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Expert Opinions

Status Migrainosus in Children and Adults

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According to the International Classification of Headache Disorders, 3rd edition (ICDH-3),[1] status migrainosus (SM) is "a debilitating migraine attack lasting for more than 72 hours." Analogous to the term "status epilepticus,"[2] "status migrainosus" was coined by Taverner in 1975,[3] used by Lance in 1978,[4] and was first added to the International Classification of Headache Disorders (ICDH-1) in 1988.[5,6] The condition occurs in those with migraine with or without aura and, aside from increased duration and severity, has features similar to the individual's prior migraine attacks. While attacks should last greater than 72 hours to fulfill the diagnostic criteria for SM (Table 1), short periods of remission (less than 12 hours) due to medication or sleep are accepted.[1]

CASE HISTORY

This is a 31-year-old woman with a history of migraine without aura for 5 years occurring twice a month lasting 1-2 hours after taking 10 mg of rizatriptan. She presented to the office with an exactly similar nonmenstrual headache continuously occurring for 5 days associated with increased stress and lack of sleep. The headache is described as a generalized, especially bifrontal-temporal, throbbing pain associated with nausea, light and noise sensitivity but no vomiting or aura. Pain intensity was initially 3/10 and since onset has been ranging from 3-8/10, at presentation to the office, her headache severity was 7/10. She had tried rizatriptan, ibuprofen, and a combination of acetaminophen (APAP) /aspirin/caffeine for the past 4 days without help. Past medical history was negative. Neurological exam was normal and she denied any recent illness, trauma, or change in medications. She was given bilateral greater occipital nerve (GON) blocks with 3 cc each and bilateral auriculotemporal, supraorbital, and supratrochlear nerve blocks with 0.5 cc each of 1% lidocaine, as well as diclofenac sodium 50 mg oral solution with resolution of the headache.

QUESTIONS

How common is SM? Are there triggers? What is the pathophysiology? Should diagnostic testing be done? Which acute treatments are effective? Is preventive medication effective? What is the prognosis?

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Table 1.—ICHD-3 Diagnostic Criteria for Status Migrainosus[1]

A.	A headache attack fulfilling criteria B and C
B.	Occurring in a patient with 1.1 Migraine without aura and/or 1.2 Migraine with aura, and typical of previous attacks except for its duration and severity
C.	Both of the following characteristics:
	1. Unremitting for >72 hours
	2. Pain and/or associated symptoms are debilitating
D.	Not better accounted for by another ICHD-3 diagnosis

EXPERT OPINION

Epidemiology.—Migraine is a common primary neurologic disorder that affects approximately 12-15% of the world's population[7] and is considered as the second most disabling condition worldwide.[8] It affects women 3 times more often than men (17.1% vs 5.6%)[9] and occurs in all ages, with approximately 5% of adolescents having a migraine headache by age 15.[10,11]

SM is a debilitating complication of migraine with or without aura that lacks clear epidemiologic data. A recent 11-year retrospective analysis of a French tertiary headache center reported a 3% prevalence of SM,[6] while a 2006 multicenter study of 253 patients with migraine reported that 24.3% of those with aura and 20.6% of those without aura experienced headache pain for more than 72 hours.[12] SM is thought to occur more frequently in those with episodic migraine (less than 15 headache days per month).[13]

Pathophysiology.—Initially thought of as a vascular phenomenon,[14] migraine is now considered as a primary neurologic disorder of central and peripheral sensory processing involving the trigeminovascular system[15] and possible "migraine centers" such as the hypothalamus.[16] While it stands to reason that the pathophysiology of SM should follow that of migraine (given that SM is a manifestation of the disorder), no clear pathophysiological mechanism has been identified for SM specifically. A case report of MRI and PET scan of the brain during SM suggests that SM can be associated with vasogenic cerebral edema.[17]

Risk Factors.—A variety of risk factors for SM have been proposed. Emotional stress, depression, and medication overuse are among the most commonly reported,[2,6] and menstruation was found to be a precipitating factor in 31.3% of women with SM.[6] A case describing persistent migrainous vertigo possibly triggering cephalic SM suggests that stimulation of the vestibular system can trigger migraine attacks and bouts of SM.[18] Studies of SM in children and adolescents are lacking, but a small retrospective study demonstrated that recent systemic illness presenting as fever and generalized malaise was seen in 2 out of 14 children (14%) hospitalized for the treatment of SM.[11]

While SM is more commonly seen in those with episodic migraine,[13] a high attack frequency may be a risk factor for its development. Chronic migraine is associated with a decreased response to both acute and preventive migraine treatments,[19] theoretically increasing the risk of developing SM.

Clinical Presentation.—ICDH-3 diagnostic criteria for SM require that it present similarly to migraine attacks an individual has had in the past, with the exception of increased severity and prolonged duration.[1] A French study of SM found an attack duration of 4.8 weeks (ranging from 3 to 10 weeks). However, there may be selection bias as this study was performed at a tertiary headache center.[13] Of note, the authors have seen cases of SM with a thunderclap onset, "crash migraine," and others with a distribution different than prior migraines.

Episodic Status Migrainosus.—SM occurring in the absence of other attacks of shorter duration has been reported.[20-22] Medina and Diamond described 27 individuals with migraine whose headaches occurred in recurrent cycles separated by headache-free intervals. These attacks, which they termed "cyclical migraine," lasted an average of 6 weeks each and occurred an average of 5 cycles per year.[23]

Evans reported 2 similar cases of "episodic daily migraine" in a man and woman who experienced 4-5 migraine attacks per year that would occur daily for 2-8 weeks at a time.[21] He speculated that Thomas Jefferson had similar headaches.

Singh et al reported 18 cases they termed "episodic status migrainosus" (ESM) affecting mostly women with an average migraine attack frequency of 2 per month with each attack lasting an average of 7 days.[22] Migraine with aura was present in 55.6% (10 patients), depression in 55.6%, and anxiety in 16.7%. Precipitating factors for ESM included emotional stress/anxiety in 61.1%, poor sleep in 50%, menses in 38.9%, and food

Table 2.—Proposed Criteria for Episodic Status Migrainosus[20,22]

Description:
A recurrent headache disorder (occurring in individuals with 14 or fewer headache days per month or no other migraines) with attacks lasting more than 72 hours manifesting in attacks otherwise meeting criteria for (1.1 *Migraine without aura* and/or 1.2 *Migraine with aura*
Diagnostic criteria:
A. Attacks fulfilling all but criterion B for 1.1 *Migraine without aura* and/or 1.2 *Migraine with aura*
B. Recurring attacks lasting greater than 72 hours (untreated or unsuccessfully treated)
C. Not better accounted for by another ICHD-3 diagnosis

Table 3.—Headache "Red Flags" Concerning for Secondary Headache

- Change in frequency, severity, intensity or associated symptoms of headaches
- Systemic symptoms (ie, fever, weight loss, rash, chills, night sweats, and jaw claudication)
- Secondary risk factors (ie, pregnancy, cancer, HIV/AIDS, and immune compromised state)
- Seizures
- Neurologic symptoms or signs
- New headache or change in headache in someone over age 50
- Thunderclap headache
- Positional component
- Pulsatile tinnitus
- Precipitated headache, specifically by cough, exercise, sexual activity or sleep

Adapted from Refs. [24,25].

triggers in 38.9%. ESM evolved into chronic migraine in 83.3% at a median age of 26.8 years. Singh et al proposed the criteria for ESM for which Evans [20] proposed modifications (Table 2).

Migraine Aura Status.—Migraine aura status is similar to SM. Criteria for migraine aura status is located in the Appendix section of the ICHD-3 and defines a condition fulfilling diagnostic criteria for migraine with aura (or its subtypes), with at least 3 episodes of aura occurring over 3 consecutive days.[1] One study showed that this condition to be rare (3 out of 8821 individuals), occurring in those with a low attack frequency, and lasting an average of 4 weeks (range of 3-5 weeks).[6]

Evaluation.—The history and a normal neurological examination should be consistent with migraine with or without aura. If headache "red flags" (Table 3) is present, further evaluation to exclude a secondary cause may be necessary.

Several SM mimics have been reported and include hemorrhagic pituitary adenoma,[26,27] cervical and vertebral artery dissection,[28] and a brain abscess.[29] There are numerous other mimics including sphenoid sinusitis, reversible cerebral vasoconstriction syndrome, subarachnoid hemorrhage, subdural hematoma, pseudotumor cerebri, brain tumor, intermittent hydrocephalus, meningitis, and acute glaucoma.[30]

Primary headaches can also be mimics to SM. A persistent unilateral headache could be hemicrania continua. A large series found that the longest duration SM attack was 10 weeks;[6] if the headache persists for more than 3 months with negative testing then primary new daily persistent headache should be considered.

Outpatient Treatment.—Most studies of SM focus on emergency or hospital-based treatment. However, this is not always an attractive choice for patients due to the cost of emergency care, unpleasant environment with many possible migraine irritants (fluorescent lights, loud noises, and unpleasant smells), or the unfortunate stigma of being viewed as a drug seeker.[31] Ideally, treatment of severe or prolonged episodes of migraine starts in the outpatient setting. Although not specific to SM, "rescue medications" of various types have been used for outpatient treatment of refractory or intractable migraine attacks.[32] A study on resource use and patient outcomes shows that emergency room visits decreased by 85% with home use of sumatriptan (oral or subcutaneous injection), and that 6 months after starting acute sumatriptan use, Migraine-Specific Quality of Life Questionnaire scores showed significant improvement in all 3 domains measuring health-related quality of life: role restrictive, role preventive, and emotional function.[33] "Sumatriptan (6 mg sc) is the first choice for patients requiring [outpatient] treatment of SM"[34] and DHE (dihydroergotamine) may be a good first-line acute treatment option in those at risk for developing medication overuse headache.[35] In addition, typical "headache cocktails" used in the emergency department (ED), such

as a combination of diphenhydramine, metoclopramide, ketorolac, and sumatriptan, can be prescribed to patients for home use, and are available in oral, intramuscular, and suppository formulations. Anecdotally, other "rescue" treatments that have been used include DHE nasal spray, powdered diclofenac, olanzapine, intranasal lidocaine, butalbital-containing combination analgesics, and opioids. Some clinicians use 4 mg of methylprednisolone for 6 days starting at 6 tablets per day the first day and decreasing by 1 tablet per day. Brief courses of corticosteroids may decrease recurrence, but it is not certain that the duration of the SM attack is shortened.[36] The potential for adverse events should also be considered.

If available, outpatient treatments from their physicians can also help abort an episode of SM. Injections of nerve blocks and trigger point injections using lidocaine or bupivacaine can be an effective abortive agent for refractory migraine attacks.

Emergent Treatment.—In the United States, there are 5 million ED visits for headache each year and approximately one-third are due to migraine.[37-40] The number of cases of SM presenting to the ED is not known. Migraine management should always be tailored to the patient's goals of care and take into account their current medications, medical comorbidities, and the presence of any contraindications to the treatments used for SM.

In a systemic review of 44 studies of acute treatment of migraine in the ED, the following 4 treatments were strongly recommended: sumatriptan, prochlorperazine, metoclopramide, and ketorolac.[41] Intravenous (IV) dexamethasone and haloperidol were not recommended as acute ED treatment because of the lack of rigorous data and the potential for significant adverse events.

The American Headache Society performed a similar systemic review, finding 68 randomized controlled trials utilizing 28 injectable medication. The recommendation is the following: "Intravenous metoclopramide and prochlorperazine, and subcutaneous sumatriptan should be offered to eligible adults who present to an ED with acute migraine (Should offer-Level B). Dexamethasone should be offered to these patients to prevent recurrence of headache (Should offer-Level B). Because of lack of evidence demonstrating efficacy and concern about subacute or long-term sequelae, injectable morphine and hydromorphone are best avoided as first-line therapy (May avoid-Level C)."[42]

Vécsei et al found that high-quality randomized trials of SM treatment in the ED are lacking. The current data suggest the use of the following: IV fluids, corticosteroids, magnesium sulfate, anticonvulsive drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), antiemetics, and serotonergic agents.[37]

Repeated doses of triptans are unlikely to provide added relief nor will they prevent recurrence of attacks.[43,44] DHE and triptans should not be administered within 24 hours of the other. Concomitant administration of triptans and DHE (or ergotamine) within a 24-hour period is contraindicated due to the risk of elevated blood pressure and coronary artery vasoconstriction.[45]

Case reports and small case series report efficacy for SM with the following: IV valproate for pediatric and adult;[46,47] DHE;[35] IV droperidol;[48] IV magnesium;[49] IV methylprednisolone for SM with migrainous vertigo;[18] IV levetiracetam;[50] general anesthesia;[51] and ziprasidone (10-40 mg).[52]

Corticosteroids.—A systemic review of 25 studies with a total of 3989 patients found that corticosteroids were most effective in cases of "higher disability, prolonged migraine duration, SM, incomplete pain relief, and headache recurrence."[53] Parenteral dexamethasone is the most commonly used steroid in the emergency room setting and has level C evidence for its use in SM in adults.[53,54] A randomized, double-blind, placebo-controlled multicenter trial of 205 adult ED patients with migraine found no statistical benefit between 10 mg of IV dexamethasone and placebo in terms of pain freedom at the time of ED discharge.[40] However, a subgroup analysis of 45 patients with SM revealed that more patients in the active treatment group reached pain freedom at the time of discharge compared to placebo (64% vs 39%, respectively) and IV dexamethasone was more effective than placebo in preventing headache recurrence at 24 hours (38% vs 13%, respectively). For adults, suggested doses of dexamethasone range from 4 to 16 mg IV.[55] Steroid use in the pediatric population has not been well studied and recommendations for their use as treatments for SM have not been made.[56]

There is a small risk of significant adverse events with short-term corticosteroid use including aseptic osteonecrosis,[57] sepsis, venous thromboembolism, and fracture.[58]

IV fluids.—In addition to providing fluid repletion, there is some evidence that IV fluids alone, such as 500-1000 mL of 0.9% normal saline solution,[37] can provide headache pain relief.[55] One study found evidence that dehydration lowers pain thresholds as well as leads to increased pain-related brain activity in the insula, thalamus, and anterior cingulate cortex; rehydration with enteral fluids reportedly reverses these findings.[59] However, single studies in adults[60] and children[61] did not find benefit from IV fluids.

Sedatives and Anesthetics.—The rapid-acting anesthetic agent ketamine is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist that has been shown to have pain-relieving properties. "In low doses, ketamine causes analgesia and sedation, whereas in high doses, it produces general anesthesia."[62] A small randomized control trial (RCT) of 17 patients with migraine found that a single dose of 0.08 mg/kg of ketamine given subcutaneously resulted in a 50% reduction in acute pain compared to placebo.[63] However, another RCT of 34 adult ED patients with migraine found that 0.2 mg/kg of ketamine IV was not an effective acute treatment.[64] Intranasal formulations of ketamine are available and have been studied in migraine treatment.[65] To evaluate intranasal ketamine's utility in the ED setting, the treatment of headache with Intranasal Ketamine Trial compared the following treatments in 53 subjects with primary headache disorders: (1) a combination of IV metoclopramide and diphenhydramine in normal saline and intranasal normal saline and (2) intranasal ketamine with IV normal saline placebo.[66] Results showed that intranasal ketamine was not superior to IV metoclopramide; however, the study suggests that intranasal ketamine may have pain-reliving effects comparable to IV migraine abortive therapies. A review of treatment trends in the ED found an increase in ketamine use in pediatric patients presenting with lacerations and skeletal fractures;[67] however, there is a lack of studies evaluating the use of ketamine specifically for acute migraine treatment in the pediatric population. One longitudinal cohort study of 63 pediatric patients treated at a tertiary care center for various chronic pain conditions, including migraine (13%), reported that "ketamine-associated reductions in pain scores were the largest in postural orthostatic tachycardia syndrome and trauma patients and the smallest in patients with chronic headache."[68] Ketamine currently has grade D recommendation for its acute use in conditions such as migraine.[62]

Propofol may be an effective acute treatment option for migraine.[42] ED-administrations of low dose propofol led to greater pain reduction in pediatric patients with migraine when compared to patients who received a standard combination of prochlorperazine, NSAID, and diphenhydramine (80.1% vs 61.1%, $P < .05$).[69] In addition, those that received propofol were discharged from the ED 80 minutes earlier than those that received standard treatment. An RCT of 66 pediatric patients found that IV propofol was as effective as an IV combination of metoclopramide, ketorolac, and diphenhydramine in reducing migraine pain in an ED setting and that treatment with combination treatment was associated with a higher number of rebound headaches compared to propofol.[70] Propofol has also shown effectiveness in treating SM in adults. Eight patients with migraine lasting >72 hours despite prior treatment with triptans, NSAIDs, opiates, and steroids were treated with IV boluses of 10 mg of propofol for every 5 minutes until a change in pain severity was seen.[71] Improvement was seen in all subjects, occurring within 5-30 minutes of administration of propofol. Doses needed for the therapeutic effect ranged from 10-60 mg. At follow up 72 hours later, 5 subjects remained headache free, while 2 developed moderate headaches 24 and 36 hours later; both of these headaches responded to treatment with NSAIDs. Propofol was also found to be superior to 6 mg of sumatriptan SC in relieving migraine pain at 30 minutes.[72]

Lidocaine has utility both as an anesthetic as well as an antiarrhythmic.[73] A trial of 76 adult ED patients with migraine compared 1 mg of IV DHE (repeated once in 30 minutes if needed), 12.5 mg of IV chlorpromazine (given in 20-minute intervals as needed, maximum dose of 37.5 mg), and 50 mg of IV lidocaine (given in 20-minute intervals as needed, maximum dose of 150 mg) and found that while chlorpromazine was the most effective acute migraine treatment, lidocaine IV resulted in a 50% reduction in pain severity with little

adverse effects.[74] To the authors' knowledge, studies evaluating IV lidocaine for acute migraine treatment in the pediatric ED population are not available. However, pediatric and adolescent patients with SM and refractory headache treated with IV lidocaine infusions in an intensive care unit show improvement in headache severity and good tolerability to treatment.[75,76]

Peripheral Nerve Blocks.—Nerve blocks can be administered in the areas of the supraorbital, supratrochlear, auriculotemporal, and occipital nerves. The GON is most commonly injected; however, the site of injection is also influenced by the location of head pain and focal tenderness found on the examination of the scalp. Injection method varies, depending on the provider's training and experience. A 2016 survey of pediatric and adolescent headache specialists found that SM was one of the most common conditions considered appropriate for treatment with nerve blocks.[77] The most common local anesthetics used in nerve blocks are lidocaine 1%-2%, bupivacaine 0.5%, or a combination of the two. A trial comparing GON (1 mL of 0.5% bupivacaine mixed with 1 mL of normal saline), IV treatment (50 mg of dexketoprofen trometamol and 10 mg of metoclopramide), and placebo (1 mL of normal saline injected in the area of GON) in 60 adult ED patients found that injection of 0.5% bupivacaine was as effective as IV dexketoprofen and metoclopramide in decreasing headache pain severity within 30 to 45 minutes of treatment.[78] Interestingly, Young et al reported that an injection of 1 mL of a 50-50 mix of 2% lidocaine and 0.5% bupivacaine over the occipital ridge not only resulted in the reduction of migraine pain, but also decreased allodynia and photophobia within 5 minutes of administration.[79]

ED Treatment Summary.—Table 4 provides a summary of SM treatments commonly used in the ED.

Hospitalization.—In 2008, over 50,000 hospitalizations in the US were related to migraine.[80] Inpatient treatment of headache should be considered in cases of (1) severe dehydration or intractable vomiting (2) persistent headache despite adequate attempts in an emergency or urgent care setting (3) persistent headache despite adequate attempts in an outpatient infusion center or no access to an outpatient infusion center (4) intractable headache associated with overuse of acute medications necessitating detoxification or (5) existence of comorbid medical or psychiatric conditions that require monitoring or concurrent treatment.[81,82] In addition, individuals experiencing a significant headache-related disability that threatens their ability to work, attend school, or engage in family and social activities may need to be admitted (Table 5). The goals of inpatient headache treatment will vary based on the indication for admission. Specifically, for SM, the goal should be the resolution of headache by the time of discharge. Ideally, patients should maintain headache freedom for at least 72 hours after treatment.[55]

Inpatient treatment of SM utilizes many of the same treatments used in the acute or emergent setting (Table 4); however, treatment is usually given via slow infusions rather than bolus. Repetitive IV DHE given per the "Raskin protocol" is a mainstay of inpatient headache treatment.[83] The "Raskin protocol" was first reported in 1986 and used repetitive dosing of DHE (0.3 to 1 mg) and metoclopramide every 8 hours. Compared to a group receiving diazepam intravenously every 8 hours, adults who received DHE became headache free within 2 days (compared to 3-6 days in the diazepam group). In addition, 39 participants in the DHE group were able to maintain improvement in headache up to 16 months after treatment. IV dihydroergotamine should be infused slowly over 10 to 15 minutes to reduce the side effects of nausea, flushing, and chest tightness. An average starting dose is 0.5 mg; however, doses up to 1 mg are also used. An exacerbation of headache may be experienced by some patients receiving DHE; however, this does not alter the response to treatment and should not be taken as an indication to stop treatment.[84]

IV lidocaine infusion is available in some hospitals and headache centers. It is most commonly used for adult headache treatment; however, children with SM have shown benefit from it as well.[75] Twenty-six patients' ages 10-19 years old were treated with IV lidocaine for an average of 4 days. Treatment consisted of IV lidocaine at doses ranging from 1.125 to 2.25 mg/kg/hr Pain relief of 50% was seen at 16 hours of treatment and complete resolution of pain occurred by 19 hours. A retrospective survey of 71 adults with chronic daily headache and medication overuse who had been treated with lidocaine infusion for 7 to 10 days reported that 90% experienced improvement in

Table 4.—Summary of Status Migrainosus Treatments in the Emergency Room Setting

Treatment	Recommended Adult IV Dosing	Recommended Pediatric IV Dosing	Clinical Considerations
Sumatriptan	6 mg	6 mg (>30 kg) 3 mg (<30 kg)	Triptans, ergots, and ergot derivatives should not be used together within a 24-hour period; cautious use in those with cardiovascular risk factors
DHE	1 mg	0.5-1 mg (age > 10 years old and/or weight > 25 kg)	
0.9% Normal Saline	500-1000 mL	10 mL/kg	Avoid fluid overload, monitor cardiopulmonary status
Acetaminophen	1000 mg	15 mg/kg	Contraindicated in hepatic dysfunction
Ibuprofen	400-800 mg	7.5-10 mg/kg	Caution in those with risk of gastrointestinal bleed. Avoid the use of ketorolac within 6 hours of other NSAIDS
Ketorolac	30-60 mg	0.5 mg/kg; max dose 30 mg	
Diphenhydramine	25-50 mg	0.5 mg/kg; max dose 25 mg (age > 8 years old)	Use as adjunctive treatment to prevent extrapyramidal symptoms (EPS) from dopamine-receptor antagonists
Dexamethasone	4-16 mg	—	More effective for preventing attack recurrence. Limit use to <6 times per year; risk of avascular osteonecrosis with any dose
Prochlorperazine	10 mg	0.15 mg/kg; max dose 10 mg (age > 2 years)	Risk of EPS; pretreat with diphenhydramine. Contraindicated in prolonged QTc
Haloperidol	2-5 mg	—	Risk of EPS; pretreat with diphenhydramine
Metoclopramide	10 mg	0.1-0.2 mg/kg; max dose 10 mg	Infuse slowly over 15 minutes to decrease the risk of sedation and EPS
Magnesium Sulfate	500-2000 mg	30 mg/kg; max dose 2000 mg	Can cause hypotension and facial flushing
Sodium valproate	500-1000 mg within 15 minutes	15 mg/kg; max dose 1000 mg	Administration in patients on oral topiramate may lead to hyperammonemia with encephalopathy
Levetiracetam	500-1500 mg	—	Can cause somnolence or irritable/hostile behavior
Ketamine	0.3 to <1 mg/kg bolus	0.1-0.3 mg/kg/hr	Doses of 1 mg/kg or greater cause dissociative sedation
Propofol	10-40 mg initial bolus + 10-20 mg additional boluses (max dose 120 mg)	0.25 mg/kg every 5-15 minutes (max dose 30 mg)	Also relieves nonheadache migraine symptoms such as nausea, photophobia, and phonophobia
Lidocaine	50 mg every 20-min (max dose 150 mg)	40-60 mcg/kg/min, infused over 2 hours	May cause tinnitus, dysrhythmias, hallucinations, and toxicity. Caution in patients with renal or heart failure

their headache, with 60% having no headache at the time of discharge.[85] Dose given was 2 mg/min. Patients admitted for IV lidocaine should have continuous cardiac monitoring, while receiving treatment.

In the inpatient setting, continuous infusion of valproate may be more practical than bolus administrations due to valproate's short half-life.[46] A protocol consisting of an initial 20 mg/kg loading dose of VPA, followed by a continuous infusion of 1 mg/kg/hr has been used in pediatric patients with SM, with 66% reporting excellent response to treatment. Serum

Table 5.—Indications for Inpatient Headache Treatment

- Severe dehydration or intractable vomiting
- Existence of comorbid medical or psychiatric conditions that require monitoring or concurrent treatment
- Persistent headache despite adequate attempts in an emergency or urgent care setting
- Persistent headache despite adequate attempts in an outpatient infusion center or no access to an outpatient infusion center
- Intractable headache associated with overuse of acute medications necessitating detoxification
- Headache with high level of headache-related disability that threatens an individual's work/education/ability to function

concentrations of VPA are checked 2-4 hours after the start of infusion, and again approximately 20 hours later. Once headache is relieved, patients are switched to oral VPA, using the same dose they had received during infusion treatment.

Prognosis.—Given that SM is an exacerbation of a primary migraine disorder, adequate treatment should lead to resolution and a return to the individual's baseline headache pattern. Beltramone and Donnet found that, among patients with SM, "all patients with low-frequency migraine attacks before SM returned to low-frequency migraine attacks after. Among patients with high-frequency migraine attacks (n = 4) half returned to high frequency, one to low frequency and one to chronic migraine."[6]

For those that require inpatient headache treatment, prolonged length of stay "can serve as an indirect indicator of poor headache control and/or a refractory underlying primary headache disorder."[86] A retrospective chart review of 4325 patients admitted for a primary diagnosis of SM between September 2008 and December 2011 found that African American women and those with chronic renal failure, congestive heart failure, opioid abuse, and/or mood disorders were more likely to have prolonged length of stay compared to those who did not fit those criteria. This study suggests that these individuals may be at increased risk of refractory headaches and SM, leading to decreased treatment response and prolonged hospitalization.

Legault et al performed a retrospective study in 187 children of 8 to 17 years of age who were treated in the ED for SM in 2008.[87] Within 1 month of headache treatment, 11.2% returned to the ED. No current treatment provided in the ED for SM altered the immediate recurrence rate.

Studies in both the adult and pediatric population suggest a link between migraine and suicidal behavior, with an increased association seen in those with chronic migraine and migraine with aura.[88-91] SM may also increase the risk of suicidality. A population-based study of adult Taiwanese patients diagnosed with either SM (n = 13,605) or migraine (n = 21,485) found that those with SM had a 1.81-fold risk of attempting suicide compared to a control group that did not have either diagnosis.[92] In addition, compared to men, individuals older than 50 years, and those who made ≥20,000 New Taiwan Dollars per month, patients with SM who were female, younger than 50 years old, and had a low monthly income had increased risk of suicide attempt (adjusted hazard ratios of 2.67, 3.27, and 2.44, respectively). There was no increased risk of suicide attempt in those with migraine without SM when compared to the comparison group.

Prevention.—It is not known if starting a migraine preventive treatment at the time of SM will shorten the duration. If headaches were frequent prior to SM, preventive medication may be indicated.

Since a cure for migraine has not yet been discovered, control over the disease is the primary goal. As discussed earlier, several triggers and risk factors can predispose an individual to increased attacks and SM. Modifications of these factors may help "prevent" the development of SM.

Hormonal changes associated with menstruation can lead to SM. Perimenstrual prophylaxis, or "mini prophylaxis," using frovatriptan, a 5HT (5-hydroxytryptamine) 1B/1D receptor agonist with a half-life of 26 hours, has been shown effective in reducing the attacks of menstrual migraine (MM).[45] "Data from RCTs for perimenstrual prophylaxis show a significant reduction in risk of MM in women using frovatriptan 2.5 mg QD or BID for 6 days compared with placebo, with no evidence of delayed or rebound headache following treatment."[45] Mini prophylaxis of MM is most effective in women with regular, predictable menstrual cycles, whose headaches occur on a consistent day in relation to flow.[93]

As per the ICDH-3, medication overuse is defined as a regular intake of triptan, ergotamine, combined analgesic, or opioid medications on 10 or more days per month, or regular use of APAP or NSAID medications on 15 or more days per month.[11] Overuse of abortive headache treatments can lead to the chronification of migraine, which is associated with decreased response to both acute and preventive migraine treatments. This decreased response can lead to SM. With treatment, however, "approximately 50% of patients with chronic migraine revert to episodic migraine after drug withdrawal."[94,95] It is important that physicians inform their patients that an initial worsening of their headaches, signifying withdrawal, can occur and last for several weeks.

CONCLUSION

SM is a clinically significant complication of migraine with or without aura. The case presented in this review illustrates several important points regarding SM. First, the patient was found to have a normal neurological exam, with no red flags in her headache history, and a headache that was similar to previous migraine attacks she had in the past. In this scenario, no further workup of her headache was needed. However, when caring for chronic pain patients, such as those with migraine, it is important to keep in mind that secondary headaches can arise at any time, and that even an attack that fits the classic definition of SM warrants a thorough investigation. Second, the patient had several migraine abortive treatment options at home, allowing her to appropriately treat her migraine attack prior to calling her physician. When combined with triptans or dihydroergotamine, creative combinations of acute migraine treatments may be enough to keep patients at home, without the need for emergency care. A key strategy in "preventing" SM is proper education of both the provider and the patient. Providers should be able to recognize risk factors that place their patients at risk for SM so that modifications and treatment plans can be made. Patients should be educated on the proper use of their migraine treatments to avoid not only overuse, but under treatment as well. A common practice among patients is to delay acute treatment until pain is severe or until they are "sure" the attack is truly migrainous.[96,97] Several studies, however, have reported improved response when acute treatments are taken earlier, especially in those who develop allodynia.[98-100] When taken earlier, either during mild to moderate pain, or prior to the development of allodynia, appropriate abortive treatment use can "result in decreased migraine burden by reducing total migraine headache duration."[101]

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