

# Expert Opinion

## Side-Locked and Side Shifting Primary Headaches

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Migraine, tension-type, and new daily persistent headache (NDPH) are usually bilateral but can also occur only on one side or be side-locked. In addition to these side-locked primary headaches, strictly unilateral headaches, trigeminal autonomic cephalalgias (TAC), and hemicrania continua (HC), can shift sides. On initial evaluation, neuroimaging is sometimes indicated to exclude a secondary cause.<sup>1</sup>

Case 1: This 40-year-old woman reports a 20-year history of migraine without aura always occurring on the right side with a frequency of about 3 times monthly, usually going away within 2 hours after taking a triptan (several have worked well). Triggers include her menses, lack of sleep, and alcohol. Questions: How often do migraines occur only on one side, side-locked? Is unilaterality stable over time? Are side-locked migraines more frequent in those with aura than those without? Why would migraines only occur on one side? Is onabotulinumtoxinA effective if given on the affected side only for side-locked chronic migraine? How often do side-locked headaches occur in tension-type and new daily persistent headaches? In contrast, how often do patients with side-locked

primary headache disorders (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing [SUNCT], cluster, paroxysmal hemicrania [PH], and HC) and cervicogenic headaches (CEH) switch sides?

### EXPERT COMMENTARY

The case above depicts a classic example of episodic migraine without aura. It has known triggers, responds to triptans, and in this patient's case, is always unilateral.<sup>2</sup>

**How Often Do Migraines Occur Only on One Side, Side-Locked?**—Migraines are the most common side-locked headaches seen in the clinic because migraine is the most prevalent form of primary headaches among patients consulting their physician with a chief complaint of episodic headaches.<sup>3</sup> When assessing a patient complaining of side-locked headaches, the rarer TAC and other indomethacin-responsive headaches should be in the differential diagnosis, but the most probable diagnosis would be migraine.

The common unilateral nature of migraine has been recognized for centuries since the ancient Greeks coined the word *hemikrania*, and unilaterality

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is one of the International Headache Society (IHS) criteria used for the diagnosis of migraine.<sup>2</sup> One validation study included 1283 migraineurs, and reported hemicranial location in 66.6% of the patients, 71.2% with episodic migraine, and 61.4% with chronic migraine.<sup>4</sup> Lance and Anthony in a prospective survey of 500 patients found that 68% had hemicranial pain.<sup>5</sup> Friedman et al, studying 2000 patients with migraine and tension-type headaches (TTH), reported unilateral pain in 80% of the migraineurs.<sup>6</sup> Side-locked pain was not assessed in these studies.

Selby and Lance studied 500 migraine cases and found unilaterality in 38% of the patients, with 21% being side-locked.<sup>7</sup> Side-locked migraine headaches were reported by D'Amico et al in 20.8% of 307 patients with IHS migraine.<sup>8</sup> Chakravarty et al, in a prospective study of 800 adult migraineurs, reported unilaterality at onset in 41.38% of the patients, and pain was side-locked in 31%.<sup>9</sup>

Thus, reviewing these 3 series, from a total of 1607 patients, pain was side-locked in 26% of the cases.

**Is Unilaterality Stable Over Time?**—Leone et al found 17% of side-locked unilaterality among 767 patients with migraine.<sup>10</sup> This study also found that unilaterality was relatively stable overtime, with patients followed  $13 \pm 10$  years.

Sjaastad et al assessed 31 patients with classic migraine during the initial consultation, and found strict unilaterality in 42%, unilaterality combined with bilaterality in 42%, and bilaterality in 16%. After 3-9 years follow up, 22 patients were reassessed, and there was consistency between the 2 observations, but only 1 case (possibly 2) showed persistence of side-locked unilaterality.<sup>11</sup> That is, although strict unilaterality was constant, the side of the migraine switched in the majority.

**Are Side-Locked Migraines More Frequent in Those With Aura Than Those Without?**—Unilateral location seems to be more common in patients in migraine with aura. Among 66.6% of migraineurs with hemicranial location, Kelman found that 59.7% had migraine without aura and 68.9% had migraine with aura.<sup>4</sup> That confirms the previous study by Russell et al that assessed 342 migraineurs without aura and 156 migraineurs with aura, and found unilaterality in 55% and 59% of the cases, respectively.

They also noticed that unilateral location was more prevalent in females in both groups.<sup>12</sup>

The discrepancies between studies may be explained by differences in definition. In some studies, the definition of unilateral migraines may include alternating sides as well as side-locked migraines.

**Why Would Migraines Only Occur on One Side?**—Our current understanding of migraine pathophysiology indicates that both abnormal cortical activity and abnormal brainstem activity may lead to activation of the trigeminovascular system resulting in meningeal vasodilation and neurogenic inflammation, in addition to central sensitization.<sup>13,14</sup> Since the central nervous system and cranial nerves have bilateral representation, how do we explain the propensity of migraine to occur on one side?

Fernandez-de-las-Penas et al studied pressure point thresholds (PPT) of the head and neck in 25 patients with strictly unilateral migraine and 25 healthy subjects. They found lower PPT levels and increased pericranial tenderness on the symptomatic side as compared with the non-symptomatic side and on either side in controls. However, no significant differences were identified between the non-symptomatic side and controls.<sup>15</sup>

The same group assessed PPT over the supra-orbital nerves (V1) and peripheral nerve trunks on both upper extremities in 20 patients with side-locked migraines and 20 matched healthy controls. Again, side-locked migraineurs had increased mechano-sensitivity of the supra-orbital nerve on the symptomatic side. On the upper extremities, migraineurs also had an increased mechano-sensitivity of the main peripheral nerves compared with healthy controls, without asymmetries. Based on these findings, the authors suggest the presence of a state of hyperexcitability of the central nervous system in patients with unilateral migraine, with asymmetry clinically demonstrated.<sup>16</sup> Further research is needed to elucidate the mechanism of unilateral trigeminovascular system activation in unilateral migraines.

**Is OnabotulinumtoxinA Effective if Given on the Affected Side Only for Side-Locked Chronic Migraine?**—Migraine treatment is identical, independent of pain location. OnabotulinumtoxinA was approved for chronic migraine, and the sites of drug

delivery were fixed bilaterally according to the PREEMPT protocol.<sup>17-19</sup> In the PREEMPT trials, unilateral migraines were always treated bilaterally. One study suggested a trend toward effectiveness, not statistically significant in injecting onabotulinumtoxinA bilaterally for unilateral cervicothoracic, paraspinal, myofascial pain syndrome.<sup>20</sup> There has not been a study evaluating unilateral injection of onabotulinumtoxinA for side-locked migraine.

#### **How Often Do Side-Locked Headaches Occur in Tension-Type and New Daily Persistent Headaches?—**

Laterality in TTH and NDPH also has been studied. In migraine, unilaterality is one of the International Classification of Headache Disorders-2 (ICHD-2) criteria for diagnosis, but bilateral pain is one of the criteria for TTH diagnosis.<sup>2</sup> Analyzing data from 49 patients with TTH diagnosis, Choi et al found a 36% incidence of unilateral headaches.<sup>21</sup> In another case series of 210 patients in which TTH was analyzed in different age groups, the incidence of unilaterality was 18%, and patients with bilateral headaches were significantly older than those with unilateral or fronto-median headaches.<sup>22</sup> Friedman et al reported a 10% incidence of unilateral pain among patients with TTH in a cohort of 2000 patients with migraine and TTH.<sup>6</sup> Leone and D'Amico, in consecutive articles, reported an incidence of 4% and 12.5% of side-locked unilaterality among cohorts of 244 and 96 cases of TTH.<sup>8,10</sup>

Again, sample size and lack of a unique criterion defining side-locked pain vs unilateral shifting pain may be responsible for the inconsistencies found.

NDPH, the last subtype of primary headache added to the ICHD-2 classification, also seems to have a bilateral predominance. In an abstract, Vanast reported the first 45 cases of NDPH, and pain was bilateral in 62% of the cases.<sup>23</sup> Li and Rozen, studying 56 patients, found bilateral location in 64% of the cases. Takase et al, in a cohort of 30 patients, reported bilateral pain in 86%. Meineri et al, reviewing 18 new cases of NDPH, described bilateral pain in all cases.<sup>24-26</sup> Robbins et al reported on a series of 71 patients with NDPH, and 88.7% of them had bilateral pain consistent with TTH. These patients were further stratified into a group with TTH features, thus meeting ICHD-2 criteria for NDPH (n = 31) and

another group that had migrainous features (n = 40), and the incidence of bilateral pain was 93.5% and 85% in the 2 groups, respectively. Patients with NDPH and migrainous features had a slightly higher incidence of unilateral pain, but it was not statistically significant.<sup>27</sup>

The reason why the initial series of NDPH showed a high incidence of unilateral headaches may have been the inclusion of patients with HC, as both entities were described only a few years apart.

#### **In Contrast, How Often Do Patients With Side-Locked Primary Headache Disorders (SUNCT, Cluster, PH, and HC) and CEH Shift Sides?—**

Unilateral headache is a core diagnostic feature of TAC, including cluster headaches (CH), SUNCT, and PH, and also of the primary headache, HC. Manzoni et al, investigating clinical findings in 180 patients with CH, found fixed unilateral pain in 84.5%, and a change in pain side in 15.5% of the subjects. Among these patients with side change (n = 28), 19 patients changed sides from one cluster to another, and in 9, the side changed during one particular period.<sup>28</sup>

Schurks et al, in a cohort of 246 cluster patients, found unilateral pain in 97.2% and bilateral pain in 2.8%. Among patients with unilateral pain, 78.5% had strictly unilateral pain, and in 18.7%, the pain changed side.<sup>29</sup>

Leone et al found side shift common in chronic cluster patients. His group reported side shift in 50.8% of 63 patients. They also found that the duration of the chronic cluster was longer in patients with side shift than those without ( $6.8 \pm 4.91$  years vs  $1.8 \pm 4.91$  years;  $P < .0001$ ), and that 62.5% of the patients who developed side shift did so in the first 2 years after developing the chronic form of CH.<sup>30</sup>

Pain laterality in CH is particularly important when considering invasive procedures. As deep brain stimulation of the posterior hypothalamus and occipital nerve stimulation become therapeutic options for the treatment of chronic cluster patients, it is noteworthy that these procedures are only effective if performed ipsilaterally to the affected side.<sup>31-34</sup>

SUNCT and short-lasting unilateral neuralgiform headache with cranial autonomic features (SUNA) are rare, typically side-locked headache syndromes, and included in the group of TAC. Cohen et al, in a

group of 52 patients (43 with SUNCT and 9 with SUNA), found that 42 patients (80.7%) had either strictly left-sided pain (20 patients) or right-sided pain (22 patients). Eight patients had attacks alternating sides, one patient with SUNCT had unilateral attacks on either side in equal proportions, and other SUNCT patient had bilateral attacks.<sup>35</sup> Williams and Broadley, reviewing 24 patients with SUNCT or SUNA, found side-locked pain to the left in 13 patients (54%) and to the right in 8 (33%), 1 patient had a side change, and 2 patients had attacks on alternating sides.<sup>36</sup>

PH is also unilateral in nature. Antonaci and Sjaastad reviewing 84 cases in the literature found strictly unilateral cases, with the exception of one case in which bilateral pain was described.<sup>37</sup> Boes and Dodick, reviewing 74 cases from the Mayo Clinic, found strictly unilateral pain in 93%, bilateral pain more prominent in one side in 4%, and primarily bilateral pain that rarely became unilateral in 3%. They also noticed that pain switched sides in 15% of the cases.<sup>38</sup> Evans reported the first bilateral case meeting all of the PH criteria.<sup>39</sup> Cittadini et al, in a prospective clinical study including 31 cases of chronic PH, found strictly unilateral pain in 30 patients (15 side-locked to either side) and only 1 with side alternating attacks.<sup>40</sup>

HC, by definition, is a unilateral continuous daily headache without side shift.<sup>2,41-44</sup> At least 9 patients with side alternating HC have been described.<sup>45-51</sup> One case of bilateral, unremitting headache, with concurrent autonomic symptoms, and complete response to indomethacin was reported.<sup>52</sup>

A seminal HC series in the literature is the elegant review by Cittadini and Goadsby of 39 cases showing 92% of side-locked pain to either side (18 on the right and 18 on the left) and 8% (3 patients) with side alternating attacks.<sup>51</sup> The authors suggested the IHS criteria be revised to exclude the absence of side-shift pain as a diagnostic criterion.

CEH is a headache caused by disease or dysfunction of cervical structures.<sup>53</sup> Sjaastad et al in 1983 initially defined diagnostic criteria for CEH as recurrent, long-lasting attacks of moderately severe unilateral headache, beginning occipitally and radiating forward, without side shift between

attacks.<sup>54</sup> Sjaastad's group reported the clinical manifestations of CEH in 2 cohorts of 11 and 75 patients, respectively, and unilaterality was found in all subjects in both series.<sup>55,56</sup> Unilaterality without side alternation seems to be one of the core diagnostic criteria of CEH, although a co-involvement of the opposite side may occur particularly when the headache is severe.<sup>57</sup>

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