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Review

Harlequin Syndrome: Unraveling the Complexities of Etiology, Clinical Presentation, and Management: A Comprehensive Review

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Abstract

Harlequin Syndrome (HS) is a rare autonomic disorder characterized by distinctly demarcated facial discoloration and increased sweating on one side of the face. While idiopathic cases are common, secondary etiologies are increasingly recognized, including iatrogenic causes such as surgical procedures and anesthesia. This review provides an overview of HS, including its etiology, clinical presentation, and management strategies. The etiology of HS is multifactorial, with idiopathic cases comprising a majority. Secondary causes include compression of sympathetic trunks, autoimmune diseases, and iatrogenic factors. The pathophysiology involves disruption of sympathetic flow to the affected side of the face, resulting in compensatory flushing and sweating on the opposite side. Clinical presentation typically includes unilateral facial flushing and sweating, often triggered by physical activity or emotions. HS may coexist with other neurological syndromes, posing diagnostic challenges. Management options range from reassurance for benign cases to surgical interventions or botulinum toxin injections for symptomatic relief. Despite its benign nature, HS can have a significant psychological impact on patients. Increased awareness among healthcare professionals and society is crucial for proper diagnosis and management, ensuring individuals with HS receive the necessary support and care.

Keywords: Harlequin syndrome, Horner's syndrome, sympathethic nervous system, stellate ganglion blocks, sympathectomy

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Harlequin Syndrome (HS) is a rare autonomic disorder characterized by a distinctly demarcated half-sided facial discoloration accompanied by increased sweating.[1] The name of this syndrome originates from its appearance. It refers to the checkered costume of Harlequin, a comedian from Italian theater of the 16th century.[2] The direct cause of HS is the blockage of sympathetic fibers responsible for vasodilation and sudomotor innervation of half of the face, leading to compensatory flushing and sweating on the other half.[3] While idiopathic cases predominate, reports of specific clinical situations leading to the development of HS as a secondary symptom are increasingly appearing in the literature including iatrogenic ones, primarily attributed to surgical procedures and anesthesia in the neck area.[4,5] The expanding knowledge about the pathophysiology of the syndrome and the increasing significance of secondary etiology may pose a challenge for physicians and raise the question of how to prevent this disease.

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In this review article, we present the available knowledge about this condition—its multifactorial etiology, clinical presentation with emphasis on differentiating HS from other similar diseases, and management focused on holistic patient care.

Etiology

HS is a rare condition characterized by dysfunction of the sympathetic nervous system. Among the causes, idiopathic etiology can be distinguished, which accounts for up to 54.6%.[4] An example is the case of a woman from Ethiopia who had a negative medical history regarding injuries and chronic illnesses, and detailed laboratory and imaging studies did not indicate a clear cause of the symptoms.[6]

In 45.4% of cases, the symptoms occur secondarily. One of the described causes in the literature is the compression of the sympathetic trunks at T2 and T3 levels, caused by conditions such as Pancoast tumor, mediastinal neurofibroma, carotid artery dissection, neuroblastoma, or thyroid goiters.[4,7–12] There have been few reports of HS occurring in patients after cerebellar hemorrhage and brainstem infarction.[10] Additionally, certain autoimmune diseases, including multiple sclerosis, hyperthyroidism, Guillain-Barré syndrome, and diabetic neuropathy, may affect nerve fibers and thus represent a probable pathomechanism for the described symptoms.[3,13–15]

Increasingly, iatrogenic causes are being reported. Harlequin face has been observed in patients after procedures such as carotid endarterectomy, thyroidectomy, anterior cervical discectomy, excision of cervical neurofibroma, spinal surgeries, placement of VA ECMO, thoracic sympathectomy, and jugular vein catheterization.[3,16] HS may also result from the local blockade of sympathetic fibers, which can occur during anesthetic techniques such as thoracic epidural anesthesia, paravertebral blocks, erector spinae blocks, or multi-level intercostal nerve blocks.[17–21] In a few reports, we can observe a connection between the occurrence of symptoms and the use of higher doses of vasodilatory prostaglandin E1.[22]

The authors disagree on whether HS can be congenital. According to J. H. Kang et al.,[23] 10 cases with probable congenital pathology have been reported so far, with half of them also having Horner's syndrome.[24,25] Other authors attribute the occurrence of nerve dysfunction to birth injury. Additionally, they identify hypothalamic immaturity as a causative factor, resulting in symptoms fading as the nervous system develops.[1] A summary of information regarding the etiology of HS is located in Table 1.

Pathophysiology

The autonomic nervous system consists of the sympathetic and parasympathetic divisions. The former is responsible, among other things, for the tension of the pilomotor muscles and increased sweating. Sympathetic innervation of the face originates from the hypothalamus. Nerve fibers descending through the lateral aspect of the brainstem synapse at the lateral horns of the spinal cord with preganglionic neurons. Fibers of these secondary neurons run in the intermediolateral cell columns and exit the spinal cord through the anterior roots. Passing through the anterior branches of spinal nerves T1-L2, they enter the sympathetic trunks. Within them, they synapse in paravertebral ganglia with postganglionic neurons, i.e., tertiary neurons.[26–29]

Vasomotor and sudomotor fibers supplying the face exit the spinal cord at the level of T2-T3. After joining postganglionic neurons in the superior cervical ganglion, they run along the internal and external carotid arteries on both sides of the neck until they reach their effectors on the face. Oculo-sympathetic fibers responsible for dilating the pupils originate at the T1 level.

Unilateral damage, compression, or blockade of sympathetic fibers at the T2-T3 level on their pathway from the hypothalamus to the face disrupts sympathetic flow to the

Table 1. Summary of the etiology of Harlequin Syndrome

Etiological Factor	Description
Idiopathic	Up to 54.6% of cases: cause unknown, but likely related to dysfunction of sympathetic nervous system
Secondary Causes	45,4% of cases: various underlying conditions can lead to HS as a secondary symptom, including: • Compression of sympathetic trunks at T2 and T3 levels by conditions such as tumors (e.g., Pancoast tumor, neuroblastoma), carotid artery dissection, or thyroid goiters • Neurological conditions (e.g., multiple sclerosis, brainstem infarction, Guillain-Barre syndrome) • Iatrogenic causes such as surgical procedures (e.g., carotid endarterectomy, thyroidectomy), anaesthesia in the neck area, or administration of vasodilatory medications
Congenital	Disputed whether HS can be congenital: some reports suggest a possible congenital pathology with associated syndromes like Horner's syndrome or birth injury Hypothalamic immaturity may contribute, with symptoms fading as the nervous system develops

affected side of the face. This results in vasoconstriction and lack of sweating on the diseased side, while the other half of the face appears visibly flushed and sweats intensely, explained by compensation of sympathetic blockade on the opposite side. If T4 fibers are additionally affected, facial discoloration may extend to the upper chest and arms, and with impaired T1 function, symptoms of Horner's syndrome may occur.[30,31]

Clinical Picture and Differential Diagnosis

The main symptom of Harlequin Syndrome is increased sweating and simultaneous flushing on one side of the body, most commonly in the facial area. Changes can be observed on both the right and left sides of the body.[32,33] Sometimes, the described symptoms may also manifest on one side of the neck and limbs as well as the upper part of the torso.[32,34]

The opposite side to the one that is flushed and more sweaty is almost always anhidrotic and pale.[35] The most common feature is a distinct demarcation at the body's midline between the affected side and the healthy side.[33]

The changes may occur during physical activity, under the influence of various emotions, or increased ambient temperature, including during heatwaves, and sometimes they appear spontaneously.[36] The symptoms usually resolve without any intervention or after the cessation of the triggering stimulus within several minutes. Neurological, ophthalmological, or imaging studies do not show significant deviations.[33]

HS often coexists with other neurological syndromes, which can pose diagnostic challenges. Bremner and Smith described that the most commonly associated abnormality with HS is Horner's syndrome, characterized by ptosis, miosis, and enophthalmos.[37] Cases have also been documented where HS occurred simultaneously with Holmes-Adie syndrome, characterized by tendon areflexia and tonic pupils.[37] During such occurrences, there was a lack or reduction of sweating in the left upper and lower extremities, the left side of the torso, and the right side of the neck and face, with increased or normal sweating observed on the opposite sides.[30] A case has been described in the literature involving a patient who exhibited pallor on one side of the face along with a lack of tearing on the same side, but the described symptoms occurred only during crying and were more likely due to the simultaneous presence of HS and parasympathetic neuropathy.[38] Patients with HS may also exhibit symptoms of Ross syndrome: tonic pupils, hyporeflexia of tendons, and segmental anhidrosis, affecting the face and body.[15] HS can also be a late manifestation of disorders that damage the sympathetic innervation of the face: Guillain-Barré syndrome, multiple system atrophy, diabetic autonomic neuropathy, and tumor-related or post-traumatic changes within the stellate ganglion.[15]

So far, significantly more cases of HS have been reported in women than in men. It appears that women are more frequently affected than men, but this may be related to a greater tendency for women to seek advice in case of facial appearance issues rather than a greater susceptibility to injuries of their sympathetic vasodilator facial fibers.[37]

Management

Diagnostic possibilities in HS are limited (Table 2). Based on the anatomy of sympathetic pathways and the location of HS symptoms, it is possible to determine the site of sympathetic damage. Subsequently, imaging studies such as MRI

Table 2. Summary of the management options in Harlequin Syndrome

Management Options	Description
Diagnostic evaluation	• Limited diagnostic possibilities: based on the anatomy of sympathetic pathways and the location of symptoms, imaging studies such as MRI or ultrasound, and electrophysiological procedures can be performed to determine the etiology
	• Diagnosis often relies on clinical presentation and ruling out other conditions with similar symptoms
Psychological support	• Explanation to patients about the benign nature of the condition and its favorable prognosis
	• Addressing the psychological impact of the syndrome, providing reassurance, and support to cope with social embarrassment
Surgical Treatment	• Reserved for cases where symptoms significantly impact quality of life or psychological well-being
	• Contralateral sympathectomy: Surgical procedure involving the removal or interruption of sympathetic nerve fibers on the unaffected side
	• Risks include compensatory flushing and sweating in other parts of the body
Pharmacological Interventions	• Repeated temporary stellate ganglion blocks with local anesthesia
	• Botulinum toxin injections: causes atrophy and involution of sweat glands, delaying the recurrence of excessive sweating. Temporary relief with effects lasting from 4 to 12 months, necessitating subsequent injections

or ultrasound, as well as electrophysiological procedures, can be performed in that location to determine the etiology of the condition.[39] Nevertheless, patients without an underlying disease generally do not require treatment. It is important to explain that the condition is benign and has a favorable prognosis.[35] Harlequin Syndrome can have a significant psychological impact on the patient, as some individuals may struggle with social embarrassment resulting from unilateral skin flushing.[40] For such individuals, surgical treatment is possible. The procedure involves contralateral sympathectomy; however, it carries the risk of compensatory flushing and sweating in other parts of the body.[41]

Another possible therapeutic option is repeated temporary stellate ganglion blocks (SGB) with local anesthesia, which can serve as both a screening test for subsequent sympathectomy or as a less invasive treatment for HS.[42] Patients can also be treated with botulinum toxin injections.[43] Botulinum toxin causes atrophy and involution of sweat glands, thus delaying the recurrence of excessive sweating. This treatment is relatively safe, effective, and does not require hospitalization as with sympathectomy. However, the therapeutic effects of botulinum toxin injections are temporary and last from 4 to 12 months, necessitating subsequent injections.[43]

Conclusion

Despite the unsettling clinical picture characterized by significant changes and their location, HS is a benign syndrome, and symptoms usually resolve spontaneously. However, patients often experience significant anxiety and distress due to the condition, which undoubtedly can have a negative impact on their mental well-being. The rare occurrence, combined with the unusual appearance of the patient, further intensifies feelings of isolation. Therefore, it is crucial to familiarize oneself with this syndrome, not only for the patients themselves but especially for healthcare professionals and society. This way, individuals suffering from HS can be properly diagnosed and receive professional care.

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