Chapter 3

The Patient Sir William Osler Never Met

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Case History

A 36-year-old part-time stenographer presents with a history of headache since she was a teenager. The number of attacks has varied over the years, ranging from 4 per year to 4 per month. The patient describes her headache episodes as beginning with a funny feeling in her forehead and temples: "Not pain exactly, but my head just doesn't feel right." Over the next 6 to 8 hours, intense throbbing pain may develop in the occipital region of the head, with associated tenderness of the neck, and fatigue. This lasts "all day, until I get to sleep." The patient does not spontaneously report any associated symptoms, but when questioned closely, says that with most of her attacks her stomach "is a little bit unsettled"; once a year, she may vomit with a headache. She admits to light and noise sensitivity with headaches, but notes "I'm always like that. I don't think it has anything to do with my headache."

The patient is unable to identify aggravating or relieving factors for her headache. Specifically, she notes no connection between headaches and her menstrual periods, sleep or eating habits, or stress levels. She estimates that over the last 3 months, she has missed 6 to 8 days of work or social activities because of headache. She is seeking medical consultation because she recently had a headache that did not respond to her usual treatment regimen of a cup of strong coffee, and 6 ibuprofen and 2 "night-time cold and sinus" tablets. When vomiting developed, she went to the local emergency department. A computed tomography scan of the head and a lumbar puncture were performed because of her complaints of prominent neck stiffness; the results were normal. A diagnosis of "severe muscle contraction and tension" headache was made. Intramuscular meperidine was administered, with partial resolution of the headache. She was given a prescription for a muscle relaxant and discharged home with instructions to see a headache specialist.

The patient denies a family history of troublesome headaches. Her medical history is remarkable for hypothyroidism, allergic rhinitis, eczema, and an appendectomy. Medications include intermittent use of the previously mentioned over-the-counter medications for headache, Levoxyl, and beclomethasone nasal spray. She reports allergies to penicillin and codeine. Her physical and neurologic examinations are normal. She says that she would like "something to take when I have a bad headache, but I don't want to take drugs all the time."

Questions on the Case

Please read the questions, try to answer them, and reflect on your answers before reading the author's discussion.

- Do you agree with the emergency department diagnosis of severe muscle contraction and tension headache?
- Should this patient be encouraged to begin daily prophylactic medication?
- What issues should be considered when selecting an abortive therapy, and how can its success be optimized?
- Is there evidence to suggest that lifestyle changes, physical therapy, biofeedback, or a "migraine diet" might be helpful for this patient?

Case Discussion

Sir William Osler, who famously proclaimed that "if you listen long enough, the patient will tell you the diagnosis," obviously never met *this* patient. A few strategic, clarifying

questions posed by an alert clinician can make the correct diagnosis of migraine without aura seem self-evident and simple. It is easy to understand however how the patient's spontaneous description of the headache episodes might lead a busy or less headache-savvy clinician to an incorrect diagnosis of tension-type headache or even (as happened in the emergency department) to a suspicion of meningitis or other serious causes of headache. As the consequences of her emergency department visit illustrate, incorrect or delayed diagnosis of even a "benign" disorder such as migraine can have implications that are far from benign for the patient. These range from unnecessary diagnostic testing to years of missed treatment opportunities and subsequent disability.

A recently completed study of headache diagnosis in primary care demonstrated that when physicians make a diagnosis of migraine, they are almost always (98% of the time) *correct*. Unexpectedly, however, their diagnoses of nonmigraine headache are nearly always (82% of the time) *incorrect*. Furthermore, they are incorrect for essentially one reason: the patients really had migraine. Clearly, migraine is a diagnosis that is prone to be missed. Why is this so?

Three things likely contribute to the underdiagnosis of migraine. First, as with this patient, many patients do not provide textbook descriptions of their maladies; patients are "surprisingly inconsistent in recalling symptoms," according to a recent review of the subject. This patient did not readily offer up or admit to the symptoms that many clinicians rely on to make a diagnosis of migraine, and she emphasized others that, although not incompatible with a diagnosis of migraine, are viewed as more characteristic of tension-type headache, or the commonly used but not the International Headache Society (IHS)-recognized term "muscle contraction" headache. (A seasoned headache expert will also immediately recognize the diagnosis of "severe muscle contraction and tension" headache as an oxymoron: according to the IHS classification system, tension-type headache must be mild or moderate, and cannot be severe.)

Second, physicians tend to make diagnoses based on pattern recognition. In the case of the primary headache disorders, this tendency is reinforced by the symptom-based IHS system used to make diagnoses. Although the diagnosis of migraine is based on a combination of signs and symptoms, clinicians may not be sufficiently aware that no single symptom, with the exception of headache, is absolutely required for diagnosis (Table 3-1). When certain very common features—unilateral location, aura, nausea, and light sensitivity—are not present (or not described), clinicians may underestimate the possibility that the patient *still* may have migraine. In this patient's case, the occipital location of the headache, her failure to report associated symptoms such as nausea, the absence of aura, and the prominent complaint of neck involvement

Table 3-1. Diagnostic Criteria for Migraine without Aura

Migraine without Aura
A. At least five attacks fulfilling criteria B to D
B. Headache lasting 4 to 72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
1. Unilateral location
2. Pulsating quality
3. Moderate or severe intensity (inhibits or prohibits daily activities)
4. Aggravation by or causing avoidance of routine physical activity
D. During headache, at least one of the following occurs:
1. Nausea and/or vomiting
2. Photophobia and phonophobia
E. At least one of the following is present:
1. History and physical and neurologic examinations do not suggest an organic disorder.
2. History and/or physical and/or neurologic examinations do suggest such disorder, but it is ruled out by appropriate investigations.
3. Such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder.

Adapted from Headache Classification Subcommittee of the International Headache Society, 2004.

probably all combined to make a diagnosis of migraine less likely. Many of the firmly held ideas that physicians have about migraine are understandable, especially the common and enduring view that the pain of migraine must be unilateral: the word migraine derives from the Greek term "hemicrania," which translated means "half of the head."

Finally, the presentation of migraine is increasingly recognized as being more variable than has been commonly appreciated. In particular, much of what is termed by the lay public and relentless media advertisements in the US as "sinus" headache is likely to represent undiagnosed migraine. The same appears to be true for many headaches that are associated with neck muscle tenderness and stiffness, misdiagnosed as "tension" headache. Milder headaches without associated symptoms that occur in patients otherwise known to have migraine are also likely to be migrainous in origin. These headaches often represent the early stages of an evolving migraine attack, before the development of associated symptoms, or may be less typical "forme fruste" versions of the disorder. Appreciation of the spectrum of headache presentations seen in migraine is important when evaluating a patient who presents with headache.

In summary, these three factors—variable patient symptom reporting, physician reliance on pattern recognition, and the spectrum of migraine presentations—all combine to make migraine a diagnosis that is often missed. The oft-repeated rule of thumb that "severe recurrent headache in a patient with a normal neurologic examination and stable pattern of attacks is migraine until proved otherwise" serves us well here. With the few exceptions you will learn about in later chapters of this book, a pre-

sentation such as that of this patient should prompt formulation of a short differential diagnosis with migraine at the top of the list. This has been recognized in a practice parameter issued by the American Academy of Neurology, which concludes that patients who meet criteria for migraine, and who have a normal neurologic examination, do not require further diagnostic testing.

While patients with headache want an explanation from the doctor for their problems, most also want treatment of some sort. The majority of patients who seek medical care for migraine have tried, with limited success, over-the-counter remedies for headache. Many are overusing or misusing these drugs and, in some, the drugs are aggravating the headache problem (medication-overuse headache). Careful questioning about the amount and frequency of medication use for headache, including prescription, nonprescription, and "natural" or herbal remedies, is important. Some form of abortive prescription medication for headache will be required for nearly all patients. Table 3-2 lists commonly used abortive medications for migraine.

In contrast, prophylactic therapy will be necessary for only a subset of patients. In general, the patient's preferences over treatment should be carefully elicited and respected. Many patients are reluctant to commit to daily medication treatment for what is an intermittent disorder; who can blame them when the preventive medications available are only modestly effective and sometimes poorly tolerated? The advent of specific and highly efficacious medications for the treatment of acute migraine attacks has resulted in changed patient and physician attitudes toward the use of prophylactic therapy for migraine headache. Traditionally, prophylaxis has been recommended for patients experiencing more than two headaches per month. This recommendation is increasingly questioned based on the excellent tolerability and efficacy of acute medications. Few patients who get reliable, rapid relief of individual headache attacks with the newer abortive drugs will wish to expose themselves to the inconvenience, side effects, and long-term health risks associated with daily use of prophylactic medications.

Table 3-2. Abortive Agents for Migraine

Over-the-Counter Drugs for Mild to Moderate Attacks
Aspirin
Acetaminophen
Ketoprofen
Naproxen sodium
Aspirin-acetaminophen-caffeine
Prescription Drugs for Mild to Moderate Attacks
Isometheptene-acetaminophen-dichloralphenazone
Tramadol
Aspirin (or acetaminophen)-butalbital-caffeine combinations
Prescription Drugs for Moderate to Severe Attacks
Sumatriptan
Zolmitriptan
Rizatriptan
Almotriptan
Eletriptan
Naratriptan
Frovatriptan
Ergotamine preparations
Opioids
Drugs to Treat Associated Nausea/Vomiting
Metoclopramide
Chlorpromazine
Hydroxyzine
Prochlorperazine
Ondansetron

Of the categories of prophylactic medications in use for prevention of migraine, many have never been approved for that indication by the US Food and Drug Administration. Most are only modestly effective for prophylaxis, as indicated by the fact that the current low standard a medication must meet to be considered effective as a prophylactic migraine drug is usually close to a 50% reduction in the frequency of migraine attacks in 50% or more of patients. In addition, many prophylactic agents have tolerability or safety concerns of special importance to the young, largely female population with migraine. Tricyclic antidepressants cause weight gain and sedation, beta-blockers may increase the risk of depression and certainly decrease exercise tolerance, and sodium valproate is a known teratogen (a particular concern because the majority of patients requiring migraine prophylaxis are women of childbearing potential), which is associated with menstrual irregularities and may be associated with polycystic ovaries. A common view among headache experts is that prophylactic migraine therapy should be reserved for patients with more than one headache a week, or for those who do not obtain adequate relief despite aggressive use of abortive medications. Table 3-3 lists commonly used prophylactic medications for migraine.

In this patient's case, headache frequency is well within the range where attempts to optimize abortive therapy alone are appropriate. Several strategies increase the likelihood of rapid, consistent relief from abortive treatment (Table 3-4). First, reliable, experienced patients who are familiar with their own headache patterns should be encouraged to treat headaches while they are still mild. A wealth of evidence suggests that intervention when the headache is mild increases the chances of complete, rather than partial, pain response, decreases headache recurrence, and results in less medication use overall. This patient's history, for example, suggests that she would be a good candidate for strategies emphasiz-

Table 3-3. Preventive Agents for Migraine

Agent	Typical Dose
Low-dose tricyclic antidepressants (eg, amitriptyline)	25–150 mg/day
Beta-blockers (eg, propranolol)	80–160 mg/day
Sodium valproate*	250 mg bid–500 mg bid
Topiramate*	15–25 mg PO qhs to initiate; increase as tolerated to 50 mg PO bid or higher
Calcium channel blockers (eg, verapamil)	80–240 mg/day
Cyproheptadine	4–8 mg bid
NSAIDs (eg, naproxen sodium)	550 mg bid

NSAIDs = nonsteroidal anti-inflammatory drugs.

*Approved by the Food and Drug Administration for prevention of migraine.

ing timely abortive treatment, since she recognizes a clear headache prodrome and reliable headache evolution over time.

A second strategy that improves effectiveness of abortive treatment is use of an adequate dose of medication. In contrast to the conservative "one size fits all" dosing approach used in the early days of headache treatment with triptans, it is now recognized that many patients benefit from initial use of higher doses of medication (100 mg instead of 25 mg of sumatriptan, 10 mg instead of 5 mg of rizatriptan, 5 mg instead of 2.5 mg of zolmitriptan, and so forth). Again, early use of an adequate dose of medication appears to improve pain-free rates and decreases headache recurrence and medication use. Finally, seasoned clinicians commonly recommend that patients use simultaneously synergistic combinations of medications to increase the likelihood of treatment response. Commonly used combinations include a triptan and a nonsteroidal anti-inflammatory drug (NSAID), or a triptan and an antiemetic medication.

Most experienced headache clinicians increasingly recognize the immediate and long-term benefits of newer disease-specific migraine treatments, such as the triptans, as compared with older, nonspecific, or semi-specific agents, such as barbiturate or narcotic-containing compounds or ergots. Triptans are significantly less prone to abuse or overuse than narcotics or barbiturates. Although it has been suggested that frequent use of the triptans can produce rebound headache, information to date suggests that the risk may be lower, and treatment easier, than for other combination analgesics or ergot compounds. The vasoconstrictive side effects associated with triptans are significantly less pronounced and shorter in duration than those associated with the use of ergots. In addition, the majority of migraineurs are young, otherwise healthy, and in the most productive years of their lives, making the sedation and disability associated with nonspecific treatments hard to defend. Gastrointestinal bleeding from the overuse of aspirin or NSAIDs is a well-recognized complication of migraine treatment, as is the development of renal dysfunction.

Although all of these risks are small when viewed in the context of treating an individual attack, migraine is a chronic illness, and risks must be viewed cumulatively over a lifetime of attacks. Since we lack the ability to determine which patients are at risk for the serious long-term morbidity that can be associated with nonspecific treatments, it makes sense to avoid exposure to these agents in patients who are candidates for disease-specific therapy.

Another reason to favor the use of disease-specific agents for the acute treatment of migraine is the reasonable supposition that scrupulous management of individual attacks may, over time, decrease the long-term burden and disability attributable to migraine. Such a possibility can be suspected by analogy with other illnesses, such as rheumatoid arthritis, in which early disease-specific therapy appears to retard progression to more malignant and disabling forms of the illness. Whether the early use of triptans in young headache patients will reduce the number of middle-aged patients with intractable chronic daily headache remains to be seen, but it seems a distinct possibility.

It is thus reasonable to conclude that the use of triptans for the acute treatment of migraine is the current standard of care for migraine among experts in the field of headache. In the present case, a reasonable initial treatment strategy would be early use of an adequate dose of any of the highly efficacious, rapid-onset oral triptans, such as sumatriptan, zolmitriptan, rizatriptan, almotriptan, or eletriptan, either alone or in combination with an NSAID (eg, naproxen sodium 550 mg PO bid). The chosen regimen should be used for two headaches and its usefulness

Table 3-4. Strategies to Improve the Effectiveness of Abortive Treatment

Strategy	Example
Treat at mild stage of pain	Patient whose headaches commonly progress to severe pain and disability initiates abortive-treatment use when headache is 3/10 on a 1–10 scale
Use adequate medication dose	Patient uses 1,000 mg of aspirin instead of 650 mg; patient uses 100 mg sumatriptan rather than 25 mg
Combine medications with different mechanisms of action	Rizatriptan 10 mg plus naproxen sodium 550 mg PO bid

then evaluated. If one triptan is ineffective or associated with unacceptable side effects, another can be tried, with a good chance of success.

The absence of nausea makes it unlikely that this patient will require treatment with a nasal spray or subcutaneous triptan preparation, although those are good options for patients in whom gastrointestinal symptoms or rapid evolution of the headache is common. This patient, similar to most patients, is likely to prefer the convenience and acceptability of oral treatment (either a standard pill that is swallowed or one of the triptans available in orally disintegrating tablets) to the use of subcutaneous injection. A case can be made, however, for encouraging her to keep a supply of nasal spray or injectable triptan on hand at home, since even the best-controlled patient may occasionally have an attack associated with intractable vomiting that precludes oral therapy, or find that oral treatment is for whatever reason ineffective. At-home availability of back-up "rescue" treatment, even if rarely needed, may obviate an expensive trip to the emergency department.

She may also benefit from established nonpharmacologic treatments such as the use of biofeedback-assisted relaxation therapy or institution of regular sleep and wake times, both of which have been established as helpful in migraine. Although food is commonly mentioned as a trigger by many migraine patients, there is little evidence that rigid "migraine diets" provide substantial relief for large numbers of patients; one study suggests that it is being placed on a special diet, rather than the diet itself, that is therapeutic. In the absence of such evidence, it is best to avoid promoting unjustified anxiety about food and inadvertently encouraging excessively rigid and limited diets. Unfortunately, there is limited or poor quality evidence about many of the alternative treatments promoted for migraine, including acupuncture, herbal, and vitamin therapies.

Treatment Guidelines

Guidelines are available that summarize the quality of the evidence for individual abortive and prophylactic pharmacologic treatments for migraine and for nonpharmacologic treatments such as biofeedback-assisted relaxation therapy. (See list of Selective Readings.) These are invaluable as a reminder of the evidence base on which treatment should be based, and serve as a useful way of comparing various individual treatment strategies. However, the limitations of guidelines, especially in treating a condition as complex as migraine, must also be borne in mind. The rigorous process of evidence gathering and the evaluation necessary to produce guidelines inevitably means that they will lag one or several years behind the evidence at the time of publication. In addition, because standards and requirements for clinical trials improve over time, newer medications tested with more careful methodology may be judged more favorably than older drugs that were studied when standards were different; this does not necessarily mean that the newer drugs are a better choice. Finally, guidelines are silent on many issues of great clinical importance, such as *when* to initiate treatment, *how long* treatment should be continued, and the efficacy of treatment *combinations*. For these and many other fundamental decisions, there is no substitute for good clinical judgment.

Management Strategies

- Tailor treatment strategies to patient preferences and desires.
- To optimize abortive therapy, use an adequate dose of a migraine-specific drug when the headache is mild. Consider combining this with a second drug that has a different mechanism of action.
- Plan ahead for nonoral "rescue" treatment when first-line abortive therapy fails.
- Encourage the use of reasonable lifestyle alterations and nonpharmacologic treatment, especially if preferred by the patient to the use of pharmacologic therapy.
- Consider prophylactic therapy for patients whose attacks do not respond well to abortive therapy alone, or who have more than two headache episodes per week.

Case Summary

- This patient has migraine without aura that has not responded optimally to treatment with over-the-counter medications.
- Because her presentation is not obvious, a specific diagnosis of migraine without aura was delayed, along with disease-specific treatment.
- Her headaches should respond well to optimal abortive therapy. If this is not the case, a variety of prophylactic drug and nonpharmacologic treatments may be useful.

Selected Readings

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Editorial Comments

Migraine without aura is diagnosed on the basis of headache characteristics, unlike migraine with aura, where neurologic features are paramount. As a result, many patients with migraine without aura may be not diagnosed if careful scrutiny and time to listen are not given to the patient's story during the history. Diagnosis is the cornerstone of appropriate management, and this case provides a solid basis for diagnostic considerations and reasonable therapeutic options. One suspects that Dr. Loder knows very well that Osler would have made the diagnosis ultimately in a patient such as the one she describes, as he had the time to listen, and did not need to be concerned with neuroimaging, managed-care organizations, and complex modern pharmacotherapy!

Final diagnosis:

Migraine without aura