et al. 2023 [4].

Case presentation

Patient information

A 50-year-old active female who was an avid exerciser, reported having noticed a slight redness on the left side of her face during exercise in the recent year. She started practicing high-intensity interval training in addition to her usual running and weightlifting training. She reported that in recent years she has noticed a little notable redness on the left side of her face. Following the progressive increasing of her physical exertion volume, she become concerned by flushing on the opposite side of the face (i.e. the right side) associated with hyperhidrosis during training sessions, causing her social embarrassment. At the time of her first manifestation, she sought help from her general practitioner (GP) who suggested an X-ray and Magnetic Resonance Scans. Imaging revealed normal age-related changes; however, the GP did not offer any explanation for the symptoms. Lately, the second and third fingers of her left hand were pallid, and her left foot colder especially during cold seasons. She did not report any red flags, familiarity for dermatological/sweating disorders or concomitant significant pathologies. However, she had two close car accidents years ago; the second of which was major (i.e. car rollover) that caused bruising and pain on the left neck-shoulder and chest region due to the seat belt. The patient was unable to remember the exact date but reports that they occurred more than 10 years ago. She reported that she had no serious consequences after the emergency room visit and had fully recovered without consequences. The first signs of a slight redness of slight left facial redness after exercise were noticed following the second whiplash injury.

Physical examination

A comprehensive examination was performed with the goal to exclude any specific pathologies underlying the clinical presentation. Because of the correlation to physical exertion as a trigger, a blood pressure examination was performed at baseline and 5 mins after her familiar physical activities (i.e. running and high-intensity interval training). Blood pressure values were within normal limits with a stable value of 110–70 mmHg at baseline. No exaggerated response (exaggerated increases in blood pressure in response to exercise is defined as systolic blood pressure >190 mmHg for women) was also detected after exercise that may be predictive of masked hypertension [25,27,28]. Also, the cardiopulmonary system was screened: the subject did not report any fainting nor chest pain or shortness of breath during exercise. The musculoskeletal examination (including cervicothoracic and neurodynamic testing) was unremarkable.

Based on the unusual presentation (i.e. flushing or anhidrosis of half of the face), and as skin sudomotor supply is related to cranial nerve function, cranial nerve testing was performed [20]. The subject demonstrated difficulties in the visual accommodation of the left eye during the reading of a Snellen chart (1 lines difference between the eyes). Visual accommodation loss may rely on the Optic nerve (CN II) palsy [19]; however, a progressive failure of the pupil to react either to light or to near vision may be found with cervical autonomic dysfunction, such as Holmes – Adie's syndrome or, more rarely, Harlequin and Horner syndrome [29–31]. As the rest of the cranial nerve examination was unremarkable, the decision was made that the patient was in need for further examination with no urgency [32,33].

Midline pallor and anhidrosis on one side of the face associated with contralateral excessive flushing and hyperhidrosis was observed during facial visual

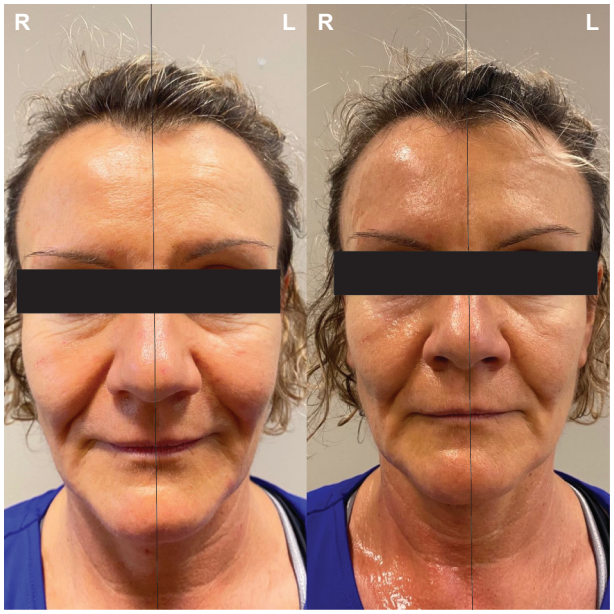

Figure 1. A, midline loss of flushing and anhidrosis on the left side of the face during facial visual inspection. B, contralateral excessive flushing and hyperhidrosis reproduced after physical exertion (i.e. running on the treadmill).

inspection (Figure 1a), especially reproduced after physical exertion (i.e. running on the treadmill) (Figure 1b). Peripheral neurological examination (i.e. sensory, deep tendon reflexes and force reduction) was normal.

The clinical manifestation of the Raynaud's phenomenon was reproduced by asking the subject to leave her hands in a bowl full of ice for few minutes leading to skin pallor of the left hand, especially on the II and III fingers (Figure 2).

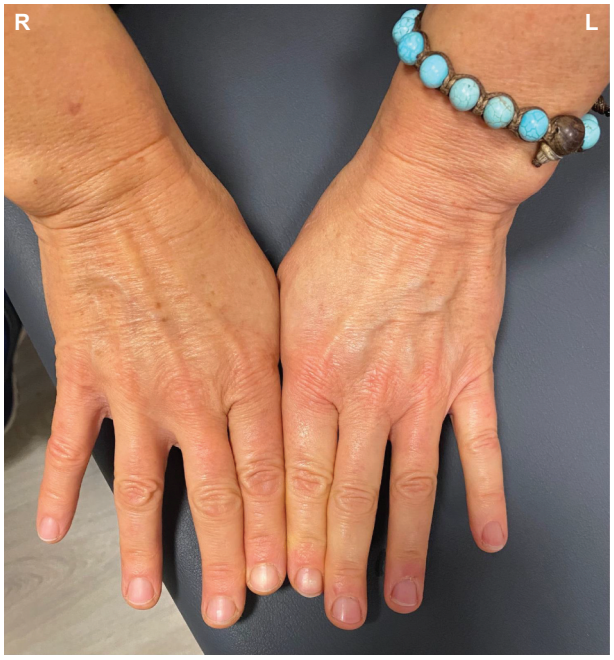

Figure 2. Skin pallor of the left hand, especially on the II and III fingers reproduced after cold exposure of the person hands.

There are no interview items or standard rules indicating when to suspect an ANS involvement [4,19,34]. In addition, little literature on the diagnostic utility of the autonomic/neurological examination is available [35,36]. Therefore, identifying cervical autonomic dysfunctions relies on the physiotherapist's clinical reasoning skills [4]. As no autonomic signs of the eyes were detected – an imbalance between SNS and PNS may cause anisocoria, ptosis, and miosis – an interruption of the oculosympathetic fibers was unlikely. However, because the left upper arm was also affected (but not the hemi body), the sudo- and vaso-motor lesions were more likely located at the site of the stellate ganglion or proximal to it.

Follow-up

The patient was referred to an ophthalmologist for further examination: a diagnosis of myopia was made with no other eye disorders, excluding autonomic dysfunction as a primary cause of convergence and visual acuity issues. Accordingly, a left-sided segmental sympathetic dysfunction with Harlequin sign diagnosis was made (i.e. pallor and anhidrosis), followed by a progressive compensatory adaptation of the right face (i.e. flushing and hyperhidrosis) due to the increased physical exertion. Based on these findings, the patient was educated and reassured about the benign nature of her condition to minimize anxiety and apprehension. The patient was discharged after having received information about surgical treatment (i.e. sympathectomy) and a report to the GP was forwarded. Although the patient refused to undergo any supplementary medical visits, diagnostic test, and invasive treatment, she was advised to discuss it upon shared decision making between both patient and the GP. For a detailed diagnostic triage timeline refer to Figure 3.

Discussion

Autonomic dysfunction has been reported in conditions commonly encountered in physiotherapy, such as chronic low back pain [37–40], fibromyalgia [41], neck pain [42], frozen shoulder [43], and osteoarthritis [44]. The sympathetic and parasympathetic balance may have a direct role in joint tissue homeostasis [45]. Several connections between ANS and the osteoarticular system (synovial membrane, cartilage, articular capsule, etc.) have been also described [45,46]. Whiplash or other cervical/thoracic trauma have not been previously reported in literature as the cause of Harlequin syndrome or other autonomic syndromes.

Autonomic dysfunction manifestations rely on the anatomical location of the lesion along the vasomotor and sudomotor sympathetic pathways [6]. Signs and

Timeline	Care pathway	Clinical Findings	Examination	Imaging and laboratory testing
>10 years earlier	Emergency room. No treatment was required.	Majormotor vehicle accidents with car rollover	Bruising and pain on the left neck-shoulder and chest region due to the security belt	
Early progression		Initial signs and progressive left facial rednessafter exercise		
Late progression		Flushing on the opposite side of the face (i.e., the right side) associated with hyperhidrosis after increasing the volume of the trainingsessions		
Few weeks earlier	GP Consultation	No diagnosis nor explanation offered		Cervical X-Ray and MRI revealed normal age-related changes
Day 1	PT Consultation		Pallor and anhidrosis of the left side face associated with right excessive flushing and hyperhidrosis reproduced after physical exertion. The clinical manifestation of Reynaud's phenomenon was reproduced by leaving the patient's hands in a bowl full of ice.	
Day 3	Ophthalmologist visit	Diagnosis of myopia		
Day 5	Final Diagnosis	Left-sided segmental sympathetic dysfunction with Harlequin sign diagnosis was made (i.e., pallor and anhidrosis), followed by a progressive compensatory adaptation of the right face (i.e., flushing and hyperhidrosis) due to the increased physical exertion.		

Figure 3. Diagnostic triage timeline. GP: general practitioner; PT: physiotherapy; MRI: magnetic resonance imaging.

symptoms differ based on the location of three levels of the cervical sympathetic chain (i.e. superior, middle and inferior cervical ganglia). The first neuron of the sympathetic fibers begins in the posterior hypothalamus and synapses with the preganglionic neuron between C8 and T1. The second neuron travels through the stellate ganglion and the vertical sympathetic trunk to synapse at the superior cervical ganglion [47,48]; there, two branches leave this ganglion and innervate the face and the iris dilator muscle [48]. Lastly, postganglionic fibers from stellate ganglion innervate the upper extremity, so a lesion at this level or proximal to the stellate ganglion would affect sudomotor and vasomotor responses to the neck, arm, and upper extremities [48]. In our case, the patient presented symptoms attributable to Raynaud's phenomenon on the second and third fingers of her left hand. The patient also reported flushing on the opposite side of the face (i.e. the right side) associated with hyperhidrosis. This is a typical compensatory adaptation to provide normal face heat regulation in HS [49]. All the above, is suggestive of a preganglionic lesion proximal to the stellate ganglion due to the compression/strain/damage provided by the seat belt and the whiplash injury during the car accident.

Impaired peripheral sympathetic vasoconstrictor responses and involvement of sympathetic nervous system have been observed in both acute and chronic whiplash, but clinical presentation and outcomes are still unclear [21,50,51]. These responses may occur immediately after the trauma and could persist unchanged to the chronic stage in some whiplash individuals [51]. The occurrence of Raynaud's phenomenon following whiplash or cervical trauma was also well documented. However, the relationship between whiplash, peripheral sympathetic vasoconstrictor responses, and the Raynaud's phenomenon is still unclear [21,52,53]. Raynaud's phenomenon is a clinical diagnosis used to describe a common vasospastic condition; the following tissue ischemia leads to pain, numbness, feeling of cold and impaired function [53,54]. All the above, raise the need to consider autonomic [55] dysfunctions when dealing with patients presenting with whiplash and cervical spine trauma and makes it a topic that deserves to be explored [51].

Typically, HS is most common in women and the onset of symptoms is triggered by hot weather, emotions, or physical activity. Most patients do not need medical or surgical management, but when the social embarrassment is significant and the disorder is interfering with the person's daily living, psychological support and a contralateral sympathectomy may be required [1]. However, autonomic dysfunctions, such as HS, are challenging to diagnose. Conventional diagnostic imaging and electrophysiology cannot detect sympathetic function or compromise. The most common diagnostic tests to assess the function of the ANS

are the sympathetic skin response (SSR) [37,42], blood pressure [41], heart rate variability analysis [42], the tilt table test [41] and laser Doppler flowmetry [43]. Among these tests, SSR is a reliable test for assessing postganglionic sudomotor sympathetic fibers [37,42].

Physiotherapists should be aware of autonomic dysfunctions and their clinical implications to provide appropriate referral and multidisciplinary support. Their recognition has the potential to facilitate the early identification and the following management of those patients at risk of developing persistent pain [56–58]. Autonomic dysfunction may also be important clinical predictors for early recognition for serious cervical pathologies [19,20,59–61]. Physiotherapists working in a direct access setting [24] require skills in a wide range of examination procedure [19,59] in order to rule out autonomic signs or symptoms of serious pathologies mimicking common musculoskeletal disorders [62–64], such as congenital craniovertebral anomalies [65,66], cervical vascular pathologies [19,60,61], anatomical instabilities, and autonomic disorders [4] in patients with neck pain or whiplash. Therefore, the relationship between autonomic syndromes and musculoskeletal conditions confirms that ANS must be a foundational knowledge of physiotherapy practice [67].

Our case report presents a single episode of care and may represent an exception in physiotherapy daily practice, and therefore necessitates caution about its generalizability. Furthermore, as no validated diagnostic tests are available to identify focal autonomic dysfunctions [37,41–43], our diagnostic hypothesis has not been confirmed by any diagnostic tests or medical consultation. In addition, the clinical utility of most clinical predictors to suspect cervical autonomic dysfunctions is limited [4,68]. Examination (including skin color/texture changes, sudo/vasomotor alteration, visual deficit, or oculomotor alteration, pathological reflex testing) has limited diagnostic psychometrics [35,36].

Conclusions

Although challenging, physiotherapists should develop the knowledge and ability needed to perform appropriate triage for autonomic dysfunctions. This case report describes relevant aspects for direct access physiotherapists to screen HS. Further research is warranted to investigate the diagnostic utility of clinical predictors and signs for autonomic dysfunctions.

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F.M. (Firas Mourad) conceived and designed the study. A.G., G.M., and F.M. (Firas Mourad) completed all examinations and decided about final diagnosis. F.M. (Firas Mourad) and I.S. wrote the first draft. F.M. (Filippo Maselli), R.K. (Roger Kerry), A.T., R.K. (Rik Kranenburg), N. H., and J.D. reviewed the article critically for important intellectual content. All authors approved the final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. F.M. (Firas Mourad) is the guarantor.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki. According to local legislation, ethics approval is not required for case reports (Regolamento del 'Comitato Etico nazionale per le sperimentazioni degli enti pubblici di ricerca (EPR) e altri enti pubblici a carattere nazionale', presso l'Istituto Superiore di Sanita, Art. 2 – Funzioni, 11 aprile 2022).

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