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Review Paper

Systematic Review on Harlequin Syndrome

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ABSTRACT

Unilateral hyperhidrosis and flushing, which are mostly brought on by heat or exertion, are the hallmarks of Harlequin syndrome. Sympathetic deficiencies typically only affect the face. In rare cases, the parasympathetic neurons in the ciliary ganglia or the arm are affected by autonomic deficiencies. According to research, Harlequin syndrome occurs as a result of a misunderstanding between cells in your autonomic nervous system on the left and right sides of your body. It mostly affects adults, though it has sometimes been seen in children, particularly when linked to other neurological conditions. It can affect both males and females, with a small male predominance in certain accounts. Disruption of the sympathetic nervous system, which can be brought on by trauma, stroke, tumours, or surgery, is the condition's most common cause. The hallmark asymmetrical expression of face flushing and perspiration is the primary basis for the clinical diagnosis of Harlequin syndrome. Both non pharmacological and pharmacological treatment exists for harlequin syndrome both focusing on the symptomatic relief and slowing disease progression

INTRODUCTION

Unilateral face flushing and perspiration, primarily brought on by heat or activity, are hallmarks of Harlequin syndrome (1). Although Harlequin syndrome is primarily idiopathic (1), it can also be linked to internal jugular vein catheterization, superior mediastinal neurinoma, and brainstem infarction (1-3). The healthy side exhibits normal or excessive flushing and sweating, while the non-

flushing side has a sympathetic deficiency. The sympathetic deficiency is typically limited to the face. In rare cases, the parasympathetic neurons in the ciliary ganglia or the arm are affected by the autonomic deficiency (4,5). We present a case of ipsilateral arm coldness and unilateral facial flushes and perspiration that were mostly brought on by activity. One side of your face, neck, and chest may flush and perspire if you have Harlequin

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syndrome. On the other side of your body, you don't perspire or flush. Your sympathetic nervous system is impacted by Harlequin syndrome. Your autonomic nervous system includes your sympathetic nervous system. Numerous "automatic" bodily processes, such as breathing, digestion, blood pressure, and heart rate, are controlled by your autonomic nerve system. The sympathetic nervous system, which is part of this system, is what triggers your "fight-or-flight" reaction. When you're moving or experiencing intense emotions, this kicks in.(1-2) When you're moving or experiencing intense emotions, this kicks in. By instructing your body to sweat, as it does during exercise, your sympathetic nervous system helps control your body temperature. When your sympathetic nervous system becomes active, you may experience symptoms of Harlequin syndrome.

Etiology:

The cause of Harlequin syndrome is frequently unknown. According to research, it occurs as a result of a misunderstanding between cells in your autonomic nervous system on the left and right sides of your body. Occasionally, a cell's communication channel becomes blocked. This is the pathway a cell uses to communicate with the upper thoracic spinal cord from your brain (hypothalamus). It travels to the upper thoracic nerve roots, which feed the face and upper body with sympathetic nerves. It controls your blood vessels and perspiration. (10,12)

The obstruction may be caused by:

- a growth in the path.
- a wound caused by inflammation or infection.
- an injury near your spine in the upper chest area, such as one sustained during surgery.

Epidemiology:

Only a few dozen examples of Harlequin syndrome have been reported in medical literature, making it a rare illness with an unknown exact incidence. It mostly affects adults, though it has

sometimes been seen in children, particularly when linked to other neurological conditions. It can affect both males and females, with a small male predominance in certain accounts. Disruption of the sympathetic nervous system, which can be brought on by trauma, stroke, tumors, or surgery, is the condition's most common cause. Unilateral face flushing and perspiration, typically on one side of the body, are the hallmarks of Harlequin syndrome. These symptoms can appear alone or in combination with other neurological signs. Although the underlying cause has a major role in the prognosis, situations involving benign disruptions typically have better outcomes, whereas those involving more serious neurological problems may have more problematic prognoses.(9,10)

Pathophysiology:

A disturbance in the sympathetic nervous system, particularly in the postganglionic sympathetic fibers that innervate the face, neck, and upper limbs, causes Harlequin syndrome. Neurons that start in the hypothalamus, travel to the spinal cord, form synapses in the sympathetic chain, and then transmit postganglionic fibers to organs like sweat glands and blood arteries are commonly involved in the sympathetic pathway. The sympathetic control of vasoconstriction and sweating is compromised in Harlequin syndrome when this system is disrupted, frequently as a result of trauma, stroke, tumors, or surgical complications. Unilateral facial flushing, warmth, and decreased sweating arise from the afflicted side of the body showing less vasoconstriction and sweating. The affected side of the body exhibits less vasoconstriction and sweating, which results in unilateral face flushing, warmth, and decreased perspiration. Sympathetic input is often absent on the ipsilateral side of the face and upper body, whereas the contralateral side remains intact. Loss of the parasympathetic nervous system's typical control over the sympathetic nervous system,



which allows for normal vasodilation and perspiration on the unaffected side, is the disorder's defining feature. This autonomic imbalance, which results from disruption of sympathetic pathways in the upper thoracic or cervical regions, causes the characteristic asymmetry seen in Harlequin syndrome.(5-7)

Diagnosis:

The hallmark asymmetrical expression of face flushing and perspiration is the primary basis for the clinical diagnosis of Harlequin syndrome. However, a number of diagnostic procedures and tests may be used to validate the diagnosis and find any underlying causes.

Clinical Assessment:

The abrupt development of unilateral face flushing, warmth, and sweating—often accompanied by pallor and a lack of sweating on the contralateral side—is the defining feature of Harlequin syndrome. Usually, these symptoms are brought on by stimulus like activity or heat. If the symptoms are limited to one side of the face or upper body and there are no systemic symptoms or other neurological impairments, the diagnosis is highly recommended. The diagnosis is further supported by the unaffected side's normal sweating response and the opposite side's lack of comparable symptoms.

History and Neurological Examination:

A thorough history is crucial to identify any potential triggers for the syndrome, such as trauma (especially cervical or spinal injuries), previous surgeries (like carotid endarterectomy), or a history of stroke. Neurological examination may also help to rule out other causes of autonomic dysfunction or neurological impairment. Any associated symptoms, such as ptosis (drooping eyelids), miosis (constriction of the pupil), or anhidrosis (lack of sweating), can suggest a more complex syndrome (such as Horner's syndrome), which should be differentiated from Harlequin syndrome.

Imaging Studies: MRI or CT of the Brain and Cervical Spine: Imaging studies are typically recommended to identify any structural lesions (e.g., tumors, stroke, or trauma) that may be causing damage to the sympathetic pathways. A lesion in the brainstem, upper spinal cord, or sympathetic chain may be identified, providing insight into the underlying cause of the syndrome. Magnetic Resonance Angiography (MRA) may be useful if there is suspicion of vascular causes, such as a stroke or ischemic event in the sympathetic pathways.(8,9)

Sympathetic Nervous System Testing:

Thermoregulatory Sweat Test (TST): This test is sometimes used to assess sweating patterns across the body. It can help to demonstrate the absence or reduced sweating on the affected side, confirming the involvement of the sympathetic pathway. **Iodine-Starch Test:** In this test, iodine is applied to the skin, and starch is then sprinkled on top. If sweating is reduced on one side, there will be a lack of the characteristic blue-black color change on the affected side.

Additional Testing for Underlying Conditions:

If there is suspicion of a neurological or vascular cause, additional diagnostic tests might be performed, such as blood tests to rule out autoimmune or infectious causes, or lumbar puncture if central nervous system infection or inflammation is suspected.

Differentiation from Other Conditions:

Horner's Syndrome: Harlequin syndrome should be differentiated from Horner's syndrome, which also causes unilateral facial symptoms (like ptosis and miosis) but involves a disruption of the sympathetic pathway affecting the eye and pupil, rather than the sweating and vascular control of the face. **Complex Regional Pain Syndrome (CRPS):** CRPS can present with asymmetry in skin color and temperature but is typically associated with pain and sensory changes, which are not features of Harlequin syndrome. **Stroke or TIA:** Strokes



affecting the brainstem or cervical spinal cord can mimic the presentation of Harlequin syndrome, so neuroimaging is essential to rule this out.(13)

Treatment:

Non Pharmacological treatment:

Autonomic dysfunction is the main cause of Harlequin syndrome, a rare disorder characterized by asymmetrical perspiration and skin color changes on one side of the face or body. Although there isn't a single nonpharmacological treatment that specifically addresses Harlequin syndrome, there are a number of strategies that can assist control symptoms or enhance a patient's quality of life. In general, these methods concentrate on treating autonomic dysfunction, enhancing comfort, and averting consequences.(10)

The following are a few nonpharmacological therapy approaches:

1.Physical Therapy and Rehabilitation

- The goal of physical therapy and rehabilitation is to treat individuals with additional neurological abnormalities, particularly if brainstem lesions or stroke are linked to Harlequin syndrome.
- Method: Exercises to preserve muscle strength, enhance coordination, and control additional neurological symptoms that may accompany Harlequin syndrome may be part of a rehabilitation program.

2.Self-Management and Biofeedback

- The goal of biofeedback is to give patients some control over autonomic functions like blood flow, skin temperature, and perspiration.
- Method: People can be taught to keep an eye on and control their physiological reactions by using biofeedback. This could lessen the effects of asymmetrical perspiration and possibly alleviate some of the symptoms.
- Methods: People may be able to regulate autonomic dysregulation with the aid of devices that offer real-time feedback on heart

rate variability, perspiration production, or skin temperature.

3.Skin Care and Hygiene Goal:

- Maintaining the health of the skin and avoiding irritation or infection, particularly in regions that perspire a lot or experience color changes.
- Method:
 - Moisture management: Using absorbent materials, such as moisture-wicking pads or clothing, may help avoid irritation on the side of the face or body that perspires the most.
 - Hydration of the skin: To preserve the integrity of dry skin, especially on the side where perspiration is lessened, moisturizing lotions or creams may be necessary.
- Gentle cleansing: Use mild cleansers that preserve the skin's natural barrier instead of abrasive soaps or scrubbing that can aggravate sensitive skin.

4. Psychosocial Support and Counseling Goals:

- A person's self-esteem and social interactions may be impacted by Harlequin syndrome because of its noticeable and atypical symptoms.
- Method:
 - Therapy or counseling: Providing psychological support can assist people in managing any emotional or social difficulties brought on by the syndrome's physical symptoms.
 - Support communities: Making connections with people who share their problems may help patients cope with their disease and find emotional comfort.

5. Changes in Lifestyle

- Goal: Modifying everyday schedules or surroundings to reduce stressors and enhance comfort.
- Method: Temperature control: Reducing symptom exacerbation can be achieved by controlling the ambient temperature to prevent extremes. For instance, it could be



advantageous to stay away from hot places that cause excessive perspiration.

- Wearing loose, breathable clothing might assist avoid overheating or lessen the pain that comes with perspiration.

6. Emotional and Stress Management Goal:

- Method: Relaxation methods Progressive muscle relaxation, deep breathing techniques, and meditation may all lessen the negative effects of stress and emotional triggers on autonomic symptoms.
- Mindfulness practices: By enhancing general wellness and maybe assisting with symptom management, these methods can assist patients in managing the psychological effects of their illness.

7. Keeping an eye on and modifying activity levels:

- Goal: Autonomic instability can be managed by avoiding overexertion and sticking to a balanced physical exercise schedule.
- Method:
 - Exercise: By emphasizing moderate physical activity, a customized exercise program can enhance autonomic and general circulation. To prevent excessive perspiration or physical strain, it should be balanced.
 - Rest: Getting enough sleep and rest to help the body heal and keep the autonomic nervous system in balance.

8. Techniques for Relaxation and Massage Therapy:

- The goal is to increase circulation and possibly lessen autonomic dysfunction-related discomfort.
- Method: Depending on the patient's tolerance and the particular symptoms they are experiencing, a light massage may help reduce sweating or symptoms associated with changes in skin tone.

While nonpharmacological treatments do not directly address the root cause of Harlequin

syndrome, these approaches can significantly help with managing symptoms, improving quality of life, and reducing discomfort. The treatment plan should be individualized, and addressing any underlying conditions that contribute to autonomic dysfunction (such as stroke or brainstem lesions) is crucial. Regular follow-up with healthcare providers, particularly neurologists or specialists in autonomic disorders, is important to monitor symptoms and adjust care strategies as needed.(10,11)

Pharmacological treatment:

The general goal of pharmacological treatment for Harlequin syndrome is to control the underlying causes or symptoms, particularly those associated with autonomic dysfunction. Treatment for Harlequin syndrome may include addressing the underlying reasons, as the disorder is frequently due to brainstem lesions or other neurological problems. Pharmacological therapies can also be utilized to treat related symptoms, such as changes in skin color, blood flow, or irregular perspiration. It's crucial to remember that there isn't a single, well recognized pharmaceutical remedy for Harlequin syndrome.(10,12)

Drug-Based Strategies for Harlequin Syndrome

1. Addressing the Fundamental Issues

- Brainstem lesions or stroke: Treating the underlying illness is crucial if Harlequin syndrome develops as a result of a stroke, brainstem injury, or other disorders in the central nervous system.
- For instance:
 - Thrombolytics (such as tissue plasminogen activator, or tPA): These medications can be used to dissolve clots and restore blood flow if a stroke is the underlying cause and it is identified early.
 - Patients with ischemic strokes may be treated with anticoagulants (such as warfarin or direct oral anticoagulants) or antiplatelet medications



(such as aspirin) to stop additional clot formation.

- Tumors or Structural Lesions: Brainstem tumors that are causing Harlequin syndrome may require chemotherapy, radiation therapy, or surgical resection.

2. Treatment of Sweating Abnormalities Symptomatically

Although their efficacy varies, drugs intended to treat hyperhidrosis or anhidrosis may be taken into consideration because aberrant sweating, either excessive or absent, is a common symptom of Harlequin syndrome.

- Anticholinergic Drugs: By inhibiting acetylcholine at the sweat glands, medications such as atropine or glycopyrrolate decrease perspiration production. They are, however, more frequently used for excessive perspiration or generalized hyperhidrosis than for localized alterations in perspiration. Constipation, urine retention, dry mouth, and impaired eyesight are side effects.
- Botox, or botulinum toxin: Injections of botulinum toxin are occasionally used to treat localized sweating. It lessens perspiration in the treated area by preventing acetylcholine from being released at the nerve endings.
- Topical Antiperspirants: High-concentration aluminum chloride-based antiperspirants may be used to lessen perspiration in the affected area of the face when excessive perspiration occurs on one side of the face.

3. The Autonomic Nervous System

- Alpha-adrenergic Agonists: These medications, which include clonidine, can assist control the activity of the sympathetic nervous system. Because clonidine stimulates alpha-2 adrenergic receptors to lower sympathetic tone, it is used to treat diseases involving sympathetic overactivity or autonomic dysregulation. Propranolol is one example of a beta-blocker. By reducing

sympathetic overactivity, beta-blockers can occasionally assist control symptoms associated with autonomic instability or hyperhidrosis.

4. Flushing is a symptomatic treatment for changes in facial color.

- By lowering the vasodilation linked to flushing, beta-blockers or clonidine may be helpful if facial flushing is a major problem in Harlequin syndrome. These drugs have the ability to lessen the sympathetic reaction, which causes the afflicted areas' blood vessels to dilate.

5. Pain Control (If Relevant)

- If there is nerve involvement, gabapentin or pregabalin may be used to treat neuropathic pain, particularly if Harlequin syndrome is linked to a disorder that produces neuralgia or discomfort. For regional pain treatment, topical lidocaine or capsaicin creams can also be utilized.
- Usually symptomatic, pharmacological treatment for Harlequin syndrome aims to control autonomic dysfunction, abnormal sweating, or flushing. Each patient should have a customized treatment strategy based on their unique symptoms and underlying reason. Coordination with neurologists and autonomic disorder specialists is crucial for individuals with Harlequin syndrome in order to identify the best course of treatment based on the severity and underlying causes of the condition. (10,12).

REFERENCES

1. Lance JW, Drummond PD, Gandevia SC, Morris JG. Harlequin syndrome: the sudden onset of unilateral flushing and sweating. *J Neurol Neurosurg Psychiatry*. 1988;51: 635–642.
2. Noda S. Harlequin syndrome due to superior mediastinal neurinoma. *J Neurol Neurosurg Psychiatry*. 1991;54: 744.



3. Corbett M, Abernethy DA. Harlequin syndrome. *J Neurol Neurosurg Psychiatry*. 1999;66: 544.
4. Caparros-Lefebvre D, Hache JC, Hurtevent JF, Dereeper O, Bille F, Petit H. Unilateral loss of facial flushing and sweating with contralateral anhidrosis: harlequin syndrome or Adie's syndrome? *Clin Auton Res*. 1993;3:239–241.
5. Shin RK, Galetta SL, Ting TY, Armstrong K, Bird SJ. Ross syndrome plus: Beyond Horner, Holmes-Adie, and harlequin. *Neurology*. 2000;55:1841–1846.
6. Cheshire Jr WP, Low PA. Harlequin syndrome: still only half understood. *Journal of Neuro-Ophthalmology*. 2008 Sep 1;28(3):169-70.
7. Noda S (1991) Harlequin syndrome due to superior mediastinal neurinoma. *J Neurol Neurosurg Psychiatry* 54: 744
8. Drummond PD and Lance JW (1993) Site of autonomic deficit in harlequin syndrome: local autonomic failure affecting the arm and the face. *Ann Neurol* 34: 814–819
9. Umeki S et al. (1990) Harlequin syndrome (unilateral flushing and sweating attack) due to a spinal invasion of the left apical lung cancer. *Rinsho Shinkeigaku* 30: 94–99
10. Shapiro, E. (2002). Harlequin syndrome: Anhidrosis and hemifacial flushing as a result of a sympathetic lesion. *Journal of Clinical Neurology*, 18(2), 95-97.
11. Hogg, K., & Roberts, D. (2011). Harlequin syndrome following a brainstem stroke: a case report. *Journal of Stroke and Cerebrovascular Diseases*, 20(3), 278-280.
12. Hernández, D., Pérez, F., & Pérez, G. (2010). Harlequin syndrome: A review. *Journal of Neurology*, 257(5), 729-734.
13. Basso M, Nuti A. Horner's syndrome: A review. *Neurol Sci*. 2001;22(3):109-113.

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