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CASE REPORT

# Harlequin syndrome associated with mediastinal ganglioneuroma: a case report

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## ABSTRACT

Harlequin syndrome (HS) is a rare disorder of the autonomic nervous system, caused by unilateral damage to sympathetic fibers innervating the face. The symptoms appear in response to physical activity or heat exposure and present with hemifacial flushing and asymmetric sweating. HS can be idiopathic or associated with an underlying disease. One of the causes of HS in the pediatric population might be a differentiated benign neuroblastic neoplasm-ganglioneuroma. It is often detected in older children and adults, with the most typical location within the posterior mediastinum. In this paper, we present the case of a 3-year-old patient with face discoloration and a massive mediastinal tumor (ganglioneuroma). This study highlights the importance of identifying the cause of HS and the possibility of ganglioneuroma occurring in younger children.

KEY WORDS:
**Harlequin syndrome, ganglioneuroma, mediastinal tumor.**

## INTRODUCTION

Harlequin syndrome (HS), first described by Lance *et al.* [1] in 1988, is an uncommon autonomic disorder presenting with hemifacial redness and hyperhidrosis sharply demarcated at the midline from the contralateral, affected side, which remains pale and sweatless. The symptoms appear in response to heat, emotional stressors, or physical activity.

The condition is generally benign and idiopathic, but it can also indicate an underlying disease. One of the causes of secondary HS might be mediastinal organic pathology which presses on the cutaneous sympathetic fibers, arising from the spinal cord. This compression leads to the blockage of vasomotor and sudomotor nerves that supply the face and neck area. In pediatric representation, secondary HS can be caused by neoplasms of neuroblastic origin, often detected in the posterior mediastinum. Below we present a description of a pediatric patient with ganglioneuroma associated with HS.

## CASE REPORT

A 3-year-old boy presented to an emergency department with a 4-month history of left hemifacial flushing and excessive heating with a clearly marked demarcation line. These symptoms often occurred and were exacerbated after bathing or physical activity. Afterwards, they spontaneously disappeared within several minutes. The right part of the face was pale and cold during episodes. The week before hospitalization the frequency of the episodes increased. Additionally, paleness and abnormally increased surface temperature of the right arm were observed for several weeks.

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Upon admission to the hospital, the patient's general condition was good. The child was conscious, with normal verbal and logical contact. No symptoms of shortness of breath or dehydration were detected. The heart function was regular, without pathological murmurs. No auscultation phenomena over the lungs were found. The clinical examination of the patient's abdomen showed no abnormalities except for a slightly enlarged liver, which was palpable about 0.5 cm below the costal margin. Meningeal and peritoneal symptoms were negative. No swelling was detected.

Laboratory tests showed elevated levels of urine catecholamines. The concentration values of vanillylmandelic acid, homovanillic acid and dopamine were less than twice the upper limit of the reference range. Additionally, the serum level of neuron-specific enolase was slightly elevated, 28.8 ng/ml (reference, < 16.3 ng/ml). Chest computed tomography confirmed solid opacification in the right superior mediastinum, pressing on the Th2/3 section of the spine. Based on the presence of the mediastinal tumor, along with elevated neuron-specific enolase and increased secretion of urine catecholamines, the patient was presumed to have a neuroblastic tumor in the sympathetic pathway.

A biopsy of the tumor was performed, revealing an adipose tissue mixed with nervous tissue and scattered ganglion cells. Therefore, a preliminary diagnosis of lipomatous ganglioneuroma was made. Due to the observed symptoms of HS, elevated levels of urine catecholamines and concerns about the final nature of the tumor (ganglioneuroma, neuroblastoma or mixed ganglioneuroblastoma) thoracoscopic surgery was performed to remove the mediastinal tumor. Post-operative histopathological examination identified the presence of mature ganglion cells among predominant Schwann cell stroma and adipose tissue. It confirmed the preliminary diagnosis of ganglioneuroma, and excluded the dual nature of the change.

The patient responded well to the treatment. His condition improved and the recovery was uneventful. After observation, he was discharged home with the recommendation of regular check-up visits.

## DISCUSSION

This paper presents a description of a patient with ganglioneuroma associated with HS. The syndrome was first described by Lance *et al.* [1] in 1988 and is characterized by asymmetric facial flushing and sweating [2]. These symptoms can be accompanied by headache, nausea, vomiting and photophobia [3]. Interestingly, the literature describes a subclinical type of HS which is only detected by comparing the temperatures of hemifaces [4]. In specific cases, the isolated symptom occurring in this dysautonomia might be hyperhidrosis of one side of the head [5].

HS is an uncommon disorder triggered by exercise, spicy food or heat. The condition is often benign and idiopathic and can be caused by other pathologies, which poses a significant diagnostic challenge for clinicians [6]. One of those pathologies can be ganglioneuroma. Neuroblastic tumors originate from the sympathetic nervous system. They consist of mature ganglion cells, nerve fibers, Schwann cells and mucous matrix. Their microscopic nature is created by mature ganglion cells, eosinophilic cytoplasm, large nuclei and prominent nucleoli [7].

Ganglioneuromas are slow-growing and benign tumors. They are found at any age, but more frequently in children over the age of 10 and adults. The most common localizations are the posterior mediastinum and retroperitoneum [7, 8]. Ganglioneuromas are asymptomatic in most cases, even if they are large, and symptoms are caused by the mass effect. Pressure on the local structures is a factor that might trigger cough, shortness of breath or Horner syndrome. Neurologic symptoms occur when the tumor extends into the spinal canal [7, 9].

Imaging examinations are used to identify the location of the ganglioneuroma. The mediastinal tumors are often observed in ultrasonography (US) or computed tomography (CT). Those which originate from the nerve roots are identified by magnetic resonance imaging (MRI). US shows a homogeneous, hypoechoic mass. On unenhanced CT, ganglioneuroma may be homogeneous or heterogenous and has low muscle attenuation. Following contrast administration, the tumor shows mild to moderate enhancement on CT scanning. Ganglioneuroma appearance in MRI is less specific than the image observed in CT. However, MRI is more effective in evaluating chest wall involvement and identifying intraspinal extension. In T2-weighted images, ganglioneuroma shows heterogeneous intermediate to high signal intensity, depending on the composition of the tumor, compared to the T1 projection, in which low signal intensity is observed. It is not possible to assess the malignant or benign nature of the neoplasm by imaging examination. In this study, CT showed a solid heterogenous mass with calcifications affecting the apex of the lung and posterior mediastinum (Figure 1).

The histologic diagnosis of ganglioneuroma had always been controversial, especially for its differentiation from ganglioneuroblastoma, until the International Neuroblastoma Pathology Committee criteria were introduced. The new diagnostic standard defined ganglioneuroma as a tumor composed of ganglioneuromatous stroma with a minor component of mature ganglion cells [10]. This study showed large ganglion cells among predominant Schwann cell stroma. Additionally, lobules of fat tissue were present. This clinical picture indicated lipomatous ganglioneuroma (Figure 2).

The secretion of catecholamines is an uncommon finding in ganglioneuroma [8]. This condition is presumed to be associated with the increased size of the tumor.

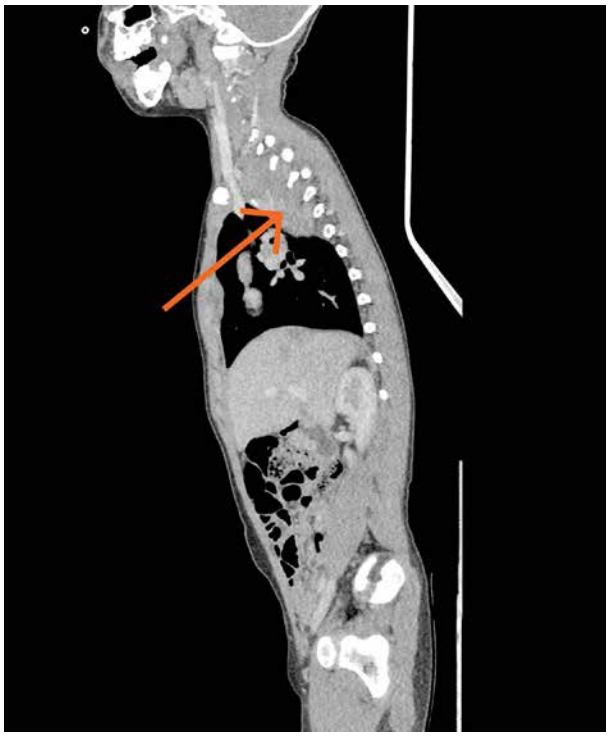

**FIGURE 1.** Computed tomography. A huge mass in the posterior mediastinum

Increased amounts of catecholamines may cause labile hypertension or flushing, although the metabolic character of ganglioneuroma is rather low. However, studies show that some patients with ganglioneuroma have elevated catecholamine levels [7]. The patient described in this study had elevated vanillylmandelic acid, homovanillic acid and dopamine in urine.

The management of secondary HS is related to the treatment of the underlying cause, but most HS cases do not require medical treatment [6]. One of the causes may be neoplasms of neuroblastic origin such as ganglioneuroma. These tumors can grow rapidly and should be considered for nonradical resection [11]. In this study, the patient had a large mass in the posterior mediastinum compressing the Th1–Th3 spine sections, which was an indication for organ resection.

HS may coexist with other syndromes, such as Horner syndrome (miosis, ptosis, enophthalmos), Holmes-Adie syndrome (slow pupil response to light) or Ross syndrome (slow pupil response to light and sweating) [12]. Also, idiopathic HS may be the first manifestation of Guillain-Barré syndrome [13]. The secondary HS might appear during epidural analgesia with levobupivacaine and fentanyl administration [14] or after surgical treatment such as neck schwannoma resection [15].

## CONCLUSIONS

It is worth noting that even though HS occurs mostly in teenagers and adults, it can also affect younger patients. Also, quick recognition and diagnosis of the cause

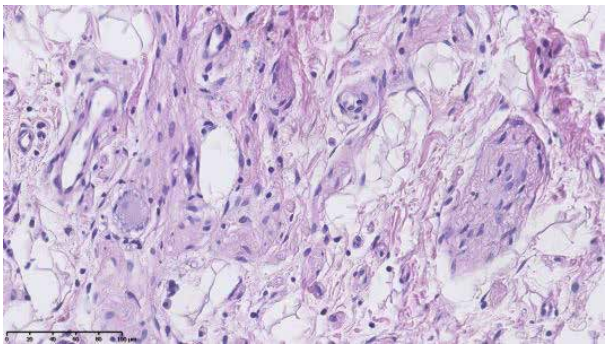

**FIGURE 2.** Lipomatous ganglioneuroma composed of mature adipocytes and ganglion cells in the neural background. HE, ×400

of characteristic HS symptoms are essential. In the present case, HS was caused by a benign tumor. However, it is crucial to realize that HS can be a manifestation of a malignant neoplasm, such as neuroblastoma, and because of that, it is of the highest importance to make a prompt diagnosis and start treatment as quickly as possible to increase the patient's chances of a cure.

## DISCLOSURES

1. Institutional review board statement: Not applicable.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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