Headache in the Emergency Department

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Abstract Emergency-medicine clinical researchers concentrate on optimizing diagnostic workups and treatment protocols, as well as improving throughput in an emergency department. This past year has yielded a wealth of clinical research focused on headache, which should streamline the diagnostic workup of nontraumatic headaches (particularly the search for subarachnoid hemorrhage) and several comparative efficacy trials, which help clinicians determine how best to treat acute migraine with parenteral medications. Herein, we review and contextualize the most important recent developments with regard to management of headache in the acute care setting.

Keywords Headache · Emergency room · Emergency department · Update

Introduction

Emergency departments (ED) are a resource well suited to the expeditious diagnostic workups of worrisome headaches and to effective treatment of severe primary headaches refractory to oral medications. Emergency-medicine clinical researchers with an interest in headache focus on defining efficient approaches to diagnosis, optimizing acute treatment paradigms, improving throughput in the ED, and reducing the need for future ED care. During the past year, clinical researchers in emergency medicine produced a variety of manuscripts of general interest to the headache-medicine community.

Diagnosing Serious Secondary Headache Disorders

In the past year, there were several important publications that addressed the diagnostic evaluation of headaches in the ED. These focused on improving the diagnosis of subarachnoid hemorrhage and cerebral venous sinus thrombosis, which we will consider one at a time.

The pursuit of the subtle subarachnoid hemorrhage remains a diagnostic challenge for emergency physicians and headache specialists alike. Authoritative reviews recommend a complete diagnostic workup, including noncontrast head computed tomography (CT) and lumbar puncture (LP), for all patients who present with a “first,” “worst,” or “changed” headache [1]. Unfortunately, in our experience, just about every patient who presents to an ED describes their headache as “first,” “worst,” or “changed.” In the current environment of spiraling health care costs, concerns about radiation exposure, and ED overcrowding, there is a pressing need to find reliable clinical parameters that accurately identify patients at significant risk of malignant intracranial pathology without resorting to imaging in all patients. Limited clinical data suggest that headaches requiring more than several minutes to peak in intensity are low risk for subarachnoid hemorrhage [2], though whether this historical feature can reliably and definitively rule out aneurysmal subarachnoid hemorrhage is not yet known.

A decision analysis published early in 2010 contextualizes the evolving decision faced by emergency physicians: in
patients at high risk of aneurysmal subarachnoid bleed, should a noncontrast head CT followed by a CT angiogram (CTA) replace the traditional pathway of CT followed by LP [3••]? The answer is multifactorial. This analysis addressed just the question of sensitivity: is CT followed by CTA as sensitive as the traditional standard? Using published sensitivities and the expectation that aneurysmal subarachnoid hemorrhage is relatively uncommon, even in patients with acute onset headache and an average risk of subarachnoid hemorrhage, CT followed by CTA is a reasonable diagnostic strategy with comparable sensitivity to a CT followed by LP. Left unanswered by this analysis (and acknowledged by the authors) are the other factors that influence a physician’s decision to pursue one strategy or the other: the risks, if any, of discovering incidental and asymptomatic aneurysms, the risks of additional radiation exposure, the risks of contrast, the relative costs of the two procedures, and the effects on ED throughput time. Incidental aneurysms are managed differently than symptomatic aneurysms; thus, patients in whom the CT/CTA strategy identifies an aneurysm then will have to undergo an LP. Beyond that, they will have to live with the knowledge that they have a cerebral aneurysm. The relevance of radiation exposure from medical imaging is not yet well defined, though it is an increasing topic of discussion. It is clear that it has more relevance in younger patients than older patients, and thus, age of the patient may be a consideration when deciding which strategy to pursue. A final factor for the emergency physician to consider is throughput: because the CTA can be performed in nearly the same amount of time as the noncontrast head CT, an overcrowded ED may find it makes more sense to rely just on the imaging studies. Because the definitive study to answer this question would be both complex and expensive, we probably will never see a clear-cut answer. Although the CTA may be problematic for the reasons mentioned above, the downsides of the CTA are less immediate and less relevant to the patient than the immediate discomfort of an LP and the very real possibility of a post-LP headache.

A long-anticipated prospective cohort study that may lower the frequency of diagnostic testing interpreted as “normal” by identifying patients at very low risk of aneurismal subarachnoid hemorrhage recently has been published. Perry and a group of Canadian researchers [4••] performed a multicenter prospective cohort study to identify high-risk clinical features that are associated with nontraumatic subarachnoid hemorrhage. The goal of this work was to identify a low-risk subgroup of patients who did not need brain imaging or LP in the acute setting. Patients who presented to one of six EDs were enrolled if they were 16 years or older, if they had a nontraumatic headache that peaked in intensity within 1 h, and if the headache occurred within the previous 14 days. Patients who presented with a clear exacerbation of a well-defined recurrent headache syndrome were excluded from the study. Of 1999 patients enrolled in this study, 130 had a subarachnoid hemorrhage. To ensure no patients with subarachnoid hemorrhage were missed, 6-month follow-up was performed. Using clinical features readily available on history or physical exam, the authors derived three overlapping 4-item decision rules, each of which had 100% sensitivity for identifying subarachnoid hemorrhage. The rules were as follows:

Rule #1: a) age over 40 years; b) complaint of neck pain or stiffness; c) witnessed loss of consciousness; and d) onset with exertion;

Rule #2: a) arrival by ambulance; b) age over 45 years; c) vomited at least once; d) diastolic blood pressure over 100 mm Hg;

Rule #3: a) arrival by ambulance; b) systolic blood pressure over 160 mm Hg; c) complaint of neck pain or stiffness; and d) age 45 to 55 years.

In this derivation cohort, the absence of all four criteria in any one rule excluded subarachnoid hemorrhage as the diagnosis. As with all clinical research, these rules must be validated in a separate clinical trial before being relied upon for clinical decisions; it is as yet unclear if the same clinical features would identify 100% of patients with subarachnoid hemorrhage in a different cohort of patients in a different practice location. A separate problem with these rules is that the gains in efficiency they produce are not all that dramatic. In the development cohort, the rules eliminate the need for diagnostic testing in a quarter of all patients who presented with a headache that peaked in intensity within 1 h. This was similar to the rates of diagnostic testing performed by the clinical teams caring for these patients.

A second cohort study is needed to validate these rules in an independent sample. Until then, these clinical decision rules are best used by clinicians as a tool to help risk-stratify patients who present to the ED with a de novo headache that peaks in intensity within 1 h. Patients who meet low risk criteria could be informed that their risk is low and can help decide how best to proceed.

These same clinical researchers surveyed emergency physicians from four English-speaking countries to determine practice patterns with regard to the diagnostic workup of nontraumatic headaches [5•]. Emergency physicians from Australia, Canada, the United Kingdom, and the United States were sent a series of questions regarding a hypothetical neurologically intact patient who presents to an ED with an acute severe headache that peaks in intensity within 1 h of onset. The overall response rate was 55%, with physicians from Canada most likely to return the survey and those from the United Kingdom and the United
States least likely to return the survey. Overall, 50% of respondents believed that all such patients should get a head CT. Country-specific rates were as follows: Australia 49%, Canada 46%, United Kingdom 47%, and United States 56%. When asked if a normal head CT should be followed in all cases by a LP for this type of patient, 56% of Australian respondents said yes, as did 60% of Canadian respondents, 66% of those from the United Kingdom, and 51% of those from the United States. Of all respondents, 60% stated that they manage patients like those in the example with a CT followed by an LP all or most of the time (country-specific rates: 65% of Australian respondents, 58% of Canadian respondents, 53% of respondents from the United Kingdom, and 58% of respondents from the United States). The authors use this research to demonstrate the need for a clinical decision rule for subarachnoid hemorrhage. However, these data provide an opportunity to compare practice across international boundaries; specifically, to address the question of whether American physicians are overly dependent on imaging and practice a particularly defensive form of medicine. United States physicians were indeed slightly more likely than their Canadian colleagues to image their headache patients, though overall practice patterns, as evidenced by the final question, were no different among the countries.

Another serious cause of secondary headache that may present to the ED, cerebral venous sinus thrombosis (CVST), was the subject of a retrospective review [6•]. CVST is much less common than aneurysmal subarachnoid hemorrhage. A high index of diagnostic suspicion is required because the usual evaluation for headache in the ED, with noncontrast CT and spinal fluid analysis, is unlikely to suggest the diagnosis. The recent retrospective review was intended to define clinical features that suggest the possibility of CVST. Using a search strategy based on the ninth revision of the International Statistical Classification of Diseases and Related Health Problems, the authors combed through 5 years of ED records from three academic referral centers with a total combined annual volume of 190,000 visits. There were 17 identified cases of de novo CVST. Characteristics of the presentation of CVST reinforced by this review are that it is rare and subtle. Headache and seizure were the two most common presenting complaints. More than half of the patients had been seen in the ED within the previous 60 days and nearly one third had symptoms lasting longer than 1 week. Thrombophilic risk factors were identified in 11 of the 17 patients, including oral contraceptives in five patients, inflammatory bowel diseases in two patients, history of venous sinus thrombosis in two patients, solid tumor malignancy in one patient, and lupus in one patient. Of the six patients without thrombophilic risk factors, two had recent neurosurgery and three reported head trauma. All but 3 of the 17 patients had persistent findings on neurological examination, including motor and sensory deficits, memory deficits, visual field cuts, or papilledema. The three patients with normal neurological exams all had good long-term outcomes. Only 6 of the 17 patients experienced a disability-free survival, highlighting the high-stakes nature of this illness. This study was limited by its retrospective nature: inaccurately diagnosed or coded cases were probably missed, thus potentially skewing this sample toward sicker patients.

### Treatment of Migraine in the Emergency Department

Opioids commonly are used as treatment of acute migraine in the ED. Over the years, emergency-medicine researchers have published a variety of studies looking at effective parenteral alternatives. One class of therapeutics, the antiemetic dopamine antagonists, has shown a great deal of promise as primary treatment of migraine and continues to be a focus of emergency-medicine researchers. Kostic et al. [10] compared one of the dopamine antagonists, prochlorperazine, to parenteral sumatriptan, the guideline-endorsed standard of care [7••]. Prochlorperazine already has been shown to be an effective treatment of migraine, superior to placebo [8], valproate [9], and ketorolac [10]. The investigators randomized 66 patients with acute migraine who presented to their ED to intravenous prochlorperazine, 10 mg, plus intravenous diphenhydramine, 12.5 mg, or to subcutaneous sumatriptan, 6 mg. Pain intensity was assessed for 80 min in the ED and then by telephone within 72 h of ED discharge. By 80 min, the prochlorperazine group had improved by 73 mm on a 100-mm visual analogue scale compared to 50 mm in the sumatriptan group. This difference surpassed statistical and clinical thresholds. Headache recurrence tended to be more common in the sumatriptan group, though the study was underpowered to identify statistically significant differences in this outcome. Surprisingly, sedation scores between the two groups were nearly identical. A large-scale validation of this work is needed, but it is in keeping with results from several other trials of dopamine antagonists versus sumatriptan, in which these comparators have done no worse than the guideline standard of care [11, 12]. This body of work raises the question of whether the dopamine antagonists, nonanalgesics that they are, should be considered to be migraine-specific therapy along with the triptans and ergotamines.

Metoclopramide, another antiemetic dopamine antagonist, has clearly demonstrated efficacy for acute migraine [13]. However, the optimal dose of this medication for treatment of acute migraine is not known. Protocols using as much as 80 mg of metoclopramide, dosed in 20 mg boluses, have been used [12]. We recently published a
randomized dose-finding study in which 10 mg of metoclopramide was compared to 20 mg and 40 mg as initial intravenous therapy [14]. The metoclopramide was combined with diphenhydramine, 25 mg, to prevent the development of akathisia, which was feared to be more likely with higher doses of metoclopramide. In this study, 350 patients were enrolled. Outcomes and adverse event profiles were comparable. In the 10-mg, 20-mg, and 40-mg arms, the 2-hour headache relief was 82%, 80%, and 86%, respectively. Sustained pain-free rate in each of the arms was 16%, 20%, and 21%, respectively. ED dwell time also was comparable among the study arms. Although surprising, these data are in keeping with data from a droperidol for acute migraine dose-finding study, in which a relatively modest dose of intramuscular droperidol was more effective than larger doses [15], and with data on subcutaneous sumatriptan, for which doses larger than 6 mg do not lead to higher rates of headache relief [16].

Another ED-based clinical trial compared sumatriptan to an alternate therapy, though this study addressed treatment of recurrence of headache after ED discharge [17]. Recurrence of headache after ED discharge is common; 50% of patients report functionally disabling headache within 24 h of ED discharge, even when not treated with opioids [18]. Strategies to address the recurrence are not well defined. Dexamethasone is an evidence-based therapy, though clinicians should not necessarily utilize this therapy, with a number needed to treat of 10 for preventing headache recurrence after ED discharge [19], for all patients. It is unclear which oral therapies clinicians should prescribe to treat the headache recurrence. Oral dopamine antagonists do not have an evidence base as monotherapy, though they have demonstrated efficacy when combined with salicylates or nonsteroidals. The choice for most clinicians when deciding among specific oral therapies to use for treatment of recurrent migraine is an NSAID or an oral triptan. To determine which of these therapies is best for patients discharged from an ED after successful treatment of their migraine, we conducted a clinical trial that was published in 2010 [17]. We randomized patients to one dose of oral sumatriptan, 100 mg, or oral naproxen, 500 mg, to take if their headache recurred and required treatment. Of 166 patients discharged from the ED after treatment of migraine, 88 (53%) had a headache of sufficient severity to require their medication. During the 2 h after medication ingestion, those who took naproxen improved by a mean of 4.3 points on a scale from 0 to 10, while those who took sumatriptan improved by 4.2 points over this same period. In this group of patients discharged from an ED, naproxen was as effective as sumatriptan for the treatment of recurrent migraine. Of some concern is that only 12 of 48 patients who took naproxen and only 12 of 40 patients who took sumatriptan obtained complete relief of their recurrent headache during the 2 h after medication administration. Obtaining sustained headache relief after an ED visit remains a refractory problem. Combining these two agents has proven to be a useful therapeutic option for treating the initial headache [20] and may be useful for the recurrent headache as well.

**Pediatric Migraine**

Practice variability is common in ED-based migraine management; there is no one clear favorite therapeutic agent. In one review of national data, over 20 different parenteral medications were used to treat migraine [21]. Practice variability usually represents uncertainty in the clinical science, a fact that, because of the relative dearth of comparative efficacy studies, is true for parenteral treatment of migraine. Variability in the treatment of pediatric migraine in the ED setting was analyzed by comparing medications administered to children who were treated for migraine in 10 tertiary care hospitals across Canada [22]. Overall, dopamine antagonists were administered most commonly, in 39% of visits (versus 34% for oral analgesics, 24% for intravenous fluid bolus, and 10% for parenteral nonsteroidals). Triptans were administered in 0.5% of visits. That no one type of medication was used in more than 50% of visits speaks to substantial practice variability. This is further illustrated by the ED-to-ED variability in class of medication used among academic EDs within Canada. In two EDs, dopamine antagonists were administered to 60% of patients, while three EDs administered dopamine antagonists to 20% or fewer of patients. Similarly with intravenous fluid, some EDs administered this therapy to more than 50% of patients and several administered it to fewer than 10% of patients. Practice variability speaks to the need for clinical trials to help define a standard of care. For pediatrics, this is true in the emergency arena as much as it is in the outpatient or inpatient headache setting.

More prochlorperazine data come from a pediatric ED, where the investigators reported their outcomes after administering 0.15 mg/kg of prochlorperazine combined with diphenhydramine to 92 children with migraine [23]. This was a retrospective review and, therefore, not a high-quality study within a specialty notorious for a high placebo rate. However, these data are useful because there are very limited high-quality data on parenteral treatment of pediatric migraine. In this situation, where, as evidenced in the Richer et al. [22] study reviewed above, there is not one clearly preferred therapy, knowing the experience of and doses used by others can be helpful to suggest treatment. After receiving the combination treatment with prochlorperazine and diphenhydramine, only 14% of their patients had treatment failure, defined as requiring rescue therapy, admission to the
hospital, or return to the hospital within 48 h for recurrence of symptoms or a medication-related adverse event. Akathisia, the only substantial side effect to occur, developed in 7% of patients despite the coadministration of diphenhydramine. Prochlorperazine is a very reasonable treatment to consider for the parenteral management of acute pediatric migraine.

Conclusions

In conclusion, 2010 has yielded a wealth of ED-based clinical research to help streamline the diagnostic workup of nontraumatic headaches and to treat acute migraine. We can hope the next year brings validation of the findings reported this year so that management of acute headache in the ED setting continues to advance.

Disclosures

Dr. B. W. Friedman: none. Dr. Richard Lipton has served on the advisory boards of Allergan, Merck and Co., and MAP Pharmaceuticals; has served as a consultant for Allergan; has received grants, or has grants pending, from GlaxoSmithKline, Allergan, Merck and Co., and Bristol-Myers Squibb; has received payment for manuscript preparation from Allergan; has received payment for the development of educational presentations from Allergan; and had received travel expense compensation from Allergan and Merck and Co.

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