



A pediatric case of idiopathic Harlequin syndrome

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Harlequin syndrome, which is a rare disorder caused by dysfunction of the autonomic system, manifests as asymmetric facial flushing and sweating in response to heat, exercise, or emotional factors. The syndrome may be primary (idiopathic) with a benign course, or can occur secondary to structural abnormalities or iatrogenic factors. The precise mechanism underlying idiopathic harlequin syndrome remains unclear. Here, we describe a case of a 6-year-old boy who reported left hemifacial flushing and sweating after exercise. He had an unremarkable birth history and no significant medical history. Complete ophthalmological and neurological examinations were performed, and no other abnormalities were identified. Magnetic resonance imaging was performed to exclude lesions of the cerebrum and cervicothoracic spinal cord, and no abnormalities were noted. His final diagnosis was classic idiopathic harlequin syndrome. Herein, we report the first pediatric case of idiopathic harlequin syndrome in Korea.

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Introduction

Harlequin syndrome (HS) is an uncommon disorder of the sympathetic nervous system characterized by unilateral diminished flushing and contralateral sweating of the face in response to heat, exercise or emotional stimuli^{1,2}. More than 100 cases have been reported in the literature since the initial description of HS by Lance et al. in 1988³. Most reported cases of HS are primary (idiopathic) in which no underlying etiology could be identified, and HS is more commonly seen in female⁴. In contrast, most of the reported cases of HS in children have been heterogeneous secondary causes⁵. However, the precise mechanism of idiopathic HS is still unclear⁴.

HS is a clinically remarkable disorder rarely encountered in the pediatric practice. Although this disorder is usually benign and does not need any specific treatment, physicians should consider performing a detailed clinical examination, testing autonomic functions, and conducting appropriate imaging techniques to find underlying organic causes⁵. To our knowledge, only a few adult patients have been reported from Korea⁶. We report a pediatric case of idiopathic HS in a 6-year-old boy.

Case report

A 6-year-old boy visited the pediatric outpatient clinic, complaining of unilateral hemifacial flushing and sweating occurring within minutes during or after physical exercise

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or heat. Over the past 2 years, these episodes had occurred as an isolated symptom without any change in severity. He had an unremarkable birth history and uneventful medical history for trauma or surgery. Additionally, he did not take any medications. None of his family members had similar symptoms. His

neurological examination showed normal findings, including normal pupil responses, cranial nerve functions, and muscle stretch reflexes. The rest of systemic examination was unremarkable. His blood pressure and heart rate were normal, and no signs of asymmetric flushing or sweating at rest were noticed. Electrocardiographic findings were within normal limits. Laboratory tests, including the white blood count; levels of hemoglobin, glucose, and electrolytes; and renal, liver, and thyroid function were normal. To objectify hemifacial flushing and sweating, we performed a provocation test (i.e., running for 90 seconds in direct sunlight outdoors). After exercise-induced sweating, there was pale and nearly complete anhidrosis on the right side of the face with compensatory hyperhidrosis and flushing on the opposite side with sharp demarcation (Fig. 1). By using an oil control film, we found that the oil-paper firmly stuck to the left side of the patient's face owing to sweating, but that it immediately slipped off the right side of his face (Fig. 2). On ophthalmological examination, he had mild anisocoria. The right pupil was 1.5 mm in size, while the left pupil was 2.5 mm in size; however, no ptosis, miosis, or enophthalmos was noted, and both pupils responded normally to light and accommodation. Subsequent testing showed no evidence of Horner's syndrome. Magnetic resonance imaging (MRI) was performed to exclude lesions in the cerebrum and cervicothoracic spinal cord, and no abnormalities were noted. In summary, the clinical picture was compatible with idiopathic HS. The child and his parents were explained the benign nature of this condition, and we advised regular follow-ups without medication.



Fig. 1. Image of asymmetrical flushing and sweating after exercise in the patient.



Fig. 2. Results obtained from the oil control film after the patient ran for 90 seconds in direct sunlight outdoors. (A) Flushing and sweating, on the left side of the face. (B) Hypohidrosis and pallor, on the right side of the face.

Discussion

Classically, HS is defined as unilateral facial flushing and sweating with normal ocular sympathetic innervation, but it has been gradually considered a spectrum of partial dysautonomias affecting sudomotor, pupillary, and vasomotor responses in the facial or facio-brachial region⁵. The nonflushing side of the face has autonomic dysfunction, while the flushing side of the face has normal autonomic function. The sympathetic hyperactivity of the flushing side may be a kind of compensatory reaction that provides normal heat regulation of the whole face^{1,7}. Although listed as a rare disease, HS has been reported more widely in the literature in the past 20 years, particularly in adults^{1,2,4-7}. Since 1990, pediatric cases of HS have been sporadically published in other countries; however, this is the first pediatric case in Korea, except for that reported in a newborn.

The exact pathophysiology of axonal damage or degeneration in primary HS is still unknown. Congenital HS is regarded as a sympathetic autonomic dysfunction in the control of peripheral capillary bed tonus, probably because of the hypothalamic functional immaturity in the newborns⁸. Some authors have suggested that an anterior radicular artery at the third thoracic segment is occluded during strenuous exertion³ or asymmetric migration of the neural crest cell occurs during embryogenesis, but these cannot explain the symptom arising in adulthood⁹. Conversely, others have speculated that microvascular ischemia mediated by an autoimmune process or infectious agent such as the herpes simplex virus, cytomegalovirus, and parvovirus and human herpes virus 6 may be responsible^{7,9}. The latter point is more acceptable in pediatric HS.

The dysfunction seen in this disease, even though it is predominantly idiopathic, occurs by an alteration of sympathetic nervous system activity, secondary to the lesion of the preganglionic fibers, and superior cervical ganglion or postganglionic fibers in the external carotid plexus such as the brainstem infarct and superior mediastinum neurinoma⁶. In addition, most cases of iatrogenic HS have been reported to be caused by injury of the sympathetic nervous system and neural damage at T2 or T3¹¹. Iatrogenic HS has also occurred after endoscopic surgery for the removal of a solitary pulmonary nodule, internal jugular vein catheterization, paravertebral thoracic anesthetic block, surgical resection of a neck mass, and thoracic sympathectomy^{10,11}. In addition, unlike many adults, most of the reported cases of HS in children have been secondary⁵, and if present at birth, it may be associated with Horner's syndrome². A previous report presented 10 cases of asymmetric facial flushing in childhood and adolescence², and among them, 8 had organic lesions or structural defects, with 4 having preganglionic Horner's syndrome and one having postganglionic neuronal degeneration. The lesions included a neurinoma in the mediastinum, a cystic

hygroma in the right neck, and a cervical neck mass. Moreover, 2 cases had unknown causes, and only 1 case had no lesion.

A diagnosis of HS is made on the basis of clinical observations and examination findings. The neurons controlling sweating and blood flow in the face have been shown to innervate the same pupillary muscles; therefore, damage to these muscles or the area around these muscles may result in dysfunction of the neurons². These partial dysautonomias may indicate other diseases such as Horner's syndrome, Adie's syndrome, and Ross' syndrome⁵. Horner's syndrome is characterized by miosis, ptosis, enophthalmos, and anhidrosis, and these symptoms occur on the same side as that of the nerve injury^{12,13}. Adie's syndrome, also known as Holmes-Adie's syndrome or Adie's tonic pupil, is a neurological disorder characterized by a tonically dilated pupil that reacts slowly to light but shows a more definite response to accommodation¹⁴. Ross' syndrome involves Adie's syndrome along with segmental anhidrosis⁴. When a patient has the harlequin sign, it is important to rule out traumatic causes, identify other possible causes, and perform the autonomic function test to provide appropriate treatment. The symptoms of autonomic dysfunction include orthostatic hypotension, abnormal sweating, urinary incontinence, and irregular papillary movement. An autonomic function test is noninvasive and easy to perform, and can be used to detect autonomic dysfunction. The autonomic function test includes the tilt table test, orthostatic blood pressure measurement, head-up test, Valsalva maneuver, thermoregulatory sweat test, and electrocardiography¹⁵. An autonomic function test is necessary to rule out other causes of HS; but it is difficult to perform in a young child. Reluctantly, we performed the provocation test for increasing body temperature by vigorous exercise instead of the treadmill test in this patient. Further examinations such as MRI of the brain and spinal cord, MRI angiography of the carotid arteries and imaging of the region adjacent to the stellate ganglion may be performed to distinguish between primary and secondary forms⁵.

When a clinician encounters a patient with hemifacial flushing or sweating, the medical history of the patient should be carefully taken, and complete neurological and ophthalmological examinations should be performed. Primary HS does not involve structural abnormalities, and it can be either congenital or idiopathic. Idiopathic HS has a benign course, and therefore, medical treatment is not required; however, counseling can be provided to the patient, and regular follow-up should be suggested. Contralateral sympathectomy may be performed in patients with severe discomfort. Surgical intervention may be performed in patients with structural lesions; however, this should be carefully considered as it may result in other complications⁴. To our knowledge, a clinical presentation of idiopathic HS in children has not been previously reported in Korean pediatric literature. We hope that this report will make pediatricians aware of this rare

syndrome.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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