Status migrainosus

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Introduction

This article includes discussion of status migrainosus, intractable migraine, and pernicious migraine. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

Status migrainosus is an attack of severe migraine lasting more than 72 hours accompanied by debilitating symptoms and is not attributable to another disorder. Status migrainosus may occur in migraineurs with or without aura.

For patients presenting with the first or worst prolonged headache, a thorough neurologic evaluation with collateral imaging and/or spinal fluid sampling is indicated to assess for secondary causes of pain.

In a patient with underlying diagnosis of migraine and without a secondary attributable cause of prolonged headaches, focus should be on swift and effective treatment with the primary aim of aborting the migraine.

Historical note and terminology

The term “status migrainosus” was first used by Taverner in 1978 to describe “severe and prolonged, or frequently repeated migraine” (Taverner 1978).

The Headache Classification Committee of the International Headache Society formally defined status migrainosus with subsequent updates in the 2nd and 3rd (beta) editions of the ICHD. The most recent diagnostic criteria for status migrainosus according to the 2013 third (beta) edition of the International Classification of Headache Disorders is reviewed below:

Table 1. International Headache Society Diagnostic Criteria for Status Migrainosus

**Description:** A debilitating migraine attack lasting for more than 72 hours

**Diagnostic criteria:**

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 more than 72 hours
   2. Pain and/or associated symptoms are debilitating

D. Not better accounted for by another ICHD-3 diagnosis

(Headache Classification Committee of the International Headache Society 2013)

Clinical manifestations

Presentation and course

Status migrainosus, by definition, must occur in a patient with underlying diagnosis of migraine. Therefore, physicians should review the patient’s history for symptoms of migraine as part of the diagnostic process.

Commonly, patients with status migrainosus report a headache that is typical of their usual migraines (with or without aura) with the exception of prolonged duration of pain and associated symptoms (eg, nausea, vomiting, photophobia, phonophobia, osmophobia) with refractoriness to their usual treatments. Precipitants of status migrainosus in a migraineur include medication overuse, menstruation/other hormonal changes, stress, dietary factors (eg, alcohol intake or fasting), anxiety, and depression. A review of possible triggers is warranted to aid diagnosis and treatment.

In those with migraine with aura, the aura itself should be similar to the patient’s usual auras; entirely new or
prolonged auras different from the patient’s usual experiences should warrant further investigation into potential secondary causes (eg, seizure, intracranial mass, stroke). Pain that is drastically different in character or quality from patients’ usual migraines should always raise the clinician’s suspicion for secondary causes of headache.

When an attack of migraine headache lasts more than 72 hours, it is defined as status migrainosus. When it lasts much longer, it may become designated as chronic (previously known as transformed) migraine. In this process of transformation, headache frequency increases, and the historical characteristics used to differentiate migraine from episodic tension-type headache diminish as pain intensity and associated migrainous features become less prominent. No clear distinction is made between chronic migraine and prolonged status migrainosus because no upper time limit is given to status migrainosus. Episodic migraine may or may not transform into chronic migraine through a bout of status migrainosus. Both are intractable headaches and are often associated with abortive medication overuse and comorbid psychological conditions.

**Prognosis and complications**

Status migrainosus is typically a complication of episodic migraine. With adequate treatment, most patients with status migrainosus can achieve pain reduction.

For a certain group of migraineurs, increased frequency and duration of migraine attacks (some of which may reach criteria for status migrainosus) can lead to transformation from episodic to chronic migraine (Table 2). The yearly rate of transformation from episodic to chronic migraine has been estimated to be approximately 2.5%, with risk factors of high baseline attack frequency, older age, obesity, stressful life events, and use of certain medications such as barbiturates and opiates (Bigal et al 2008; Lipton 2009). Compared to those with episodic migraine, patients with chronic migraine are more likely to suffer socioeconomic impacts, more psychiatric and medical comorbidities, reduced quality of life, and lower social and occupational function (Manack et al 2011).

Status migrainosus and chronic migraine are the most frequent complications of migraine, but other important complications include persistent aura without infarction, migrainosus infarction, and migraine aura-triggered seizure.

### Table 2. International Headache Society Diagnostic Criteria for Chronic Migraine

**Description:** Headache occurring on 15 or more days per month for more than 3 months, which has the features of migraine headache on at least 8 days per month

**Diagnostic criteria:**

A. Headache (tension-type-like and/or migraine-like) on ≥ 15 days per month for > 3 months and fulfilling criteria B and C

B. Occurring in a patient who has had at least 5 attacks fulfilling criteria B-D for 1.1 Migraine without aura and/or criteria B and C for 1.2 Migraine with aura

C. On ≥ 8 days per month for > 3 months, fulfilling any of the following:
   1. Criteria C and D for 1.1 Migraine without aura
   2. Criteria B and C for 1.2 Migraine with aura
   3. Criteria A and B for 1.5 Probable migraine

D. Not better accounted for by another ICHD-3 diagnosis

**Clinical vignette**

A 33-year-old woman presented to the local emergency department with a severe right-sided headache for the past 3 days associated with nausea and repeated vomiting. 

**Sumatriptan** injections, which usually successfully treat her headaches, did not work this time, and the over-the-counter medication did not help at all. Her last sumatriptan injection was 36 hours prior to arrival in the emergency department. She has a long history of episodic headaches that usually occur near menstruation and are accompanied by nausea, vomiting, photophobia, and phonophobia. This headache is typical of her usual headaches, but of longer duration and increased severity. Her father died in the past week and her headache has been worsened by the stress surrounding this event.
Head CT performed in the emergency room was normal. The patient was treated with intravenous DHE and metoclopramide. Her headache subsided, and she was sent home the next morning.

Comment. This is a fictitious case.

Biological basis

Etiology and pathogenesis

Status migrainosus is 1 of the many clinical manifestations of migraine disorder and its etiology is related to the underlying causes of migraine itself. Migraine is a polygenic syndrome with non-Mendelian inheritance and significant gene-environment interactions (Friedman and De ver Dye 2009; Schürks 2012). A comprehensive review of the pathogenesis of migraine is provided in a separate MedLink Neurology article on migraine. Here, the discussion is focused on status migrainosus.

Couch and Diamond reviewed the causative and therapeutic aspects of status migrainosus by polling the members of the American Association for the Study of Headache (now the American Headache Society) (Couch and Diamond 1983). From 126 questionnaire responses, factors physicians believe to be triggers for status migrainosus included emotional stress, depression, abuse of medications, anxiety, diet, hormonal factors, and multiple nonspecific factors. An internet-based survey of migraineurs' self-reported migraine triggers showed similar factors of stress, lack of sleep, diet, hormonal changes, and other environmental factors (Migraine in America 2012).

Patients with frequent or severe headache are at risk for escalating use of analgesics, opioids, ergotamine, or a combination thereof. Overuse consists of regular daily use of simple or combination analgesics containing barbiturates or sedatives more than 3 times a week, ergotamine tartrate more than twice a week, or triptans more than 3 times a week (Silberstein and Lipton 2001). Overuse can result in a number of serious consequences including status migrainosus, development of chronic migraine, and refractoriness to acute treatment. In the American Migraine Prevalence and Prevention Study, compared to participants using acetaminophen, participants using barbiturates (OR = 2.06, 95% CI = 1.3-3.1) or opioids (OR = 1.98, 95% CI = 1.4-2.2) were more likely to have transformation of episodic migraine to chronic migraine within 1 year (Bigal et al 2008). Stopping the symptomatic medication usually causes withdrawal symptoms, a period of increased headache, and eventually headache improvement in many, but not all, patients (Silberstein and Lipton 2001).

Epidemiology

Migraine itself is a common disorder affecting approximately 17% of women and 6% of men based on a 120,000 person survey as part of the American Migraine Prevalence and Prevention Study (Bigal et al 2008). A portion of migraineurs, amounting to 2% of the general population, have chronic migraine (Manack et al 2011).

The prevalence of status migrainosus, as a separate entity from chronic migraine, is not reported. Patients with high headache burden are at higher risk for developing status migrainosus, but it can also occur in those with infrequent or well controlled migraines, particularly if precipitated by triggers such as illness or stress.

Prevention

Patients with undertreated or inappropriately treated migraines are at risk for developing status migrainosus.

Many patients with migraine have milder tension-type headaches in between disabling episodes of migraine or status migrainosus. The current consensus is to treat the mild headache of migraine before it becomes severe (Evers et al 2009). Early treatment of migraine pain can reduce headache time and disability (Burstein et al 2000; Silberstein 2000). Migraine headache may progress to involve cutaneous allodynia through a process of central sensitization (Burstein et al 2000) after which abortive medications such as triptans may have reduced efficacy (Landy et al 2004).

Differential diagnosis

The differential diagnosis for a severe and prolonged headache is numerous. As there is no confirmatory laboratory or imaging test for migraine, clinical history is key to narrowing the differential diagnosis and deciding on appropriate investigations. In Table 3, the differential diagnosis based on the presenting characteristics is reviewed.
Table 3. Differential Diagnosis of Status Migrainosus*

**Acute single headache**
- Cerebral venous sinus thrombosis
- Reversible cerebral vasoconstriction syndrome
- First attack of migraine
- Acute glaucoma
- Hypertensive encephalopathy
- Meningitis
- Pituitary apoplexy
- Postconcussion or posttraumatic syndrome
- Retroclival hematomas
- Sinusitis
- Spontaneous intracranial hypotension
- Subarachnoid hemorrhage
- Systemic infection

**Acute recurrent headache**
- Reversible cerebral vasoconstriction syndrome
- Cerebral tumors
- Cerebrovascular insufficiency
- Idiopathic intracranial hypertension
- Intermittent hydrocephalus
- Migraine
- Subarachnoid hemorrhage

**Subacute headache (days or weeks)**
- Brain abscess
- Pseudotumor cerebri
- Subdural hematoma
- Temporal arteritis (in elderly)
- Chronic daily headache (months or years)
- Analgesic rebound
- Chronic tension-type headache
- Psychiatric state
- Tumor

*(List is not all inclusive.)*

In a series of 3799 patients who were seen over a 3-month period at an emergency headache center in Paris, 3299 patients (86.3%) were diagnosed with primary headaches; 244 (6.4%) had secondary headaches, 38 (1%) cranial neuralgias, and 218 patients (5.7%) had no precise diagnosis (Ducros et al 2001). Sinusitis was the most frequently reported cause of secondary headache (66 patients, 1.7%), followed by post-traumatic headache (58 patients, 1.5%) and CSF hypotension (24 patients, 0.6%). Vascular disorders were detected in only 20 patients (0.5%), including subarachnoid hemorrhage (7), cervical artery dissection (5), and cerebral venous thrombosis (2).

Serious vascular conditions were rare but often misleading, presenting only with headache and without the other classical signs of these conditions. New or changed headaches should always prompt a careful history and exam in addition to neuroimaging study or CSF studies before diagnosing a primary headache.

**Acute headache.** The first or worst attack of apparent status migrainosus requires careful history, examination, and other appropriate studies to assess for secondary causes of headache. Changes in awareness or cognition are atypical for migraine and always require further assessment. Older patients presenting with their first headache are less likely to have migraine and should be evaluated for underlying inflammatory disease, CNS tumors, or infection.

The first or worst attack of migraine may be difficult to differentiate from a subarachnoid hemorrhage, particularly if the pain is of acute onset (thunderclap headache). Meningitis or meningoencephalitis is possible if the headache is associated with a febrile illness, stiff neck, and changes in cognition; under these circumstances, neuroimaging and lumbar puncture can be used to confirm the diagnosis. Nonbacterial (aseptic) meningitis may be more difficult to
Chronic migraine.

Patients with acute purulent sinusitis are usually acutely ill and febrile and with localized pain and tenderness. This disorder is more difficult to diagnose when it involves the sphenoid sinus, which is not accessible to direct clinical examination and may not be seen clearly on routine radiologic examination.

Spontaneous internal carotid or vertebral artery dissection occasionally causes headache and acute neurologic deficits. Headache, the most common symptom, is often unilateral. In the case of carotid dissections, pain is located in the orbital, periorbital, and frontal regions; in the case of vertebral dissections, pain is located in the cervical region (Schwedt 2015). The pain is usually moderate to severe and steady or throbbing in nature. A history of head or neck trauma (even if minor), bruit, or Horner syndrome may assist in the diagnosis of vascular dissection. Focal cerebral symptoms (transient ischemic attack or stroke) can precede the headache, but frequently follow it by as long as 2 weeks. Imaging of the cervical arteries with CTA, MRA, or traditional arteriography should be performed to confirm the diagnosis.

Reversible cerebral vasoconstriction syndrome is a recently characterized syndrome that can cause nonaneurysmal thunderclap headache. In a prospective study of patients with nonaneurysmal thunderclap headaches treated in a hospital in the Netherlands, 8.8% of those who consented for follow-up were subsequently diagnosed via vascular imaging to have reversible cerebral vasoconstriction syndrome (Grooters et al 2014). The presentation of reversible cerebral vasoconstriction syndrome commonly consists of recurrent thunderclap headaches over the course of a week with a female predominance (Ducros et al 2007). The vascular constriction is thought to occur due to dysregulation of cerebral arterial tone. Triggers of reversible cerebral vasoconstrictive syndrome (Ducros et al 2007; Chen et al 2010) include disorders affecting autonomic balance (eg, catecholamine secreting tumors), illicit drugs (eg, cocaine, amphetamines, cannabis), alpha-sympathomimetic drugs (eg, pseudoephedrine), hormonal changes (eg, pregnancy, postpartum status), and severe stress (eg, surgery or trauma). As the large vessel vasoconstriction associated with reversible cerebral vasoconstriction syndrome may not be angiographically visible until several weeks after onset of clinical symptoms, there must be a high clinical suspicion based on history in order to correctly follow and diagnose the condition (Ducros 2007). For those suspected of having reversible cerebral vasospasm syndrome, follow-up with vascular imaging via MRA, CTA, conventional angiography, and/or transcranial Doppler ultrasound may be necessary (Chen et al 2010; Schwedt 2015). Although most patients with reversible cerebral vasoconstriction syndrome had spontaneous resolution of angiographic vasoconstriction in weeks to months, a significant percentage suffered ischemic complications (transient ischemic attack or infarct at 16% and 4% respectively), cerebral hemorrhage (6%), posterior reversible encephalopathy syndrome (9%), and seizure (3%) (Ducros et al 2007). Although the long-term risk of reversible cerebral vasospasm syndrome recurrence is unclear, patients with reversible cerebral vasoconstriction should avoid subsequent exposure to vasoactive substances.

Idiopathic intracranial hypertension (pseudotumor cerebri) may occur with or without papilledema and mimic either migraine or tension-type headache. Patients typically have risk factors of female gender, young age, and obesity. The presence of these risk factors, a history of pulsatile tinnitus, and transient visual obscurations with Valsalva are suggestive of pseudotumor. Physical findings may include papilledema or cranial nerve palsies. The diagnosis is made with a spinal tap that is performed with the patient lying down either in the lateral decubitus or prone position (not seated). Opening pressures greater than 25 cm of water may be consistent with this diagnosis (Friedman et al 2013).

Status migrainosus epilepticus, or an ictal epileptic event presenting as acute migraine, gained attention in 2009 and may be underappreciated. Although ictal headaches are typically paroxysmal, brief, non-specific in character, and occur in association with other ictal phenomena, awareness of the possibility is appropriate in cases of status migrainosus refractory to most therapies, but responsive to antiepileptics (Striano et al 2011).

**Subacute headache.** A new headache that has been present for days or weeks may be the beginning of a chronic daily headache or prolonged status migrainosus. The differential diagnosis is, of course, quite broad, and appropriate medical and neurologic investigation is warranted.

**Chronic nonprogressive headache.** Chronic daily headache may be related to analgesic overuse, pseudotumor cerebri, systemic disease (eg, sleep apnea), or underlying psychopathology. Patients may present to the emergency department having exhausted their coping skills (“last straw syndrome”).

**Chronic migraine.** Patients with chronic daily headache frequently have a history of episodic migraine (with or
without aura) that evolves into chronic daily headache, sometimes as a result of symptomatic medication overuse (Mathew et al 1990; Silberstein and Lipton 2001). The symptoms of chronic migraine include the progressive intensification of severe, debilitating pain accompanied by the usual characteristics of acute migraine (nausea, vomiting, light sensitivity, etc.) and by increasing prostration. Dehydration, electrolyte alterations, autonomic disturbances, and emotional despair are frequently present. Chronic migraine may evolve from episodic migraine through status migrainosus. Because there is no upper limit to the length of an episode of status migrainosus, no clear distinction is made between these disorders.

**Chronic tension-type headache.** Chronic daily headache may also develop in patients with a history of episodic tension-type headache or it may begin de novo and meet the International Headache Society criteria for chronic tension-type headache. The headaches are often diffuse and bilateral, frequently involve the posterior aspect of the head and neck, and may have some migrainous features. The major difference between chronic tension-type headache and chronic migraine is the absence of a clear history of episodic migraine in patients with the former condition (Silberstein and Lipton 2001).

**New daily persistent headache.** New daily persistent headache is a relatively newer primary headache diagnosis. In this disorder, patients develop a headache that becomes constant/unremitting within 1 day of onset in the absence of a clear history of episodic migraine or tension-type headache. Some remember the exact day or time the headache started. Patients with new daily persistent headache are generally younger than those with chronic migraine.

**Diagnostic workup**

An extensive neurologic evaluation, including CT or MRI scan and lumbar puncture, is indicated in patients presenting with their first or worst prolonged headache, particularly if it is of sudden onset or associated with focal neurologic signs, stiff neck, or changes in cognition. Follow-up vascular imaging may be indicated for those with suspected reversible cerebral vasoconstriction syndrome as vascular changes may not be apparent on imaging until several weeks later (Chen et al 2010; Schwedt 2015).

**Management**

There are few large series or double-blind treatment trials in status migrainosus, although reports of isolated migraine attacks include patients whose attacks approximate the 72-hour criterion mentioned above.

Many patients present to the hospital emergency department, either at the recommendation of their treating primary physician or on their own, for evaluation and treatment of severe persistent headache. The initial and paramount goal of the emergency department team is to establish whether there is a serious and/or life-threatening secondary cause of the head pain. Assuming an appropriate and thorough evaluation has taken place in the emergency department, the next decision is to identify the most appropriate venue for continued treatment: the emergency department, inpatient hospitalization, outpatient treatment, or some combination thereof.

The treatment of status migrainosus often takes place in the emergency department initially, with a goal of breaking the pain cycle or decreasing the severity significantly. The emergency department staff may choose to send a patient home with a specific abortive therapy for the head pain. Prescriptions for opioids or butalbital are not recommended. Lifestyle changes, prophylactic medications, or comorbid psychological conditions may be broached during the emergency department visit and should be further addressed by outpatient physicians.

Acute inpatient hospitalization for the treatment of migraine should be considered in the appropriate circumstances (see Table 4), and the goals of admission should be clearly defined.

In addition to treatment of severe pain, hospitalization should address concurrent medication overuse, particularly of drugs containing butalbital or opiates, as the detoxification progress can be difficult and requires symptomatic treatment to prevent dehydration from intractable nausea or vomiting, seizures, or other severe acute withdrawal effects (Table 5).

**Table 4. Hospital-Based Treatment Options**

The principles of treatment for status migrainosus include the following:
Fluid and electrolyte replacement (if indicated)

Drug detoxification

Intravenous pharmacotherapy to control pain

Treatment of associated symptoms of nausea and vomiting

Concurrent implementation of migraine prophylaxis (if indicated)

Criteria for hospital-based treatment include severe, intractable headache accompanied by (1) dehydration (requiring parenteral therapy for pain interruption); (2) dependence on analgesic or ergotamine medication; or (3) significant comorbid neurologic, medical, or psychiatric illnesses (Silberstein et al 2001).

Table 5. Detoxification guidelines

- Fluid replacement for 24 to 48 hours
- Ergotamine tartrate can be discontinued abruptly if dihydroergotamine is administered. Otherwise, it should be tapered over 2 to 3 days.
- Analgesics not containing opiates or barbiturates can be stopped abruptly.
- Combined analgesics containing barbiturate should be discontinued gradually. Rapid discontinuation can be achieved by giving phenobarbital.
- Opioid withdrawal must be carried out slowly or through replacement with methadone and subsequent rapid taper. Side effects can be reduced by giving clonidine hydrochloride, phenobarbital, or a benzodiazepine derivative (Nicholls et al 2010).

(Silberstein and Lipton 2001)

Treatment of status migrainosus should be tailored to the patient's history, medication tolerances, presence of potential contraindications, and responses from past treatments. Table 6 reviews the general strategies and classes of medications that are frequently used in combination to treat status migrainosus.

Table 6. Treatment of Status Migrainosus

- IV fluids
- Pretreat with:
  - prochlorperazine (5 to 10 mg IV) or
  - metoclopramide (10 mg IV)
- Treat with:
  - dihydroergotamine (0.5 to 1.0 mg IV)
- If headache persists:
  - in 1 hour give additional dihydroergotamine (0.5 mg IV)
- Additions:
  - ketorolac (30 to 60 mg intramuscularly or IV)
  - valproate (500 to 1000 mg IV)
  - diphenhydramine (25 to 50 mg IV)
  - levetiracetam (1500 mg IV)
  - magnesium sulfate (1 gram IV push)
- Alternatives:
- dexamethasone (4 to 10 mg IV)
- chlorpromazine (2.5 to 12.5 mg IV after 250 cc saline bolus)
  or
- droperidol (0.3125 to 2.5 mg IV)
- opioids - rare use

**Intravenous dihydroergotamine.** Intravenous dihydroergotamine is a mainstay in the inpatient treatment of migraine because it has been shown to be a safe and effective means of terminating a migraine attack (Raskin 1986; Evers et al 2009; Morren and Galvez-Jimenez 2010).

Repetitive intravenous doses of dihydroergotamine were first shown to be effective by Raskin in 1986 with 49 of 55 patients (89%) being headache-free after 48 hours. After hospitalization for treatment with intravenous dihydroergotamine, patients may be able to maintain the significant improvements, particularly if medication overuse and detoxification are concurrently addressed.

**Repetitive intravenous dihydroergotamine.** Hospitalization is typically necessary for treatment with repetitive intravenous dihydroergotamine as it is given every 8 hours and generally requires aggressive premedications to reduce risk of nausea/vomiting as side effects.

The patient is pretreated with metoclopramide (10 mg IV) and then given dihydroergotamine (0.5 mg IV). If the patient has no nausea and the headache persists, another 0.5 mg of dihydroergotamine is given. If the patient's headache is not gone, 0.5 mg of dihydroergotamine is continued every 8 hours. If nausea develops, the dose is decreased, and the antiemetic adjusted or increased. Both drugs are continued as needed, the dihydroergotamine every 8 hours until the patient is headache-free, at which time it is tapered and discontinued.

**Standard dosage.** Following 10 mg of intravenous metoclopramide, dihydroergotamine 0.5 mg is administered intravenously. Subsequent doses are adjusted based on pain relief and side effects. Most patients eventually take dihydroergotamine 1.0 mg intravenously every 8 hours (Raskin 1986).

**Contraindications.** Coronary artery disease, prinzmetal angina, peripheral vascular disease, prolonged aura, basilar migraine, pregnancy, and poorly controlled hypertension.

**Main drug interactions.** Administration with other potential vasoconstrictors (triptans, ergots, isometheptene, nicotine, and beta-blockers) may potentiate the vasoconstrictor effect of dihydroergotamine. Macrolide antibiotics, especially erythromycin, may increase plasma levels of dihydroergotamine.

**Main side effects.** Noncardiac chest pain, neck or trunk pressure, head or body warmth, nausea, leg pain, diarrhea.

**Special points.** Dihydroergotamine must be given slowly (intravenous push over 2 to 3 minutes or intravenous drip over 10 to 15 minutes) to reduce nausea, flushing, and chest symptoms. Diluting with an equal volume of saline reduces side effects.

**Cost and cost-effectiveness.** Dihydroergotamine is moderately expensive.

**Pediatric consideration.** Children under 25 kg or under age 9 may be given dihydroergotamine at 0.5 mg intravenously every 8 hours (Kabbouche et al 2009).

**Neuroleptics.** Multiple drugs from the neuroleptic class have been used for the treatment of acute migraine. Of this class, intravenous prochlorperazine has the highest level of evidence (Silberstein 2000; Orr et al 2015).

Intravenous prochlorperazine was shown to be vastly superior to placebo (Jones et al 1989) in a double-blinded, randomized control trial (n = 42 each arm) with 74% of the treatment group reporting complete headache relief at 60 minutes compared to 14% of the placebo group. Additionally, intravenous prochlorperazine 10 mg combined with intravenous diphenhydramine 12.5 mg was shown to be superior to subcutaneous sumatriptan 6 mg for migraine relief at 80 minutes (Kostic et al 2010). Prochlorperazine infusion over 15 minutes versus bolus push over 2 minutes was shown to have similar rates of side effects (Collins et al 2001). Prochlorperazine has also been shown to be effective in children; Kabbouche and colleagues (Kabbouche et al 2001) studied prochlorperazine in 20 consecutive children with acute migraine and showed that 95% improved at 3 hours and 90% remained headache-free at 24 hours.
Neuroleptics are more effective when given intravenously compared to suppository intramuscular forms. However, when intravenous access is limited (e.g., patient preference or other technical limitations), rectal prochlorperazine 25 mg may be an effective alternative (Jones et al 1994).

Metoclopramide is also frequently used for the acute treatment of migraine, though it has not been as intensively investigated as prochlorperazine through randomized trials. In a blinded, randomized control study, 67% of treatment patients reported pain relief at 1 hour compared to 19% of placebo patients (Tek et al 1990).

In a randomized, controlled trial comparing intravenous prochlorperazine and metoclopramide, prochlorperazine 10 mg was superior to metoclopramide 10 mg (Coppola et al 1995). Intravenous prochlorperazine 10 mg and metoclopramide 20 mg were similarly effective in another trial (Friedman et al 2008).

Intravenous haloperidol has also been shown to be superior to placebo in a double-blind, randomized trial with 16 of 20 (80%) treatment patients reporting significant pain relief and only 3 of 20 (15%) placebo patients reporting significant pain relief 1 to 3 hours after the infusion. Although patients receiving haloperidol had better pain relief, they were also more likely to have bothersome sedation or akathisia (Honkaniemi et al 2006).

Droperidol, a butyrophenone with strong neuroleptic and antiemetic properties, has also been used for treatment of acute migraine. In an open, ambulatory infusion center study, intravenous droperidol provided significant relief (no pain to mild pain) for 22 of 25 patients with status migrainosus, although sedation and akathisia were common (Wang et al 1997).

In a randomized, double-blind, placebo-controlled, multicenter study, 305 patients with moderate to severe migraine received intramuscular droperidol at doses of 2.75 mg, 5.5 mg, and 8.25 mg (Silberstein et al 2003). At 2 hours, those treated with any dose of droperidol reported significantly higher rates of headache improvement (81% to 87% with mild pain or no pain) compared to those receiving placebo (57%). The frequency of headache recurrence (within 24 hours) for patients initially responding by 2 hours was lower in patients treated with droperidol than with placebo, but differences were not statistically significant. A significantly greater percentage of patients receiving droperidol also reported the elimination of migraine-associated symptoms (nausea, vomiting, photophobia, and phonophobia) than those who received placebo. Although most adverse events were mild or moderate, anxiety, akathisia, and somnolence were rated as severe in 30% of patients who experienced those symptoms. Hypotension was uncommon. No patients had QT prolongation. This study suggested the use of diphenhydramine or benztropine to manage droperidol-induced akathisia.

Chlorpromazine at 0.1 mg/kg can also be used effectively for the treatment of pain and associated symptoms in acute migraine (Bigal et al 2002a), although its side effects of drowsiness and postural hypotension may require extra caution.

Intravenous neuroleptics may be used as primary therapy or as adjunct treatment for migraine and its associated features of nausea. If intravenous access is limited, oral, rectal, or intramuscular forms may be used. Patients receiving neuroleptics must be monitored carefully for hypotension, sedation, dystonic reactions, and akathisia. Use of diphenhydramine with neuroleptics may mitigate the development of akathisia and/or dystonia. Orthostatic hypotension may be reduced by intravenous fluids and supination post infusion.

**Standard dosage.** Prochlorperazine, 25 mg rectally every 6 hours as necessary, 5 to 10 mg intramuscularly or intravenously every 8 hours; chlorpromazine 25 mg orally every hour as necessary, max 5 doses per day, 12.5 to 25 mg intravenously after 250 cc saline bolus; and droperidol 1.25 to 2.5 mg intravenously every 6 hours or 1.25 to 2.5 mg intravenously every hour, maximum 10 mg in 24 hours (Wang et al 1997).

**Contraindications.** Known hypersensitivity to agent, prolonged QTc.

**Main drug interactions.** Other sedative medication, other drugs that might cause QT prolongation on EKG.

**Main side effects.** Dystonia, akathisia, sedation, hypotension, tachycardia, restless leg syndrome, neuroleptic
malignant syndrome, cholestatic jaundice, rarely QT prolongation. Extrapyramidal side effects, especially akathisia, may be particularly common in daily headache patients.

**Special points.** Akathisia must be dealt with promptly.

**Cost and cost-effectiveness.** Some intravenous neuroleptics are relatively expensive; however, the cost is low compared to the cost of an emergency room visit or hospitalization.

**Nonsteroidal antiinflammatory drugs (NSAIDS).** Ketorolac is frequently used in conjunction with neuroleptics, triptans, or dihydroergotamine in the treatment of migraine due to its availability in intravenous and intramuscular forms.

In a double blind, randomized control study comparing intravenous ketorolac (n = 13) against intranasal sumatriptan (n = 16), ketorolac was found to be superior to the triptan at reducing pain score 1 hour after administration (Meredith et al 2003). Additional comparison studies of intravenous ketorolac against agents such as meperidine, chlorpromazine, or prochlorperazine generally showed similar pain relief efficacy (Taggart et al 2013).

**Standard dosage.** Ketorolac can be given as a 60 mg intramuscular injection or a 30 mg intravenous injection. The total daily dose of parenteral ketorolac is recommended to be 60 mg or less. Due to the risk of gastrointestinal and renal adverse effects, parenteral ketorolac should not be given for more than 3 days in a row.

**Contraindications.** Renal impairment, gastrointestinal perforation or ulcer, gastrointestinal bleeding, suspected intracranial bleeding, hemorrhagic diathesis, inflammatory bowel disease, pregnancy, use of anticoagulants, concurrent use of probenecid, or pentoxifylline.

**Main drug interactions.** Other nonsteroidal antiinflammatory drugs (ibuprofen, naproxen, etc.).

**Main side effects.** Upset stomach, abdominal pain, nausea, diarrhea, renal impairment, bleeding.

**Cost and cost-effectiveness.** Injected forms of ketorolac are generally inexpensive, although insurance limitations may apply.

**Corticosteroids.** Parenteral corticosteroids, either alone or in combination with other symptomatic medications, have been used to treat severe, resistant headache. One study suggests that dexamethasone (4 mg intravenously) following pretreatment with intravenous metoclopramide is effective in the treatment of acute migraine headache (Klapper and Stanton 1991). Another study proposes that 4 mg of dexamethasone in conjunction with a triptan and a nonsteroidal anti-inflammatory drug will decrease recurrence in a limited population (Krymchantowski and Barbosa 2001).

Methylprednisolone may also be helpful in the treatment of status migrainosus (Robbins et al 2010). Clinical experiences also support the view that steroids, such as a rapidly tapering short course of prednisone (starting with 80 to 100 mg/day) or dexamethasone (starting with 8 to 20 mg/day), will assist in terminating an otherwise refractory migraine (Rozen 2002). Inpatients may be treated with high dose intravenous corticosteroids, alone or in conjunction with neuroleptics or dihydroergotamine, to help terminate a headache cycle. Chronic use of corticosteroids should be avoided in the treatment of migraine.

**Standard dosage.** Methylprednisolone sodium succinate 100 to 200 mg IV q 12° for 3 days.

**Contraindications.** Active peptic ulcer disease, severe diabetes or hypertension, acute viral or other systemic infection, or psychosis.

**Main drug interactions.** May cause hypokalemia if given with NSAIDs. May increase the risk of gastrointestinal bleeding if given with ethacrynic acid, furosemide, or thiazide diuretics.

**Main side effects.** Aseptic necrosis of femoral head or occasionally other bones is the main concern (risk factors are prolonged duration of use and high doses, cigarette smoking and ethanol consumption; earliest reports after continuous use of prednisone occurs at approximately 1 month), fluid retention, nausea, insomnia, mood variability, hypertension, hyperglycemia, or hypokalemia.
Cost and cost-effectiveness. Methylprednisolone sodium succinate is inexpensive.

Anticonvulsants. The FDA has officially approved valproate sodium for the prophylactic treatment of migraine headaches. An intravenous form of this agent, which is primarily used for the acute treatment of seizures, may be a safe, effective, and well-tolerated treatment for intractable migraine (Norton 2000; Edwards et al 2001; Shahien et al 2011). An open study using intravenous valproate 300 mg in 61 patients showed the treatment was generally well tolerated and significantly reduced pain in more than half of treated attacks (Mathew et al 2000).

There is 1 comparative study of intravenous sodium valproate 500 mg verus prochlorperazine 10 mg which showed that 79% of those treated with valproate required additional rescue treatment compared to 25% of those treated with prochlorperazine (Tanen et al 2003).

Standard dosage. Intravenous valproate at 300 mg to 500 mg.

Contraindications. Pregnancy, preexisting liver disease.

Main drug interactions. Coadministration of valproate and phenobarbital may rarely result in sedation and reversible coma. Aspirin may increase free valproate concentrations, and many drugs (phenytoin, carbamazepine, phenobarbital) increase valproate clearance. Rare cases of hepatic failure have occurred (usually in young children 2 years old or in patients receiving multiple anticonvulsants).

Main side effects. Sedation, dizziness, tremor.

Cost and cost-effectiveness. IV valproate is moderately expensive.

Intravenous propofol. Subanesthetic doses of propofol have been reported to be effective in several case series for the acute treatment of refractory migraine. One series was performed in an outpatient setting with 63 of 77 patients reporting complete headache relief (Krusz et al 2000). Additional case series conducted in the emergency room setting showed that propofol significantly reduced pain for the majority of patients (Mosier et al 2013; Soleimanpour et al 2012).

Standard dosage. Propofol was given as repetitive intravenous pushes 5 minutes apart with each dose being 10 to 30 mg. The decision to give additional doses was made based on pain level, blood pressure, and respiratory parameters. Average dose reported by Krusz was 110 mg (Krusz et al 2000). A higher dose of 400 mg was reported for inpatient monitored use (Young 2001).

Contraindications. Asthma, respiratory muscle weakness, and known hypersensitivity.

Main drug interactions. Lower doses may be needed in patients using other sedating medications.

Main side effects. Bradycardia, hypotension, decreased cardiac output, hyperlipidemia, apnea, respiratory acidosis, talkativeness, sedation.

Special points. Different clinicians have different approaches to assuring cardiovascular safety.

Cost and cost-effectiveness. Intravenous propofol is expensive but doses are low compared to those given during anesthesia and those given to hospitalized intensive care patients, who receive continuous drips.

Other acute treatment. Other forms of pharmacotherapy have been suggested as potential treatment for status migrainosus. Intravenous lignocaine was used in 19 chronic daily headache patients, 3 of whom had status migrainosus (Hand and Stark 2000). Five infusions were given to those 3 patients, with 4 of the infusions relieving headache. Another study by Williams and Stark in 2003 focused on 71 patients with chronic daily headache who were admitted for lidocaine infusion (also received other treatments such as nonsteroidal antiinflammatory drugs during admission) (Williams and Stark 2003). After an average of 8.7 days of treatment, 90% of these patients noted improved headache, with 70% reporting improved pain at 6-month follow-up.

In a case series of 68 patients with chronic daily headache (mostly chronic migraine) who were treated with intravenous lidocaine, 57% had some improvement and 25% were able to be pain free after an average of 8.5 inpatient days. Of note, the patients in this study also received other treatments such as intravenous
dihydroergotamine (Marmura 2009). Major side effects of intravenous lidocaine reported were nausea, hallucinations, lightheadedness, tachycardia, tremor, and blood pressure changes (hypotension or hypertension).

A double-blind study of repeated intranasal capsaicin in 8 patients with chronic migraine (Fusco et al 2003) demonstrated improvement between 50% and 80% in the 4 patients in the active group.

Several studies have suggested a role for intravenous magnesium sulfate in the treatment of acute migraine attacks. Demirkaya and colleagues (Demirkaya et al 2001) and Bigal and colleagues (Bigal et al 2002b) performed randomized, placebo-controlled studies in acute migraines and demonstrated significant relief. Mauskop and colleagues reported that IV magnesium was successful in treating menstrual migraine in patients with low interictal free ionized magnesium levels (Mauskop et al 2002). A randomized, double-blind, placebo-controlled trial of emergency room patients with migraine showed that magnesium given as an adjunctive treatment with metoclopramide appeared to be less effective than metoclopramide alone (Corbo et al 2001); there are no other similar studies to verify this finding.

Levetiracetam, an antiepileptic medication, has also been used with varied efficacy. Several studies indicate its potential usefulness in the treatment of status migrainosus and as a migraine prophylactic agent (Brighina et al 2006; Farooq et al 2007).

In a retrospective study, 9 doses of diphenhydramine given over 3 days significantly reduced headache level but did not appear as effective as dihydroergotamine with metoclopramide (Swidan et al 2005). As dihydroergotamine is contraindicated for some patients, repetitive doses of diphenhydramine may be used for headache control.

Friedman and colleagues studied trimethobenzamide/diphenhydramine (TMB/DPH) versus sumatriptan in the treatment of acute migraine (Friedman et al 2006). Although not as efficacious as sumatriptan, 80% of patients treated with TMB/DPH achieved headache relief at 2 hours.

In addition to pharmacotherapy, other approaches have been considered. Popeney and Alo (Popeney and Alo 2003) studied 25 patients with transformed migraine who had C1 to C3 peripheral nerve stimulators implanted. The average improvement in MIDAS score was 88.7%. However, it is unclear how many of these patients would have met the definition of status migrainosus.

In the past 5 years, there have also been multiple noninvasive devices developed for the treatment of migraine. There are currently 3 such devices: a transcutaneous magnetic stimulator (SpringTMS), a supraorbital transcutaneous stimulator (Cefaly), and a vagal nerve stimulator (gammaCore). These devices have been evaluated in migraine studies as both an abortive and a prophylactic (Jurgens and Leone 2013), but there have not been studies of these devices for use in status migrainosus. As such, they are generally well tolerated and may offer patients a safe, nonpharmacologic method to treat status migrainosus.

**Maintenance therapy.** After acute treatment is completed, many patients with status migrainosus and chronic daily headache require continuing care, including a preventive treatment program using standard migraine preventive drugs. This may be initiated in the inpatient setting and then modified accordingly in the outpatient setting by the patient's primary care physician or neurologist.

**Outcomes**

Treating patients who had intractable headache in a comprehensive inpatient unit demonstrated long-term benefits as measured by a prospective outcome evaluation (Lake et al 1993), which showed a 64% reduction in the mean number of days that severe or incapacitating headache was sustained and a corresponding increase in the mean number of headache-free days. Dysfunctional days dropped by 70% and clinical depression by 69%. The mean percentage of subjective improvement was 70%, with 87% of patients reporting at least a 50% reduction in headache. Silberstein and Silberstein reported similar long-term benefits (Silberstein and Silberstein 1992). Most patients (87%) detoxified from analgesic or ergotamine overuse as part of an inpatient program continued to do well when reevaluated at 2-year follow-up.

Silberstein found that repetitive intravenous dihydroergotamine was effective in eliminating prolonged migraine, cluster headache, and chronic daily headache with or without rebound in 91% of patients (Silberstein et al 1990).

Once the headache cycle has been broken, patients may revert to episodic migraine. Recurring episodes of intractable
migraine can occur despite otherwise appropriate treatment and may be an expected component of the pernicious form of migraine.

**Special considerations**

**Pregnancy**

The major concern in managing the pregnant migraineur is the effect of both medication and migraine on the fetus. Migraine may worsen during the first trimester but generally improves during the second and third trimesters. For pregnant women with migraines, nonpharmacologic therapy such as biofeedback, relaxation techniques, rest, and massage should be optimized. Ergotamine, dihydroergotamine, and sumatriptan should be avoided (Goadsby et al 2008). Acute treatments that may be used during pregnancy include acetaminophen, opioids such as hydrocodone (pregnancy category B), and magnesium; nonsteroidal antiinflammatory drugs may be used early in the pregnancy but should be avoided in the third trimester due to risk of preterm labor (Brandes 2012). For patients with high migraine burden, preventives such as oral magnesium or riboflavin should be considered (Brandes 2012). Beta blockers may be used prophylactically for those refractory to safer alternatives (Brandes 2012).

The Cefaly supraorbital transcutaneous stimulator is reported by the manufacturer as safe for use in pregnancy, as other forms of transcutaneous electrical nerve stimulation for back pain have been safely used in pregnant women (Keskin et al 2012).

**References cited**


Bigal ME, Bordini CA, Tepper SJ, Speciali JG. Intravenous magnesium sulphate in the acute treatment of migraine without aura and migraine with aura. Cephalalgia 2002b;22(5):345-53 PMID 12110110


Brandes JL. Migraine in women. Continuum (Minneap Minn) 2012;18(4):835-52.** PMID 22868545


Demirkaya S, Vural O, Dora B, Topcuoglu MA. Efficacy of intravenous magnesium sulfate in the treatment of acute


Grooters GS, Sluzewski M, Tijssen CC. How often is thunderclap headache caused by the reversible cerebral vasoconstriction syndrome? Headache 2014;54(4):732-5. PMID 24822246


Krymchantowski AV, Barbosa JS. Dexamethasone decreases migraine recurrence observed after treatment with a triptan combined with a nonsteroidal anti-inflammatory drug. Arq Neuropsiquiatr 2001;59(3-B):708-11. PMID 11593269


Morren JA, Galvez-Jimenez N. Where is dihydroergotamine mesylate in the changing landscape of migraine therapy. Expert Opin Pharmacother 2010;11(18):3085-93. PMID 21080856


Popeney CA, Alo KM. Peripheral neurostimulation for the treatment of chronic, disabling, transformed migraine.
Headache 2003;43(4):369-75. PMID 12656708


Schwedt TJ. Thunderclap headache. Continuum (Minneap Minn) 2015;21(4 Headache):1058-71. PMID 26252591


Silberstein SD, Silberstein JR. Chronic daily headache: prognosis following inpatient treatment with repetitive IV DHE. Headache 1992b;32:439-45. PMID 1446987


Williams DR, Stark RJ. Intravenous lignocaine (lidocaine) infusion for the treatment of chronic daily headache with substantial medication overuse. Cephalalgia 2003;23(10):963-71. PMID 14984229

Young WB. Medication overuse headache. Curr Treat Options Neurol 2001;3(20):181-8. PMID 11180755

**References especially recommended by the author or editor for general reading.

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ICD and OMIM codes

ICD codes

ICD-9:
Status migrainosus: 346.81

ICD-10:
Status migrainosus: G43.2

Profile

Age range of presentation

01-23 months
02-05 years
06-12 years
13-18 years
19-44 years
45-64 years
65+ years

Sex preponderance

female>male, >2:1
female>male, >1:1

Family history

family history of migraine is common among migraineurs

Heredity

heredity may be a factor

Population groups selectively affected

Migraine affects women more than men. Incidence decreases with older age.

Occupation groups selectively affected

none selectively affected
**Differential diagnosis list**

- acute single headache
- subarachnoid hemorrhage
- reversible cerebral vasoconstriction syndrome
- cerebral venous sinus thrombosis
- pituitary apoplexy
- spontaneous intracranial hypotension
- hypertensive encephalopathy
- retroclival hematomas
- glaucoma
- meningitis
- first attack of migraine
- systemic infection
- postconcussion/post-traumatic syndrome
- sinusitis
- acute recurrent headache
- subarachnoid hemorrhage
- cerebral tumors
- cerebrovascular insufficiency
- idiopathic intracranial hypertension
- intermittent hydrocephalus
- migraine
- subacute headache
- subdural hematoma
- pseudotumor cerebri
- tumor
- temporal arteritis (in elderly)
- brain abscess
- chronic daily headache
- analgesic rebound
- psychiatric state
- pseudotumor cerebri
- chronic tension-type headache

**Associated disorders**

- Chronic daily headache
- Episodic migraine
- Transformed migraine

**Other topics to consider**

- Childhood migraine
- Chronic daily headache
- Headache guidelines
- Migraine

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