Clinical Reasoning: A Teenager With Right-Sided Headache and Periorbital Changes

Author(s):
Daniel N. Lax, MD¹; Marielle Kabbouche, MD¹,²; Joanne Kacperski, MD¹,²; Andrew D. Hershey, MD, PhD¹,²

Corresponding Author:
Daniel N. Lax, danielnoamlax@gmail.com

Affiliation Information for All Authors: 1. Division of Neurology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; 2. Department of Pediatrics, University of Cincinnati School of Medicine, Cincinnati, OH

Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.

Copyright © 2022 American Academy of Neurology. Unauthorized reproduction of this article is prohibited
Equal Author Contribution:

Contributions:
Daniel N. Lax: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Additional contributions: Clinical care of patient - Clinical care of patient - Marielle Kabbouche Clinical care of patient - Joanne Kacperski Clinical care of patient - Andrew D. Hershey
Marielle Kabbouche: Drafting/revision of the manuscript for content, including medical writing for content; Additional contributions: Clinical care of patient - Daniel N. Lax Clinical care of patient - Clinical care of patient - Joanne Kacperski Clinical care of patient - Andrew D. Hershey
Joanne Kacperski: Drafting/revision of the manuscript for content, including medical writing for content; Additional contributions: Clinical care of patient - Daniel N. Lax Clinical care of patient - Marielle Kabbouche Clinical care of patient - Andrew D. Hershey
Andrew D. Hershey: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Additional contributions: Clinical care of patient - Daniel N. Lax Clinical care of patient - Marielle Kabbouche Clinical care of patient - Joanne Kacperski Clinical care of patient

Figure Count:
1

Table Count:
1

Search Terms:

Acknowledgment:
Study Funding:
The authors report no targeted funding

Disclosures:
D. N. Lax reports no disclosures relevant to the manuscript; M. Kabbouche serves as site PI and SubPI for studies sponsored by Amgen, Biohaven, Lilly and Teva, receives research support from NIH, serves on the board for Impel and is a consultant for Theranica; K. Kacperski has received research funding to her institution for participation in ongoing studies sponsored by Amgen, Eli-Lilly, Teva, Biohaven and Currax, serves as site PI for a study sponsored by Currax, there is no other potential conflict of interest for this manuscript; A. D. Hershey has received support paid to Cincinnati Children for an advisory role to AbbVie, Amgen, Biohaven, Lilly, Lundbeck, Teva, Theranica, and Upsher-Smith, serves as site PI on studies sponsored by Amgen, Biohaven, Theranica and Upsher-Smith, has research grants from NIH (NINDS and NICHD), and received honorariums from Lundbeck, Theranica and Up-to-Date.

Preprint DOI:

Received Date:
2022-03-21

Accepted Date:
2022-09-13

Handling Editor Statement:
Submitted and externally peer reviewed. The handling editor was Roy Strowd III, MD, Med, MS.
Abstract

While migraine is the most common headache disorder in children and adolescents presenting to a neurologist, other primary headache disorders are important to recognize. Trigeminal autonomic cephalalgias represent a rare group of primary headache disorders with different characteristics, workup and management. Here, we present an adolescent with one common and one unique headache phenotype followed by a guided discussion of the differential diagnoses, workup, treatments and a brief summary of further management considerations.

Section 1

A 15-year-old right-handed boy presented with headaches since age 12. Headache #1 is described as rapid-onset severe right-sided supraorbital/frontotemporal sharp or stabbing pain typically starting in the morning or evening rated as 6-9/10 in severity. Each spike lasted approximately 1-hour followed by a briefer improvement with background pain described as “there” before recurrence in a saw-tooth pattern for a total of 2-3 days. Each initial attack began with ipsilateral eyelid edema which transitioned after a few hours into inferior palpebral erythema through the end of the last attack. There was no conjunctival injection, tearing, ptosis, miosis, sweating, congestion or rhinorrhea (Figure 1). Severe pain episodes were associated with photophobia, phonophobia and nausea but not restlessness or agitation. Each active course occurred on average 3 times per month or as frequently as 4 times in 2 weeks in the fall and winter, less commonly in the spring and summer. There were no identified triggers and ibuprofen, naproxen, and aspirin containing medications were ineffective.

Headache #2 is described as moderate to severe pressure around/behind the eyes lasting an average of 6 hours occurring 1-2/week, with associated photophobia and phonophobia without nausea, vomiting or preceding aura. They were neither nocturnal nor triggered by Valsalva maneuvers. These headaches

Copyright © 2022 American Academy of Neurology. Unauthorized reproduction of this article is prohibited
decrease his activity, and activity made these headaches worse. There were no obvious triggers, but attacks were responsive to over-the-counter medications. Pediatric Migraine Disability Scale (PedMIDAS) score was 18. Past medical history was negative, but there was family history of migraine and reported trigeminal neuralgia in maternal grandmother. A detailed neurologic exam was normal including sharp fundoscopic discs.

Questions for consideration:

1. What is the initial approach for this teen with headaches?
2. Is imaging indicated?

Section 2

The first step in evaluating children with headache is to rule out a secondary headache disorder. The following characteristics commonly referred to as “red flags” should warrant further workup in children. A common mnemonic used is SNOOP,Y: Systemic signs/symptoms, Neurologic signs/symptoms, sudden Onset, Onset in sleep/early morning, Positional exacerbation, Precipitated by Valsalva, Parents (lack of family history), Progressive symptoms, Young age.1 Whereas migraine without red flags does not necessitate imaging, other headache types do.

The patient in the vignette presented with two distinct headache phenotypes. Headache #2 meets criteria for migraine without aura2 and alone would not warrant imaging in the absence of red flags.3 The rapid-onset relatively brief stabbing/sharp attacks of headache #1 do not meet criteria for migraine and may be manifestations of more nefarious etiologies such as neoplastic, vascular and infectious diseases. Therefore, secondary causes must be ruled out with neuroimaging; MRI brain and MR angiography were normal.
Questions for consideration:

1. How do we classify headache #1?
2. How do we differentiate between migraine and headache #1?

Section 3

Headache #1 falls within the category of trigeminal autonomic cephalalgia (TAC) which are generally characterized by unilateral orbital, supraorbital and/or temporal pain with ipsilateral autonomic features and/or agitation.² Whereas onset of migraine attacks are typically gradual or in a crescendo-decrescendo pattern with duration greater than 2 hours in youth, onset of TACs attacks are rapid and most are under 180 minutes. Similarly, migraine is frequently bilateral in adolescents whereas TACs are unilateral. Another diagnostic clue is a sense of restlessness. Most children (and adults) with migraine report headache severity worsened by activity or avoid routine activities during attacks, as is included in the criteria. In contrast, patients with TACs may become restless during attacks and may not stop moving. Cluster headache is associated with agitation occasionally so severe as to elicit suicidal ideation in 55% and suicide attempt in 2% of adults in one study.⁴ Fortunately, this sense of restlessness is less common in the pediatric group,⁵ including this patient.

TAC includes 4 distinct primary headache disorders varying primarily in duration and frequency as listed in Table 1: hemicrania continua (HC), cluster headache (CH), paroxysmal hemicrania (PH), and short-lasting unilateral neuralgiform headache attacks including those with conjunctival injection and tearing (SUNCT) and those including one or other cranial autonomic symptoms (SUNA).² This patient’s attack duration of greater than 30 minutes is most consistent with CH, though the frequency >8/day is more consistent with paroxysmal hemicrania. However, frequency and duration of TAC attacks in children are not always consistent with adult criteria.⁵ One helpful distinction is that HC and PH criteria also include absolute prevention with therapeutic doses of indomethacin, though there have been observations that
this may not be as absolute for children and adolescents. See eFigure 1 in the Supplement for a diagnostic algorithm of TACs.

Indomethacin trial to 75mg TID for 2 weeks improved duration and severity of attacks but did not resolve them. Since the response to indomethacin was not absolute in this patient, CH would be the most appropriate diagnosis. Indomethacin has been reported to be effective in CH, especially in children and adolescents.\(^6\) In addition, while obtaining a more detailed family history, it was revealed that grandmother’s attacks were associated with ipsilateral ptosis, likely representing a TAC rather than trigeminal neuralgia as previously thought. Positive family histories have been reported in CH\(^7\) and other TACs.\(^8\)

Ecchymosis and erythema have rarely been reported in adults with migraine and CH,\(^9\) and V1 distribution erythema has been described in a child with probable CH,\(^10\) though erythema localized to the lower eyelid seen here is unique. Autonomic symptoms are not uncommon in migraine, and some are more frequently unilateral, though are generally milder than in CH.\(^11\) Tearing in particular is unilateral in 15.8% and bilateral in 10.7% of patients with migraine in one study, though eyelid edema and eye redness are more frequently bilateral.\(^12\) Since autonomic changes can be unilateral in migraine, this should not be considered in isolation when differentiating between migraine and TACs. Underlying mechanisms of palpebral erythema are likely similar to other autonomic symptoms including release of vasoactive intestinal peptide which is elevated in all CH and only migraine attacks with accompanying autonomic symptoms.\(^11,13\)

Cooccurrence of TAC and migraine in both the patient and his grandmother has been reported in 16.7% of patients with CH in one study\(^14\) and in 15.6% in another with a higher rate of comorbidity in those with chronic CH versus episodic CH.\(^15\) Central sensitization or biologic correlation could account for this finding. Involvement of overlapping hypothalamic and brainstem nuclei as well as calcitonin gene-
related peptide and pituitary adenylate cyclase-activating peptide elevation in migraine and CH indicate a potential underlying pathophysiologic mechanism.\textsuperscript{13} Similarly, a large genome-wide association study identified 4 susceptibility loci for CH, one of which has been associated with migraine.\textsuperscript{61}

Question for consideration:

1. Which management strategies should be considered?

Section 4

Management of these distinct primary headache disorders differ: preventive medications such as amitriptyline, topiramate or valproate may be offered to children and adolescents with migraine in which the attacks occur greater than 1-2/week or with a significant degree of disability.\textsuperscript{62} In addition, healthy habits and cognitive behavioral therapy (CBT) should be discussed.\textsuperscript{63} In contrast, treatment for TACs may depend on the specific subtype. Indomethacin is a reasonable first line therapy as it could be both therapeutic and diagnostic as reviewed above. Additionally, as the absolute distinction is not as clear for children and adolescents, a trial of indomethacin may be advantageous, even when the diagnosis suggests an indomethacin non-responsive headache. After discussing risks and benefits of all three aforementioned preventive medications for migraine, valproate titrated to 750mg twice daily with education on healthy habits and CBT improved frequency to 2 migraine attacks per month.

For his TAC, indomethacin trial was recommended at the onset of next attacks as follows: 25mg TID for 5 days up to 2 weeks if effective; if ineffective, increase to 50mg TID for 5 days up to 2 weeks if effective; if ineffective, increase to 75mg TID for 5 days up to 2 weeks with gastric protection but to no avail. High flow oxygen was recommended at onset of next attack to aid in diagnosis since this therapy is ineffective in all but CH but was only attempted once toward the end of an attack so efficacy could not be established. Sumatriptan 20mg nasal spray and gammaCore device, a noninvasive vagus nerve stimulator, were prescribed. GammaCore (three 2-minute stimulations) was effective in alleviating an

Copyright © 2022 American Academy of Neurology. Unauthorized reproduction of this article is prohibited
attack after which sumatriptan brought full relief. He continues to use gammaCore (two 2-minute stimulations) nightly as partial prevention and valproate was weaned off after migraine improved. A discussion of therapies for CH and other TACs is available in eAppendix 1 in the Supplement.

While TACs are rare in children, CH begins prior to age 21 in 35% of individuals in one large national survey and delay to diagnosis is greater in youth. It is therefore important to recognize clinical characteristics, initial workup and management to prevent prolonged high grade of disability and socioeconomic burden.

References


Copyright © 2022 American Academy of Neurology. Unauthorized reproduction of this article is prohibited.
Table 1. Diagnostic criteria for trigeminal autonomic cephalalgias based on the International Classification of Headache Disorders 3rd edition (ICHD-3) (2).

<table>
<thead>
<tr>
<th></th>
<th>Hemicrania continua</th>
<th>Cluster headache</th>
<th>Paroxysmal hemicrania</th>
<th>Short-lasting unilateral neuralgiform headache attacks*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of attacks</strong></td>
<td>At least 1 continuous attack</td>
<td>At least 5</td>
<td>At least 20</td>
<td>At least 20</td>
</tr>
<tr>
<td><strong>Pain Severity (and quality)</strong></td>
<td>At least moderate exacerbations</td>
<td>Severe or very severe</td>
<td>Severe</td>
<td>Moderate to severe (stabs)</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>&gt;3 months</td>
<td>15-180 minutes</td>
<td>2-30 minutes</td>
<td>1–600 seconds</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>Continuous</td>
<td>Every other day up to 8/day</td>
<td>&gt;5/day</td>
<td>At least daily</td>
</tr>
<tr>
<td><strong>One of the following associated symptoms</strong></td>
<td>Conjunctival injection and/or lacrimation</td>
<td>Nasal congestion and/or rhinorrhea</td>
<td>Eyelid edema</td>
<td>Forehead and facial sweating</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Miosis and/or ptosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Forehead and facial flushing, or Sensation of fullness in the ear</td>
</tr>
<tr>
<td><strong>OR:</strong></td>
<td>Restlessness or</td>
<td>Restlessness or agitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic response</td>
<td>Absolute response to therapeutic doses of indomethacin</td>
<td>Absolute response to therapeutic doses of indomethacin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>--------------------------------------------------------</td>
<td>--------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Not better accounted for by another ICHD-3 diagnosis.

*Subcategories include: Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) which requires both conjunctival injection and lacrimation ipsilateral to the headache; and Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) which can have either conjunctival injection or lacrimation, but not both.
Figure 1. Periorbital edema and inferior palpebral erythema

A-F: Single attack on indomethacin; A, first attack onset; B, 30 minutes from onset; C, 90 minutes from onset; D, 120 minutes from onset; E, 17 hours from onset; F, 18 hours from onset. G-H: Single attack off indomethacin. I: Notable inferior palpebral erythema.
Clinical Reasoning: A Teenager With Right-Sided Headache and Periorbital Changes
Daniel N. Lax, Marielle Kabbouche, Joanne Kacperski, et al.
Neurology published online October 19, 2022
DOI 10.1212/WNL.00000000000201482

This information is current as of October 19, 2022