BACKGROUND

The patient is a 44-year-old female with a chief complaint of moderate-to-severe chronic tension-type headache (CTTH) plus moderately painful and frequent (1 episode/week) migraines. She has had headaches since age 15, increasing in frequency and severity during her 30s and early 40s. Her CTTH is constant (24 hours/day, 7 days/week), all over her head, with posterior occipital tenderness and accompanied by allodynia. Previously, the CTTH had migrainous features, but currently is “just a bad ache all day.” Certain neck movements trigger the migraines, which often begin posteriorly. The migraines have a sudden onset, last 1 to 2 days, and keep her out of work 3 days/month. She has associated photophobia but no nausea. Triggers include menses, lack of sleep, changes in the weather, and stress.

MEDICAL HISTORY

She has a history of bipolar II disorder with depression since age 11. The patient also has irritable bowel syndrome (IBS) with diarrhea as her predominant symptom. She experiences moderate fatigue/daytime sleepiness (sleep apnea has been ruled out) and is obese.

FAMILY HISTORY

Her mother had migraines.

SOCIAL HISTORY

The patient is married, but is experiencing some marital difficulties. She has 2 boys, aged 10 and 12 with attention deficit disorder—one with bipolar disorder. The patient is employed full time as a computer programmer. She generally sleeps well, but is sleepy during the day, and she is afraid of losing her job because of migraines and excessive sleepiness leading to decreased productivity at work. The patient reports that she is often depressed with occasional brief periods of hypomania. She smokes 1 pack of cigarettes/day.

MEDICATIONS

Preventive therapies did not alleviate her bipolar disorder or her headaches. These included antiepileptic medications (ie, divalproex sodium, topiramate, and zonisamide), β blockers, calcium channel blockers, antidepressants, and miscellaneous medications from other categories (ie, tizanidine, cyclobenzaprine, nonsteroidal anti-inflammatory drugs [NSAID], and alternative therapies, such as feverfew, magnesium, or vitamin B₃). In addition, the patient experienced adverse effects from antidepressants, divalproex, and olanzapine.

In terms of abortive medications, triptans provide some temporary relief 30% to 40% of the time; they do not make her pain-free. Oral opioids (ie, hydrocodone and codeine) help, but do not eliminate the pain, and they cause a mild increase in sleepiness. Tramadol also provided partial relief of the CTTH. She states that the following have been completely ineffective: dihydroergotamine, MigraTen (acetaminophen, caffeine, and isometheptene), metoclopramide hydrochloride, Norgesic (orphenadrine, acetylsalicylic acid, and caffeine), ergot preparations, and butalbital.

PHYSICAL EXAMINATION AND DIAGNOSTIC TESTS

The patient is 5’ 4” in height, and weighs 190 lbs (body mass index [BMI] is 33). Neurologic examination, temporomandibular joint examination, and sleep study are all normal. Magnetic resonance imaging (MRI) of the brain is normal, as are routine blood tests and electrocardiogram.
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DIAGNOSIS AND TREATMENT

The patient has CTTHs and migraine, refractory to several pharmacologic therapies. The usual non-medication issues (eg, triggers, biofeedback, exercise, sleep, and psychotherapy) were discussed. Because of the CTTH, migraine, and bipolar disorder, the patient was placed on lamotrigine, slowly increasing the dose to 100 mg every morning. Quetiapine 50 mg was added at night. She was given sumatriptan subcutaneous injections 4 mg to use as needed for her migraine. Fentanyl lollipops were added for severe migraine pain.

CONTINUING TREATMENT AND FOLLOW-UP

The patient’s depression was greatly improved with the lamotrigine and the quetiapine, but the headaches did not abate, and she continued to be very sleepy. She could not tolerate the fentanyl suckers, but the sumatriptan injections did help. She was instructed on the use of ketorolac injections, but they not help. Amphetamine/dextroamphetamine was added as an adjunct, and the headaches improved 30%; her fatigue was better, as were her moods. She had more energy during the day. Her ability to work and take care of her children was greatly improved with the stimulant. The amphetamine did lower her appetite, causing a modest weight loss. For the prolonged migraines once or twice a month, she took a small dose of dexamethasone (7.5 mg every 8 hours as needed). This small amount did not trigger her hypomania.

In the future, other considerations would include lithium carbonate (primarily for the bipolar disorder), increased lamotrigine or quetiapine, switching the stimulant to methylphenidate, or increasing the sumatriptan to the 6-mg injections.

COMMENTARY

Several studies have shown evidence that obesity may be linked to headaches. The most complete data regarding the link of obesity and headache come from a study by Bigal and Lipton, in which the investigators assessed the influence of BMI on the prevalence and severity of chronic daily headache (CDH) and in particular, the subtypes of transformed migraine (TM) and CTTH. Using a computer-assisted telephone interview, participants were divided into 5 categories based on BMI (ie, normal weight, overweight, obese, morbidly obese, and underweight). Among 30 215 participants, the prevalence of CDH was 4.1%; 1.3% had TM and 2.8% CTTH. In contrast with the normal weight group (3.9%), the prevalence of CDH was higher in the obese group (5%; odds ratio [OR], 1.3; 95% confidence interval [CI], 1.1–1.6) and the morbidly obese group (6.8%; OR, 1.8; 95% CI, 1.4–2.2). BMI had a strong influence on the prevalence of TM. The prevalence of TM was 0.9% in the normal weight group, 1.2% among those who were overweight (OR, 1.4; CI, 1.1–1.8), 1.6% in the obese group (OR, 1.7; CI, 1.2–2.43), and 2.5% among the morbidly obese group (OR, 2.2; CI, 1.5–3.2). The effects of the BMI on the prevalence of CTTH were just significant in the morbidly obese group.

Adjusted analyses showed that obesity was associated with CDH and TM but not CTTH. The percentage of subjects with 10 to 15 days of headaches/month was 4.4%, 5.8%, 13.6%, and 20.7% in the normal weight, overweight, obese, and morbidly obese subjects, respectively. The proportion of subjects with severe headache pain increased with BMI; it was double in individuals who were morbidly obese versus those who were normal weight. Whereas other studies have shown an increase in the prevalence of migraine, these authors concluded, “BMI group was not associated with the prevalence of migraine, but was associated with the frequency of headache attacks.”

Another review of the factors that predict chronicity of migraine by Fanciullacci and De Cesaris indicated that, although attack frequency is the strongest predictor for migraine progression, obesity is also an important predictor. A population-based study by Scher et al followed patients for 1 year to determine in which patients CDH is most common initially and at follow-up. The investigators determined that those individuals with obesity were among those at greatest risk for initial development of CDH and also were among those groups unlikely to go into remission.

In another study by Peres et al, 74 patients with obesity who were undergoing gastric bypass surgery were evaluated, and 75% had some type of headache diagnosis (66% migraine, 9% tension, and 48% “incapacitating” headaches). A similar, but smaller, study conducted by Horev et al found that among 27 women needing gastric bypass, 10 had migraine with aura. Similar results are found among the pediatric population. Twenty-one percent of children and adolescents with headache are obese versus 15% in the general population.

An explanation for this association may lie with the
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pathophysiology of headache. The increased frequency of headache may be because of extraovarian production of estrogen by adipocytes, which are not inert. Adipocytes release proinflammatory substances. For example, the neuropeptide calcitonin gene-related peptide (CGRP) is widely distributed in the neural tissue of the brain, gut, perivascular nerves, and other tissues, and has several effects on the body, including vasodilatation and actions as a neurotransmitter. After a high-fat meal, CGRP is normally increased—more so in obese individuals. This, along with other proinflammatory markers, such as C-reactive protein, cytokines (interleukin-6 and tumor necrosis factor [TNF]-α), are released by adipocytes. There is some evidence that in patients with CDH, cerebrospinal fluid levels of TNF may be markedly increased. In addition, the neuropeptides, AF and NF, have definite, pain-modulating effects and are also present in adipocytes.

Insulin sensitivity in patients with migraine who do not have diabetes or obesity also may be abnormal. According to a study conducted by Rainero et al, 30 young patients with migraine who were not obese showed significantly increased glucose levels on glucose tolerance tests. Obesity is a major risk factor for sleep apnea, and according to one study by Neau et al, 53 of 164 patients with sleep apnea experienced headaches—the majority of which occurred in the morning.

Therefore, treatment for chronic headache in patients with obesity should focus on avoidance of any medications that may exacerbate weight gain. Depending on clinical considerations and comorbidities, clinicians may consider topiramate, phentermine, amphetamine/dextroamphetamine, or methylphenidate.

DISCUSSION

Dr Robbins: I would like to get everyone’s input as to how you would manage this very challenging case. For example, when you evaluate patients such as this woman, whose pain is exacerbated by occipital and neck movements, do you look at treating them differently? Do you think about trigger points or muscle relaxants or anything else?

Dr Medina: Occasionally, we see a patient that would develop pain on one side when you move the neck. Blocking the nerves in the occipital region may result in a good response.

Dr Robbins: What do you generally like to block it with—a corticosteroid?

Dr Medina: I use 1% lidocaine, approximately 6 cm³—and inject both nerves posteriorly. I would use a lidocaine patch rather than an injection.

Dr Robbins: Yes, I have used that, although it may have lower efficacy. There has been a study on occipital injections for this kind of headache, and the authors concluded that bupivacaine injections were fairly effective. Adding in steroids did not add any extra benefit. For pregnant patients, I will sometimes inject normal saline, because “dry needling” may be as helpful as actual medication. It may be partly why trigger point acupuncture is helpful for some patients.

Dr Brandes: This woman has bipolar disorder, and she is symptomatic. Her fatigue and daytime sleepiness would certainly interfere with her quality of life. I would suggest considering a daily preventative therapy with high efficacy. Topiramate would be a choice or perhaps verapamil, which could help her IBS. In a patient who has been unsuccessful with so many medications, my first questions would be what were the previous doses, what was the maximum dose achieved, how long she was at a maximum dose, and were any of the drugs given concomitantly? The most common thing I see in a patient like this is that the person is underdosed, the duration of therapy is too short, and/or the patient has not been placed on rational polytherapy. Although her bipolar disorder is affecting her daily function, it is the migraine that is producing increased disability, which is going to impact her in terms of caring for her family, maintaining her job, and being able to maintain her financial status. I think one has to look at a migraine medication’s efficacy for migraine that is likely to improve, or at least not worsen, her other medical conditions. I would place the patient on a preventative therapy and titrate upward. I would encourage her not to treat any of the headaches until they reach a certain level of intensity to avoid medication overuse. Then I would give her a high dose of sumatriptan succinate injection with something like ondansetron and maybe an NSAID, but limit her to 2 or 3 days/week. If possible, she needs a good psychiatrist and a regular exercise program.

Dr Robbins: I think that is a very good plan. We always have to have contingencies, though. What if nothing helps? Of course, the comorbidities drive where we go with the preventives. That is why I was focusing on the bipolar disorder, the obesity, and the tiredness. Acutely, any other options other than the sumatriptan
succinate injections for the once-a-week migraine?

Dr Mondell: Given the circumstances, I would just want to exercise caution about potentially enabling a scenario of medication overuse.

Dr Robbins: What if nothing is helping, and the patient is incapacitated, needing to go to the emergency department for meperidine shots once a month. The only thing that works is an opioid. The fentanyl suckers have been effective in 3 open-label studies; however, they do have all of the drawbacks of the opioids.

Dr Brandes: I can understand if somebody had severe coronary artery disease and triptans were contraindicated, how the patient may be offered a narcotic; otherwise, I would not recommend adding opiates.

Dr Robbins: This patient is calling you up and saying she is missing work 2 days at a time and wanting to know, “What do I take for my severe headache?”

Dr Mondell: Are we not in agreement that we ought to first focus on establishing a preventive therapy regimen that more effectively addresses the specific needs of and the comorbidities present in this patient? For this representative case, options not yet discussed include treatment with botulinum toxin. I recognize the fact that the older options have more data easily available to practitioners on “established efficacy.” Accordingly, I would like to invite commentary—on additional study data as well as personal experience—for the benefit of the reader.

Dr Brandes: I would treat her with drugs that have established efficacy, that have US Food and Drug Administration approval for at least 1 of the indications you are treating before you move into anything else. I would be willing to bet that she has never had polytherapy on high doses for a sustained period of time with any of those drugs. I think we should encourage more general neurologists to think about polytherapy. Of course, it also depends on the patient. If she is going to be overwhelmed with drugs, we have to start slower and/or stagger therapy.

Dr Robbins: By staggering therapy, you also can determine which drug is problematic if the patient develops side effects.

Dr Medina: We were talking about also using a protriptyline—as an activating agent?

Dr Robbins: Protriptyline is primarily norepinephrine. There is very little serotonin. It may not trigger hypomania or mania with her; however, in general, we avoid antidepressants with bipolar disorder. It may also give her a little bit more energy, but its efficacy in headache is uncertain, and patients experience a lot of anticholinergic side effects. The bipolar disorder may mitigate against the use of any tricyclic drug.

Dr Medina: If this patient continues with very severe headaches, she may even need a spinal tap to check her pressure.

Dr Robbins: There are now MRI scans that can check the pressure noninvasively—without doing a spinal tap. The only problem is that frequently the results are borderline. Certainly, high or low pressure headaches would be treated much differently. However, the vast majority of the time, we are left trying to find medications that help the pain and the comorbidities.

REFERENCES