



# Rare but Critical: Indomethacin-Responsive Headache with Long-Lasting Autonomic Symptoms

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Hemicrania with long-lasting autonomic symptoms (LASH), first described in by Rozen<sup>1</sup>, is an extremely rare headache disorder thought to be part of the trigeminal autonomic cephalalgia (TAC) spectrum. However, it is not included in the current International Classification of Headache Disorders, 3<sup>rd</sup> Edition (ICHD-3).<sup>2</sup> Notably, patients with LASH typically respond well to indomethacin. The condition is characterized by a moderate-to-severe unilateral headache accompanied by prolonged cranial autonomic symptoms, which begin before headache onset, persist for 1-3 days, and continue for some time after headache resolution. Headache attacks last longer than those of typical TACs-often for several hours-and patients remain pain-free between attacks.<sup>3</sup> A 32-year-old right-handed man presented with a 2-year history of headache attacks of moderate intensity. These episodes were accompanied by right eyelid edema and ptosis, as well as pruritus in the right eye. The headache lasted only 30-40 minutes, but ipsilateral autonomic symptoms persisted for 1-2 days. The patient did not report associated nausea, vomiting, photophobia, phonophobia, irritability, or restlessness. He denied that chewing, head or neck movements, or facial palpation provoked either headache or autonomic symptoms. Over the 2-year period, he experienced an average of one attack per month, with no other headaches between episodes. His medical history and neurological examination were unremarkable between attacks. Brain magnetic resonance imaging (MRI), MR angiography, and MR venography were all normal. Ophthalmological examination revealed no additional abnormalities.

The patient remained free of headache and autonomic symptoms for 3 months after starting indomethacin at a dose of 25 mg twice daily. However, he experienced three episodes of typical headache and autonomic symptoms within 1 month of discontinuing the medication. At his second admission, he presented during a typical

headache attack with right eyelid edema and ptosis. Neurological examination during the attack revealed right-sided ptosis without anisocoria or anhidrosis (Figure 1a). Complete resolution of the ptosis and eyelid edema was observed 2 days after the headache (Figure 1b). Indomethacin was then restarted, and the patient remained free of headache and autonomic symptoms for the following 2 months.

In the differential diagnosis of a patient presenting with headache, ptosis, and periorbital edema, Horner's syndrome and idiopathic orbital inflammation were considered. The absence of ipsilateral miosis, anhidrosis, and enophthalmos made Horner's syndrome unlikely. Furthermore, contrast-enhanced cranial MRI revealed no enlargement or contrast enhancement of the extraocular muscles or periorbital soft tissues, thereby excluding idiopathic orbital inflammation.

Previously reported cases of LASH in the literature have shown a female predominance, with a mean age of onset of 33 years (range, 19-46 years). The average time to diagnosis has been reported to be delayed by up to 3 years.<sup>3</sup> Among headaches that respond to indomethacin, only a subset present with cranial autonomic symptoms such as lacrimation, conjunctival injection, nasal congestion, rhinorrhea, ptosis, and miosis. The principal indomethacin-responsive headache disorders with autonomic features are hemicrania continua, paroxysmal hemicrania, and LASH.<sup>1,2</sup> These headache types can be differentiated by attack frequency and duration, as well as by the severity of headache and autonomic symptoms. The distinguishing features of indomethacin-responsive headache disorders accompanied by autonomic symptoms are summarized in Table 1.

Given the predominance of autonomic symptoms extending beyond the duration of headache attacks, as well as the attack duration and frequency, our patient did not meet the diagnostic criteria



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**FIG. 1.** Right-sided periorbital edema and ptosis 12 hours after the end of a headache attack (a). Complete resolution of right-sided ptosis and eyelid edema after 2 days after the end of a headache attack (b).

**TABLE 1.** The Distinguishing Features of Indomethacin-Responsive Headache Types Accompanied by Autonomic Symptoms.

Feature	Hemicrania continua	Paroxysmal hemicrania	LASH
Duration	Continuous with exacerbations	2-30 min	Hours to days
Attack frequency	Persistent pain	≥ 5 per day	Variable
Autonomic symptoms	Present, during exacerbations	Present, during attacks	Prolonged, beyond the headache
Indomethacin response	Absolute	Absolute	Variable

LASH, long-lasting autonomic symptoms; min, minutes.

for classical TAC.<sup>2</sup> Based on the robust response to indomethacin and the predominance of autonomic symptoms over headache, a diagnosis of LASH syndrome was considered most likely. Although rare, this disorder can substantially affect quality of life, and an increasing number of cases have been reported in the literature.<sup>1,3-5</sup> The temporal pattern of onset and resolution of cranial autonomic symptoms is critical for diagnosis. Considering the cases reported to date, LASH should be regarded as part of the TAC spectrum of indomethacin-responsive headaches and should be included in future ICHD revisions to enhance recognition and enable prompt, appropriate treatment.<sup>2</sup>

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