CHAPTER 9

THE PATIENT WITH HEADACHE, ARTHRITIS, AND HYPERTENSION

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Case History

A 52-year-old woman was referred to the headache center for evaluation of her headaches. She noted the onset of headache at the age of 13 years. The headaches occurred once per month, usually with menses. These headaches were described as a unilateral, pounding headache, associated with nausea, vomiting, and phonophotophobia. They would last for a day and were relieved by sleep.

In her early thirties, her headaches started to become more frequent. At that time, she began having one headache every week. She was started on propranolol and her headache frequency decreased to one per month. After 6 months the propranolol was discontinued.

In her late thirties she noted symmetrical joint pain, erythema, and warmth in her fingers, wrists, and knees. She was diagnosed as having rheumatoid arthritis and was treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Her condition continued to worsen, and she was eventually placed on hydroxychloroquine. Ten years later, due to continued progression of her arthritis, she was also given methotrexate. As a complication of her rheumatoid arthritis, she developed fibromyalgia, with pain particularly in the muscles of her neck and upper back. She also developed Raynaud's phenomenon.

At the age of 41 years, she was noted to have hypertension. The NSAIDs were discontinued, and she was treated with a thiazide diuretic. Her blood pressure was well controlled and she had no adverse effects with this treatment.

She did not smoke, rarely drank alcohol, and took no over-the-counter medications. She was married with two grown children, and was employed as an administrative assistant.

At the time of her headache evaluation, she was on hydroxychloroquine, methotrexate, and amitriptyline for her arthritis and associated fibromyalgia, and hydrochlorothiazide for her hypertension. For her migraines, which were again occurring once per week, she took naproxen sodium, 550 mg at onset, with a second dose 6 to 8 hours later if needed.

Her general examination was remarkable for a blood pressure of 138/90 and rheumatoid changes in her hands. She had multiple tender points on examination and increased muscle tension in her neck. Her neurologic examination was unremarkable.

Questions about This Case

- What are the appropriate strategies for the management of hypertension in the patient with migraine?
- How does the presence of Raynaud's phenomenon influence therapy choices?
- Could the patient's medications be contributing to her headaches?
- How is fibromyalgia related to headaches?
- How do you manage migraine in the presence of comorbid medical illnesses?

Case Discussion

There are several major issues that the physician must consider in evaluating and treating the headache patient with comorbid medical disorders. These include: (1) Do the headaches represent a primary headache disorder (i.e., migraine, tension-type, or cluster) or are they secondary to the patient's other medical problems? (2) Is the therapy for the comorbid condition triggering or exacerbating the headache problem? (3) Is the headache treatment likely to worsen the comorbid condition, or does the comorbid condition contraindicate certain therapies? (4) Does the

presence of comorbid disease offer the opportunity to use a single drug to treat both the headache disorder and the comorbid condition?

Certain medical illnesses are more common in the headache patient. Featherstone evaluated the prevalence of concomitant medical diseases in chronic headache sufferers by reviewing 1414 life insurance applications and obtaining 200 headache cases with matched controls without chronic headaches. The average age for study patients was 45 years. The groups were equally divided by gender. Headaches were not classified by diagnosis (i.e., migraine, cluster, etc.). Six conditions were found to occur more often in the chronic headache group: hypertension, dizziness (or vertigo), gastroesophageal reflux, depression or anxiety, peptic ulcers, and irritable bowel syndrome. Three conditions were significantly more common in the nonheadache population: nephrolithiasis, alcohol abuse in men, and abdominal pain in women. Several conditions had the same prevalence in both the headache and nonheadache groups: ischemic heart disease, mitral valve prolapse, cardiovascular disease, central nervous system ischemia, cigarette smoking, emphysema, and previous surgery.

Other investigators have found associations between specific headache diagnoses and diseases. To examine the association between migraine and other conditions, Merikangas reviewed the Health and Nutrition Examination Survey (HANES I), a study of 12,200 adults aged 25 to 74 years, that was used to estimate the health of the general population of adults in the United States. Merikangas found the following conditions to be strongly associated with migraine: stroke (odds ratio 3:1); heart attack (odds ratio 2:4); bronchitis (odds ratio 2:3); colitis (odds ratio 2:3); nervous breakdown (odds ratio 2:2); urinary tract disorders (odds ratio 2:2); and ulcers (odds ratio 2:2). Migraine has also been associated with an increased prevalence of coronary vasospasm, Raynaud's phenomenon, aspirin-sensitive asthma, mitral valve prolapse, epilepsy, and hypertension.

Cluster headache is associated with a threefold increase in the prevalence of peptic ulcers. Cluster patients often have multiple risk factors for coronary artery disease. Chronic tension-type headache sufferers have an increased prevalence of depressive symptoms.

1. Do the headaches represent a primary headache disorder (i.e., migraine, tension-type, or cluster) or are they secondary to the patient's other medical problems?

In medical practice, most headaches are not caused by underlying disease. It is important to recognize, however, that headache can be the presenting symptom of several diseases. Fever, regardless of etiology, is probably the most common medical problem that causes headache. Less common causes include pheochromocytoma, chronic renal failure, hyperthyroidism, and malignant hypertension. Pheochromocytoma may present with a pounding headache associated with hypertension, diaphoresis, tachycardia, and palpitations.

Rheumatologic diseases may have headache as an early manifestation. Headache is common in systemic lupus erythematosus, polyarteritis nodosa, and giant cell arteritis. About two-thirds of patients with fibromyalgia report headache, usually tension-type headache. Many types of vasculitis can also present with headache

Headache upon awakening may be the initial symptom of sleep apnea syndrome. The headache often will improve as the day progresses. Sleep apnea is most commonly observed in obese, middle-aged males. Associated symptoms include snoring, daytime somnolence, hypertension, and arrhythmias.

In the present case, the headaches preceded the onset of comorbid rheumatoid arthritis and hypertension by at least 25 years. The age at onset and presentation were typical of migraine, and the headache quality did not change over time. In this situation, there is no reason to believe that the migraine headaches are related to the patient's other medical problems.

On the other hand, the patient does suffer from chronic neck discomfort related to her fibromyalgia. Fibromyalgia can be a primary complaint or, as in this case, associated with rheumatoid arthritis. Treatment of the underlying condition may have a direct impact on the neck pain.

2. Is the therapy for the comorbid condition triggering or exacerbating the headache problem?

Certain medications can trigger the onset of headache or exacerbate headache in patients with an underlying headache disorder. Medication-induced headache has been commonly reported with the following medications: indomethacin, nifedipine, cimetidine, atenolol, a trimethoprim-sulfamethoxazole combination, nitroglycerin, isosorbide dinitrate, ranitidine, isotretinoin, captopril, piroxicam, granisetron, poetin, metoprolol, and diclofenac. Medications that may aggravate existing migraine include vitamin A, its retinoic-acid derivatives, and hormone therapy, such as oral contraceptives, clomiphene, and postmenopausal estrogens. Migraine and cluster headaches may be exacerbated by vasodilators such as nitrates, hydralazine, minoxidil, nifedipine, and prazosin.

Reserpine, a serotonin antagonist, can cause depression, migraine, and tension-type headaches. Indomethacin, while useful in treating cluster-variant headaches, can cause a generalized headache. Frequent or chronic use of some prescription and over-the-counter medica-

tions used to treat headache, including opioids, barbiturates, caffeine, and ergots, can lead to rebound or withdrawal headaches.

A careful review of this patient's medications did not suggest that the treatment of her rheumatoid arthritis, hypertension, or fibromyalgia was complicating her headache disorder. Additionally, she avoided over-the-counter or habituating medications.

3. Is the headache treatment likely to worsen the comorbid condition, or does the comorbid condition contraindicate certain therapies?

In a patient with Raynaud's phenomenon, as well as any patient with peripheral vascular disease or coronary artery disease, any medication which can exacerbate vasoconstriction should be avoided. Therefore, we would not treat this patient with ergotamine tartrate, dihydroergotamine mesylate (DHE), isometheptene mucate, the triptans, or other 5-HT-1B/1D agonists. Beta-blockers are generally avoided in patients with vasospastic diseases like Raynaud's phenomenon or vasospastic angina.

Ergotamine tartrate, DHE, isometheptene mucate, and triptans can transiently elevate blood pressure. Patients with hypertension must have their blood pressure well controlled prior to using these drugs. As hypertension is a major risk factor for coronary artery disease, a careful appraisal of other coronary risk factors should be undertaken prior to the prescription of any of these drugs. Patients with active ischemic heart disease, or those patients likely to have occult coronary artery disease, should not be treated with ergotamine tartrate, DHE, isometheptene mucate, or triptans.

To treat this patient's migraine attacks, we chose a nonsteroidal anti-inflammatory drug (naproxen sodium). We suggested she take her initial dose at onset but if the headache persisted, she should take her second dose 1 hour later. Metoclopramide, 10 mg orally, could be added to the NSAID to improve its efficacy and to reduce nausea and vomiting.

4. Does the presence of comorbid disease offer the opportunity to use a single drug to treat both the headache disorder and the comorbid condition?

Many agents used in migraine prophylaxis have additional uses in other medical conditions. Beta-blockers and calcium channel blockers are useful in treating concomitant hypertension or ischemic heart disease. The NSAIDs are useful for many rheumatologic and musculoskeletal conditions. Divalproex sodium can be used for epilepsy.

For this patient, the calcium channel blockers offer the opportunity to use a single agent to treat three diseases. Calcium channel blockers are useful in migraine prophylaxis, and in the treatment of hypertension and Raynaud's phenomenon.

We elected not to use daily NSAIDs in this patient because she was already on disease-modifying agents for her rheumatoid arthritis, and because intermittent NSAIDs were the best choice for her acute migraine management. She was already taking a tricyclic antidepressant for the treatment of her fibromyalgia. Chronic headache is reported by over two-thirds of patients with fibromyalgia. Tricyclic antidepressant drugs may also be useful in migraine prophylaxis.

Management Strategies

- Establish the correct headache diagnosis.
- Be alert for secondary headache disorders related to the patient's comorbid diseases.
- Carefully review the current medications, including over-the-counter products. Look for drugs that may exacerbate headache or cause rebound/withdrawal headaches.
- Assess for medical problems that may have an impact on your choices of headache treatments. Screen patients for ischemic heart disease and coronary artery disease risk factors prior to prescribing ergotamine tartrate, DHE, isometheptene mucate, sumatriptan, and other 5-HT-1B/1D agonists.
- Try to select headache therapies that may also treat the patient's comorbid condition. Reducing the number of medications can improve compliance, limit adverse effects, and reduce cost.

Migraine and Cardiovascular Disease

Migraine headache and cardiovascular disease are both extremely common. This section will discuss the clinical associations between these disorders, connections in their pathophysiology, and similarities in treatment.

Like coronary artery disease, migraine is a familial disorder, with a positive family history in two-thirds of cases. Three-quarters of patients will have a family history of migraine on the maternal side only, 20% on the paternal side only, and 6% on both the maternal and paternal sides. There is approximately a 70% risk of migraine in offspring when both parents suffer from migraine, 45% risk when only one parent is affected, and less than 30% risk when both parents are unaffected. The genetic basis for migraine is probably multifactorial; the genetic component is polygenic with the added effect of a number of genes which render the individual more or less susceptible to developing the disorder in response to a number of environmental trigger factors.

The increased risk of stroke in migraine patients is not associated with the age of onset of migraine—the risk of stroke is elevated regardless of the age of the migraine patient. Ten years after regularly using headache medications, patients had a risk ratio for stroke of 1:7. When comparing adjusted risk ratios for stroke, migraine was the third most common contributing factor at 1:7, behind hypertension at 2:1, and diabetes mellitus at 1:9, but ahead of heart disease and male sex at 1:4.

Circadian rhythms are those repetitions of biologic phenomena that occur at about the same time each day. Circulating catecholamines, platelet aggregability, pericranial-musculature pain sensitivity, and vasospastic events all follow circadian rhythms that may have an impact on migraine.

Migraine attacks follow a circadian rhythm, with a marked increase in attacks between 6 AM and 8 AM, a peak migraine frequency between 8 AM and 10 AM, and a dramatic decrease in frequency between 8 PM and 4 AM. A recent review of 28 migraine patients revealed that of 329 migraine attacks, 160 (49%) occurred between 6 AM and noon.

It has been demonstrated that nonfatal myocardial infarction, variant angina, exertional angina, and sudden cardiac death are all more likely to occur between 6 AM and noon than at during other times of the day. Platelet aggregability also shows an increase between 6 AM and 9 AM.

Cerebral infarction has been reported to have a circadian pattern with an increased frequency in the late-morning hours. This pattern mimics that of migraine. This is in contrast to subarachnoid hemorrhage, which has been reported to peak between 6 PM and midnight.

The circadian pattern observed in migraine may also be related to changes in the firing rate of serotonergic neurons in the dorsal raphe nucleus. Raskin has proposed that the core abnormality of migraine is unstable serotonergic neurotransmission leading to increased raphe neuronal firing rates. Dorsal raphe units maintain a slow, regular firing pattern as long as there is no change in arousal level. They become totally silent during rapid eye movement sleep. The serotonergic neurons increase their firing rate in response to visual, auditory, or somatosensory stimuli. It is possible that early morning arousal and the marked increase in sensory stimuli may trigger increased dorsal raphe nucleus firing rates, causing the increased frequency of morning migraines via serotonergic effects on platelets and vascular tone.

Nonfatal myocardial infarction, angina, and sudden cardiac death are vascular events that share some similarities with migraine. Both the cardiac events and migraine are associated with changes in vasomotor tone and ischemia. Platelet hyperaggregability has been associated with both conditions. The similarities in circadian rhythm of these phenomena raise the question of the relationship of migraine to other vascular events. Both migraine and coronary artery disease are more common in patients with hypertension and are amenable to prophylactic therapy with aspirin, beta-blockers (without intrinsic sympathomimetic activity), or calcium channel blockers.

The association between myocardial infarction and migraine may also relate to the pathogenesis of the two events. Platelet aggregability has a circadian variability that parallels nonfatal myocardial infarction and sudden cardiac death. The migraine data also suggest that the circadian variability of platelet aggregability parallels that of migraine. Platelet hyperaggregability may lead to the release of chemical mediators, such as serotonin, which may induce vasospasm. Increased sympathetic nervous system activity may also play a role in both cardiac events and migraine. Catecholamine levels in plasma rise between 6 AM and noon, and can induce vasospasm. Vasospasm may be the initiating step in migraine, either through the induction of ischemia, platelet changes, or the release of neurochemical mediators, all of which can activate the trigeminovascular system.

Migraine and cardiovascular disease share clinical associations, circadian rhythms, pathophysiologic mechanisms, and therapies. It is hoped that advances in the pathophysiology and treatment of cardiovascular disorders will bring benefits to migraine sufferers.

Selected Readings

Askmark H, Lundberg PO, Olsson S. Drug-related headache. Headache 1989;29:441–4.

Dalessio DJ. Beta-blockers and migraine. JAMA 1984;252:2614.

Featherstone HJ. Medical diagnoses and problems in individuals with recurrent idiopathic headaches. Headache 1985;25: 136–40.

Hanington E. The platelet theory. In: Blau JN, editor. Migraine: clinical and research aspects. Baltimore: Johns Hopkins University Press; 1987. p. 331–53.

Iversen H, Nielsen T, Olesen J, Tfelt-Hansen P. Arterial responses during migraine headache. Lancet 1990;336:837–9.

Merikangas KR. Comorbidity of migraine and other conditions in the general population of adults in the United States. Cephalalgia 1991;11 Suppl 11:108–9 .

Merikangas KR. Migraine and stroke: association in large-scale epidemiologic study. London: Migraine Trust; 1992.

Muller JE, Stone PH, Turi ZG, et al. Circadian variation in the frequency of onset of acute myocardial infarction. N Engl J Med 1985;313:1315–22.

Raskin NH. Headache. 2nd ed. New York: Churchill Livingstone; 1988. p. 109.

Solomon GD. Comparative review of calcium channel blocking drugs in migraine. Headache 1985;25;368–71.

Solomon GD. Concomitant medical disease and headache. Med Clin North Am 1991;75:631–9.

Solomon GD. Circadian variation in the frequency of migraine. Cleve Clin J Med 1992;59:326–9.

Tofler GH, Brezinski D, Schafer AI, et al. Concurrent morning increase in platelet aggregability and the risk of myocardial infarction and sudden cardiac death. N Engl J Med 1987;316:1514–8.

Editorial Comments

Headache and comorbid medical disorders are common. Management of the patient's headache cannot be done in isolation, and requires considerable knowledge and expertise of numerous medical disorders to effect good overall care. Dr. Solomon presents us with such a case and lends us his considerable knowledge and experience in dealing with such patients. The exact neurobiologic association between migraine and the disorders mentioned, as well as the relationship to biologically induced circadian rhythms, requires further thought and study, as suggested by Dr. Solomon in this chapter.