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Authors

Yu, Colburn

El-Haj, Nura

Kim, Sunghoon

et al.

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LETTER TO THE EDITOR

Routine Screening for Neuroblastoma in Harlequin Syndrome Without Otherwise Known Etiology

Colburn Yu¹  | Nura El-Haj² | Sunghoon Kim³ | Carla Golden⁴ | Anurag K. Agrawal⁴

¹Department of Pediatrics, UCSF Benioff Children's Hospital, Oakland, California, USA | ²Division of Hematology/Oncology, Department of Pediatrics, UMass Memorial Medical Center, Worcester, Massachusetts, USA | ³Department of Surgery, UCSF Benioff Children's Hospital Oakland, Oakland, California, USA | ⁴Division of Oncology, Department of Pediatrics, UCSF Benioff Children's Hospital Oakland, Oakland, California, USA

Correspondence: Anurag K. Agrawal (anurag.agrawal@ucsf.edu)

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To the Editor:

Neuroblastoma (NBL) tumors derive from neuronal ganglia of the peripheral sympathetic nervous system. Initial symptoms depend on tumor location, which can occur anywhere along the sympathetic chain [1]. Horner syndrome (HS) is present as an early sign of NBL in about 1%–3% of all cases of HS [2–4]. Most cases of pediatric HS are from birth trauma or trauma during thoracic, neck, or central nervous system surgery [5]. For those patients with HS and no known etiology, screening for NBL is routinely performed [6]. Harlequin syndrome is an autonomic disorder similar to the underlying anatomical pathology of HS [7]. In Harlequin syndrome, disruption of ipsilateral nerve fibers in the sympathetic chain leads to unilateral anhidrosis and lack of facial flushing in response to heat, exercise, or emotional stimuli [8]. We present a unique case of Harlequin syndrome secondary to NBL.

A previously healthy ex-full term, 7-month-old male was initially referred to neurology for acquired left-sided anhidrosis with contralateral diaphoresis and flushing that was exacerbated by heat and physical activity (Figure 1A). His neurological exam was unremarkable. The initial differential diagnoses for Harlequin syndrome included eccrine gland abnormality, underlying autonomic dysfunction, or ectoderm embryologic pathology. At 12 months, he presented with fevers and positive SARS-CoV-2 PCR. Shortly after, parents noted a non-tender left lateral neck mass. Despite recent viral illness, nodal location was concerning in the context of continued left anhidrosis with right hyperhidrosis. A literature review uncovered a previously documented association with Harlequin syndrome and NBL [9].

Urine vanillylmandelic acid and homovanillic acid levels were normal. Labs revealed mildly elevated neuronal specific enolase 19 ng/mL (reference range: 0–10.8 ng/mL) and LDH at the upper limit of normal 294 U/L (reference range: 120–300 U/L). Chest x-ray was unremarkable. Nodal biopsy confirmed poorly differentiated NBL with favorable biological and genetic markers. Computed tomography (CT) demonstrated left upper thoracic paravertebral disease with right submandibular and left cervical, supraclavicular, and axillary lymphadenopathy. I-123 MIBG detected focal uptake in the corresponding areas of lymphadenopathy (Figure 1B). Magnetic resonance imaging (MRI) of the cervicothoracic spine confirmed left paraspinal NBL with minimal extension into the T2–T3 neural foramina (Figure 1C). Bone marrow evaluation was negative.

The patient was diagnosed with Stage 3 intermediate-risk NBL (based on International Neuroblastoma Staging System), and treated with two cycles of chemotherapy with carboplatin and etoposide followed by carboplatin, cyclophosphamide, and doxorubicin per COG ANBL0531 [10]. Following partial response, he received two additional cycles and achieved very good partial response (VGPR) with negative I-123 MIBG. Subsequent imaging showed decreased lymphadenopathy, with most nodes returning to normal limits, and decreased paraspinal soft tissue mass. Since being off therapy, the size of the mass lesion has remained stable. The patient's Harlequin syndrome improved, though did not fully resolve.

Five months before NBL diagnosis, our patient exhibited autonomic dysregulation exacerbated by heat and physical activity. It was later discovered that a mass lesion in the left T2–T3 neural foramina caused disruption to ipsilateral sudomotor and

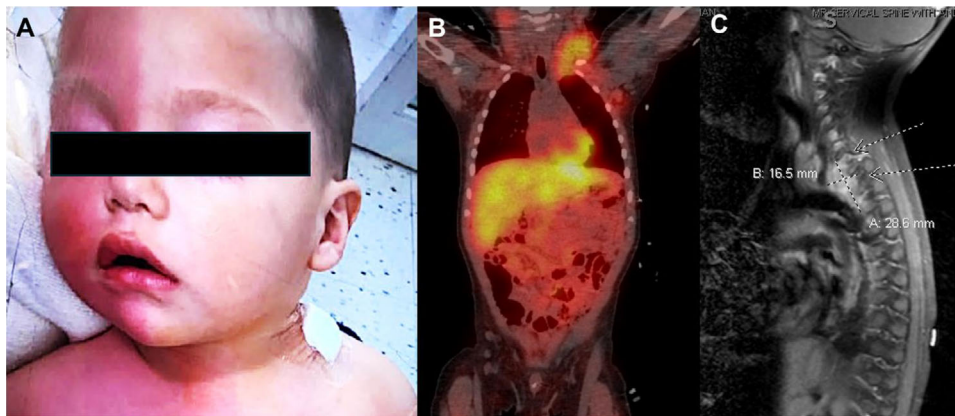


FIGURE 1 | (A) Hemifacial flushing, a clinical feature of Harlequin syndrome. (B) MIBG scan with uptake in the left axilla, left cervical and supraclavicular, and right submandibular regions. (C) Cervical spine MRI with sagittal view of paraspinal mass with minimal foraminal extension at T2–T3 (arrows).

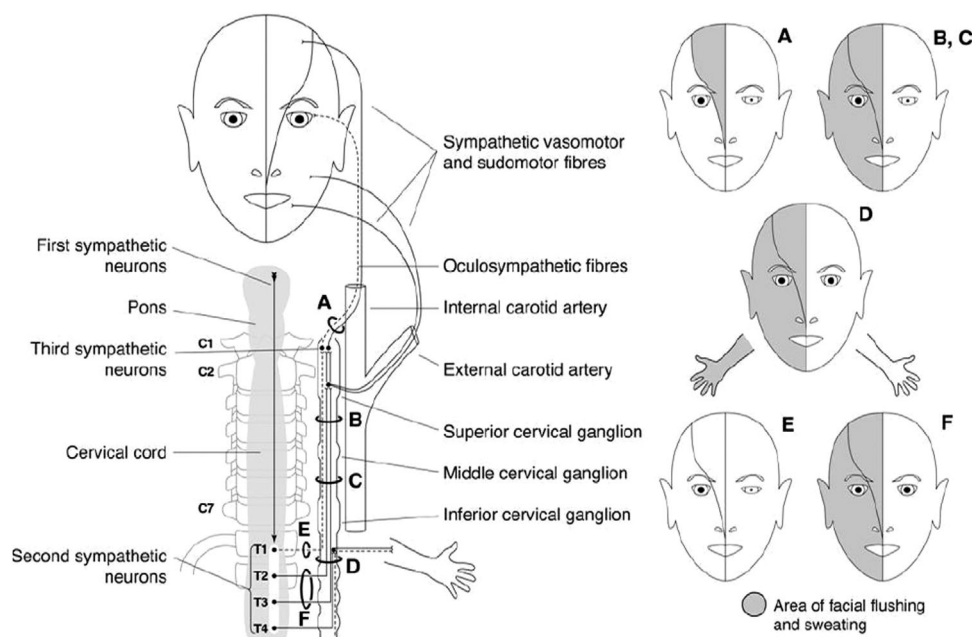


FIGURE 2 | Sympathetic fibers innervating the face and upper limb. Lesions at T2–T3 and various locations along the sympathetic chain can produce clinical features of Harlequin syndrome [15]. With permission, Journal of Neurosurgery: Spine.

vasomotor function in the face, causing contralateral compensatory symptoms. Sudomotor and vasomotor function to the face involve a three-neuron chain. First order neurons originate in the posterior and lateral hypothalamus and synapse in the lateral horn in the upper thoracic spinal cord. Second order neurons exit the spinal cord from the T2 and T3 neural foramina to the sympathetic chain comprised of the superior cervical, middle cervical, and stellate ganglion [11]. Third order postganglionic neurons travel along the external and internal carotid arteries to be distributed to the skin [12] (Figure 2).

The extent of flushing may differ depending on the lesion location in relation to sympathetic ganglia. For example, a lesion proximal to stellate ganglion affects vasomotor and sudomotor function from the ipsilateral head to the upper thoracic, including the arm. A lesion distal to stellate ganglion at the superior cervical ganglion affects the ipsilateral face. Lesions affecting neurons

along the external carotid artery exhibit dysfunction in the cheek and chin, whereas those along the internal carotid affect the forehead and nose [13].

The sympathetic innervation to the eye follows a similar pathway. Second order oculomotor nerve fibers also originate from the lateral horn at T1, synapsing in the superior cervical ganglia. Innervation to the iris dilator and superior tarsal muscles is carried by third order postganglionic neurons following the internal carotid artery. A lesion along this pathway would cause HS [14].

Anatomically, the difference between Harlequin syndrome and HS is one or two vertebral levels. Yet, there has been only one reported case of Harlequin syndrome with an underlying NBL diagnosis and none in the English literature [9]. Theoretically, a combination of Harlequin syndrome and HS can also be a

presenting sign of NBL caused by a mass lesion compressing T1–T3 neural foramina or distal to the stellate ganglia.

Harlequin syndrome and HS are clinically very distinct; however, both represent an underlying autonomic dysfunction. In addition to NBL, the underlying etiology of Harlequin syndrome includes Pancoast tumors, schwannomas at the lung apex, sympathectomy from post-thoracic surgery, and occlusion of the anterior radicular artery [13]. Our case study suggests that pediatric patients with acquired Harlequin syndrome, without a known etiology, should follow similar guidelines as patients presenting with HS and routinely undergo further testing to exclude underlying NBL.

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We want to acknowledge Yannick Fringeli, MD and Jérôme Kaufmann for giving us permission to use Figure 2 in this paper that was originally published in their case study on Horner and Harlequin syndromes after anterior cervical discectomy [15].

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Colburn Yu
Nura El-Haj
Sunghoon Kim
Carla Golden
Anurag K. Agrawal

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