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CASE VIGNETTE

"Then I can't see and I start to panic. How am I going to work? How am I going to get home?"

Theresa, a 26-year-old unmarried administrator, presents with severe headaches accompanied by vision problems. She has had several consultations in the past and is currently taking propranolol (20 mg/day) as prophylaxis. However, attacks have become more frequent. Vital signs and physical examination are normal.

Tell me about the vision problems, Theresa. What happens to your vision and how long does the problem last?
The vision problems warn her that a severe headache is developing. She first notices that any bright light "catches her eye." Then a diagonal band, mainly on the right side, slopes down across her vision "colored like a rainbow with sparkles." The bands multiply until almost all vision, mainly on the right side, is gone – she can't read or see to drive. These take 10-15 minutes to develop. The headache starts in 30 minutes and the vision problem fades in 2-3 minutes, but vision remains blurred for sometime.

How about the headache itself? Where do you feel the pain and how long does the attack last? Do you have any other symptoms with the headache? Do you ever have numbness, tingling or other unusual sensations during or before the attack?
The headache is frontal behind the eyes, mainly on the right, and spreads to include the back of the head. These severe headaches last about 2 days. Then the pain fades and she feels "bad" for another 24 hours before she can return to work. The headache is accompanied by nausea and vomiting. She cannot tolerate light or loud noise; perfumes and cooking aromas aggravate the headache. Occasionally she has diarrhea with the attack. During the attack she notices her left hand and forearm develop "pins-and-needles" sensations.

How often do you get these headaches? Has their severity or frequency changed?
Began at age 13 years; occurred 3-4 times per year. In the past, vomiting always relieved the headache. Headaches gradually worsened over the years. First consulted doctor at age 18 years and was prescribed oral ergotamine (Cafergot). The medication made her nauseated, and she had cramps in limbs. Cafergot was discontinued and she was started on propranolol 20 mg daily. Gradually became headache-free. She subsequently developed dysmenorrhea and was treated with oral contraceptives (OCs). Dysmenorrhea lessened but headaches returned; OCs discontinued. Isolated attacks of migraine recurred. They were unrelated to periods and always accompanied by visual problems. Restarted propranolol. Attacks have become more severe and frequent. She was off work 2-3 days and is worried that she may lose her new job.

How do you manage during these lengthy attacks? What do you do to try to get relief?
She had been told that nothing helps once the attack begins and prevention is the best approach. She takes over-the-counter naproxen but to little effect. Vomiting no longer gives relief. Hot compresses, warm showers help. During the attack, she becomes irritable and angry and avoids contact with others, taking the phone off the hook.

You mention feeling irritable and angry during your attacks. Have you had any other problems with your mood?
Her headaches make her very depressed and the aura makes her feel panicky, especially if at work. She also has bouts of depression unrelated to her headaches – worse during winter. She saw a psychiatrist and was treated with sertraline (Zoloft). She noticed no improvement in mood but could not continue therapy because of insurance problems.

Does anyone else in your family have headaches or depression or other mood problems?
Mother has migraine and depression.

You are worried about your job, and you also feel depressed at times. Is your social or family life affected? Are you able to enjoy yourself?
Leads full, active social life except when she has a headache bout. In probationary period with new job, which she enjoys. Lives in apartment with roommate. Both parents live locally. One sibling, a sister. Family ties close.

Aside from these severe headaches, do you have other headaches that also need attention?
She has mild headaches that can be either ignored or easily controlled with 1-2 acetaminophen tablets. They do not interfere with work and are attributed to stress or fatigue.

Does anything seem to trigger your severe headaches?
Stress, missed meals, bright sunshine and air travel have precipitated attacks.

PRETEST

1) What is the diagnosis?
2) Does this patient require imaging? If yes, which studies and why?
3) What features help to determine the diagnosis?
   a) Duration of visual symptoms.
   b) Unilateral location of visual and pain symptoms.
   c) Duration of attack.
   d) Timing of visual symptoms and headache.
   e) Paresthesias.
   f) Lack of response to propranolol.
   g) Light/sound sensitivity.
   h) Intolerance to odors (osmophobia).
   i) Positive family history.
   j) Vomiting associated with headache.
   k) Diarrhea associated with headache.
4) What are the goals of therapy for this patient?

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COMMENTARY

Theresa has migraine with aura (formerly known as "classic migraine"). She will be referred for a psychiatric consultation for evaluation and diagnosis of comorbid depression/anxiety.

Tell me about the vision problems, Theresa. What happens to your vision and how long does the problem last?
Theresa describes a typical migraine aura consisting of visual disturbances largely confined to one visual field. While she experiences some continued blurring of vision, the aura itself lasts less than one hour, meeting the International Headache Society (IHS) diagnostic criteria for migraine with typical aura.

How about the headache itself? Where do you feel the pain and how long does the attack last? Do you have any other symptoms with the headache? Do you ever have numbness, tingling or other unusual sensations during or before the attack?
The location and duration of the headache are compatible with a diagnosis of migraine. Her nausea/vomiting and light and sound sensitivity are also diagnostic. Strong odors are known to trigger and/or exacerbate attacks in some migraineurs. In migraine with aura, sensory disturbances, such as the unilateral paresthesia she describes, often follow the visual disturbances. Fatigue or weakness can occur in the postdrome or final phase of the attack; however, Theresa's comment about feeling so "bad" after the migraine that she misses work suggests the need for further questioning about depression.

How often do you get these headaches? Has their severity or frequency changed?
Even when the diagnosis seems clear and the headache condition is long-standing, it's vital to determine if there has been a change in the headache pattern that might suggest the emergence of secondary headache due to underlying pathology. Her concern about losing her new job provides an answer to a related issue: "Why is this patient with a long-standing complaint here today? What has changed?"

Onset at puberty is very common in women. Oral contraceptives are frequently implicated in worsening migraine.

How do you manage during these lengthy attacks? What do you do to try to get relief?
Theresa has been misinformed about migraine and is in need of more effective abortive therapy.

You mention feeling irritable and angry during your attacks? Have you had any other problems with your mood?
Her depressive symptoms warrant an initial psychiatric evaluation. She could then be referred to a psychologist for supportive therapy if indicated. Choice of propranolol as preventive therapy is questionable, given her depression and low frequency of attacks. However, given that Theresa also reports feeling anxious at the onset of her aura, the propranolol should be discontinued by tapering the doses since it also has anxiolytic effects. Amitriptyline may be considered after review with the consulting psychiatrist.

Does anyone else in your family have headaches or depression or other mood problems?
A positive family history is common for both migraine and mood disorders; comorbidity occurs more frequently than by chance, as shown in a number of epidemiological studies.

You are worried about your job, and you also feel depressed at times. Is your social or family life affected? Are you able to enjoy yourself?
Her active life and positive attitude suggest that her quality of life is not significantly impaired by either the depression or the migraines. She might respond well to nonpharmacologic management, such as biofeedback and relaxation therapy.

Aside from these severe headaches, do you have other headaches that also need attention?
It is not uncommon for depressed migraineurs to have frequent tension-type headaches that last days to weeks. Unless this question is asked, the clinician may fail to diagnose and treat these less severe but persistent headaches.

Does anything seem to trigger your severe headaches?
These are all common migraine triggers; they are also largely preventable or avoidable. One can mention some simple prevention strategies, such as wearing sunglasses outdoors on bright days to avoid the visual stimulation. For air travel, one can suggest packing snacks, water and pain relievers in a carry-on. Some basic instructions on deep breathing for stress reduction might also be worthwhile. Theresa's response to these suggestions will help in deciding whether she is a good candidate for behavioral approaches versus pharmacologic prophylaxis.

The propranolol is discontinued by tapering the doses. Options for acute treatment are discussed with Theresa. Given the rapid onset of her migraines, a fast-acting triptan or nasal DHE would be a reasonable choice. She is reluctant to try sumatriptan by injection. A second-generation triptan is prescribed, and Theresa is instructed to take it during the aura, rather than waiting for the headache to build.

THE CLINICAL VARIETIES OF THE MIGRAINE VISUAL AURA

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Aura symptoms occur in approximately 15% of all patients with migraine and form the basis for the classification of the migraine syndrome into those attacks with and without aura, formerly known as classic and common migraine respectively. On occasion, the aura symptoms may represent the sole manifestation of a migraine attack, a phenomenon referred to as a *migraine equivalent*. Although the aura associated with migraine may involve one or more sensory, motor or cognitive domains, the visual aura accounts for approximately 90% of all cases.

Much of our information concerning the varieties of the visual aura comes from detailed descriptions from physicians and scientists who themselves suffered from migraine with aura. Supplementary information has been obtained from retrospective reviews of patients charts, as well as from questionnaires, interviews, and drawings by artistic patients.

Although there is considerable variability in the nature, complexity, and duration of the visual aura between and even within patients, most descriptions of the aura confine themselves to the *phosphene* and the *scotoma*.

PHOSPHENE

Phosphene refers generally to a luminosity perceived when the retina undergoes non-luminous stimulation, as by pressure on the eyeball when the lid is closed. Often the first and simplest hallucination, this "positive" phenomenon takes the form of a burst of stars, sparks, flashes or simple geometric forms across the visual field. Phosphenes of this type are usually white but may have brilliant spectral colors. They may number many hundreds and move rapidly back and forth across the visual field. Occasionally a single phosphene may predominate and then disappear suddenly, leaving a trail of dazzlement or blindness in its wake. Although such phosphenes may be confined to one half or one quadrant of the visual field, they are often bilateral and not infrequently cross the midline. Other elementary hallucinations that are commonly experienced are rippling, shimmering, and undulation in the visual field, which patients may compare to the appearance of wind-blown water or heat waves rising from pavement. During or after the passage of these phosphenes, patients may notice, upon closing the eyes, a brilliantly colored motif that appears as a mosaic or honeycomb pattern which might rapidly transform into a kaleidoscope.

SCOTOMA

In some patients, these evanescent phosphenes are usually a prelude to a longer-lasting second stage which consists of a far more elaborate hallucination within the visual field – the migraine scotoma. In others the scotoma may precede the scintillations or occur in their stead. The majority of migraine scotomata present as a hazy spot or sudden brilliant luminosity near the center of vision which gradually expands and moves slowly towards the edge of the visual field, assuming the form of a giant crescent or horseshoe. At the fringes of the scotoma there may be a spectrum of colors, from which the term *migraine spectra* is derived. The term *scintillating scotoma* denotes the characteristic flickering of luminous migraine spectra, and the rate of scintillation has been estimated to range between 8–12 scintillations per second. The margin of the scotoma, which may resemble the fortifications of a walled city (*fortification spectra*), usually advances at a constant rate and usually takes between 10 and 20 minutes to pass from the fixation point to the edge of the visual field where it finally disappears. In some auras, the shape of the scotoma is very well preserved as it drifts, whereas in others the shape changes as it proceeds across the visual field.

Usually the scotoma affects both the upper and lower quadrant of the right or left hemifield of vision, but occasionally only the upper or lower quadrant is affected. Bilateral scotomas may evolve synchronously in both half-fields. The negative scotoma can last from 5 to 30 minutes, but there is considerable inter- and intra-patient variability.

The visual aura described in this case represents a typical temporal sequence and time course whereby the patient experiences a sudden bright luminous band (phosphene) which moves in her right hemianopic field and becomes filled with a scintillating spectrum of colors (scintillating scotoma) which multiply until a hemianopic field of visual loss results (negative scotoma). The aura evolves over a period of 10-15 minutes but she is left with blurred or dazzled vision for some time thereafter and well into the headache phase.

OTHER DISRUPTIONS OF VISUAL PERCEPTION

Although the phosphene and scotoma comprise the majority of migraine auras, there are other more complex phenomena that are equally characteristic. Polygonal shapes such as squares, rhomboids, trapezoids, hexagons, or more complex shapes, sometimes comprising tiny replicas of themselves, dominate the picture. These shapes may coalesce to form meshes or what patients may describe as webs, honeycombs, mosaics, networks and lattices. These latticeworks may appear superimposed upon the background visual world to create a grid-like effect. This fragmentation of the visual scene is sometimes referred to as *mosaic vision*. Sometimes spirals or circles are seen, and these complex geometric designs may continuously change shape, size and motion, a phenomenon known as *metamorphopsia*. In contrast to most visual auras, which are often accompanied by an illusion of motion, some patients experience what has been referred to as cinematographic vision, where motion appears to be lost. At such times, the patient sees only a rapidly flickering series of "stills," as in a film run too slowly.

Lilliputian (micropsia) and brobdingnagian (macropsia) vision denote an apparent diminution or enlargement in the size of objects, or an apparent recession or approach of the visual world. If such changes occur gradually rather than abruptly, patients will experience zoom vision – a closing-down or opening-out in the size of objects as if observing them through the changing focal lengths of a zoom lens.

The fascination and curiosity that the migraine visual aura has aroused since antiquity has continued into the modern era. Highly sophisticated functional neuroimaging and neurophysiologic studies are beginning to unfold the pathophysiologic mystery of the visual aura and, in the process, provide new insights into the underlying biology of the migraine syndrome.

Suggested Reading

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Diagnosis: Migraine with Aura

At least 3 of the following 4 characteristics are present:

1) One or more fully reversible aura symptoms indicating focal dysfunction of cerebral cortex or brainstem.
2) At least one aura symptom develops gradually over > 4 min, or 2 or more symptoms occur in succession.
3) No single aura symptom last more than 1 hour.
4) Headache follows aura with a symptom-free interval < 60 min (alternatively, it may develop before or concurrently with the aura). The headache usually lasts 4-72 hours, accompanied by nausea/vomiting and/or light/sound sensitivity, as with migraine without aura.

And: History, physical and neurologic exams do not suggest underlying pathology; or, suspected abnormalities have been ruled out by appropriate investigations.

UNUSUAL AURAS: WHEN TO WORRY

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The migraine aura is a complex array of symptoms representing focal cortical or brainstem dysfunction. The aura develops gradually over 5 to 20 minutes, lasts for less than 60 minutes and is followed by a migraine headache within one hour's time. Migraine auras are typically visual, although they can be characterized by sensory, motor, language and brainstem disturbances. Auras are part of the migraine process; thus, by definition, they are benign events. There are reported cases, however, of apparently typical migrainous auras caused by underlying pathologic conditions.

Arteriovenous malformations (AVMs) are one of the most feared underlying causes of aura. The true relationship between intracranial vascular malformations and migraine is not known, but AVMs are linked to migraine and a migrainous aura may be the only clinical manifestation of an indolent AVM before it bleeds. Arteriovenous malformations in the occipital, parietal, and temporal lobes are most likely to present with aura-type symptoms.

Red flags suggestive of an underlying AVM [1]:

- Late age of onset of symptoms
- Absence of a family history for migraine
- Auras of short duration (5-10 minutes)
- Aura symptoms always on the same side
- Absence of typical angular, scintillating features of migraine visual aura
- Complicated auras (eg, hemiparesis) with residual symptoms
- Unusual neurologic symptoms including seizures and coma
- Headache starts before rather than after aura
- Headaches of short duration (several hours)
- Significant examination findings including cranial bruits and distortions in one quadrant of visual field

Intracranial neoplasms can also present with secondary migrainous aura. Meningiomas, specifically involving the occipital lobes, are the most common primary tumors to present with aura symptoms.[2] Tumors involving the occipital cortex typically produce scintillating scotomas very reminiscent of those seen in migraine. Brain metastases to the superficial cortex can present with aura, probably secondary to parenchymal irritation.

Red flags suggesting an underlying neoplasm:

- Late age of onset of symptoms
- Aura symptoms always on same side
- Episodic migraine with aura that becomes a chronic daily headache in the absence of explanatory transforming factors (eg, analgesic overuse, head trauma)
- Headaches unresponsive to conventional therapies
- Associated new-onset seizures
- Abnormal examination findings including papilledema and changes in awareness

The epileptic aura can be very similar to the migraine aura and, without the presence of tonic/clonic activity, differentiation can be difficult. The characteristics of the aura will help in making the correct diagnosis.

Red flags suggestive of epileptic aura [3]:

- Auras of short duration (<2 min)
- Aura includes changes in awareness, positive motor phenomena or automatisms
- Abnormal EEG findings
- Multicolored spherical or circular patterns are more typical of epileptic visual auras
- Brief stinging, cramping or burning sensations are more typical of epileptic sensory aura

Scintillating scotomas, which are very common symptoms of the migraine aura, may also be a manifestation of a **lesion in any part of the visual sensory pathway**, the most common sites being the retina, the vitreous, and the occipital striate cortex.[4] Acute vitreous or retinal detachment can present with flashes or sparks of light that mimic photopsias or scintillating scotomas of migraine. Visual symptoms from retinal or vitreous disease affect the vision of one eye only, are longer in duration than the migraine visual aura and lack the presence of headache. Vascular malformations or tumors involving the occipital cortex can present with visual symptoms reminiscent of the migraine aura.

Cerebral venous thrombosis, when it causes damage to one or both occipital lobes, may manifest as positive visual symptoms suggestive of a migraine aura. Headache and neurologic symptoms (seizures, focal motor or sensory disturbances) are typical of cerebral venous thrombosis. Cerebral venous thrombosis should be considered as an etiology of new-onset migraine with aura in the setting of severe infection, dehydration, pregnancy, cancer, antiphospholipid antibody syndrome, sickle-cell disease, or polycythemia vera.

Systemic lupus erythematosus (SLE) can cause scintillating scotomas suggestive of a migraine aura.[4] SLE is a concomitant disorder in some migraineurs, but in others SLE probably leads to changes in the retinal vessels causing transient visual phenomena.

Multiple discrete aura attacks that occur within a single day, even with associated migraine headache, may suggest an underlying **coagulopathy**. Typically migraineurs only experience a single aura attack within a day, so multiple auras are abnormal. The author saw a female patient with a history of migraine with aura who experienced 5 distinct aura spells within a 2-day period. Some of the auras occurred with headache and some without. Laboratory testing revealed an antiphospholipid antibody syndrome. On daily aspirin she has had no repeat multiple aura events.

Although rare, **carotid artery dissection** can present with transient symptoms suggestive of a migraine aura. Differentiation from true migraine with aura can be difficult, especially when vessel dissection is associated with a unilateral headache along with focal neurologic symptoms. (Headache is the most common symptom of internal carotid artery [ICA] dissection, occurring in 84% of patients.)

Red flags suggesting ICA dissection [5,6]:

- Prolonged aura symptoms
- Maximum severity of aura symptoms at onset
- Spread of aura symptoms from one modality to another (visual to motor or sensory)
- Headache starts during rather than after aura
- Associated hemiparesis and hemineglect (eg, lapses in grooming on one side) on examination

Migraine-like auras have been associated with AVMs and tumors, seizures, carotid artery dissection, ocular disease and connective tissue disorders. A complete aura and headache history in regard to aura duration, progression of aura symptoms, age of onset of aura and headache, whether aura symptoms side-shift or are locked to one side, and a complete neurologic examination can help the physician identify which auras need to be evaluated for secondary organic causes.

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MECHANISMS OF THE MIGRAINE AURA

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It has long been thought that the migraine aura might result from an phenomenon observed in rodent brain and retina known as *spreading depression (SD) of Leao*, although it could also be termed spreading activation.[1,2] In this neuroelectric event, neuronal depolarization is followed by suppression of neuronal activity and associated oligemia in a wave that spreads slowly across the surface of the brain from the occipital cortex. This experimental phenomenon correlates well with the features of a typical visual aura, in which peripheral scintillations (a stimulative, positive symptom) precede an expanding visual scotoma (a suppressive, negative symptom). Cerebral blood flow (CBF) has been observed to fall to oligemic values in posterior regions of the cortex during attacks of migraine with aura.[2] Investigation of this model in humans, however, remains far from complete and has not yet served to establish SD as the mechanism of aura.

The early depolarizing or activation phase of experimental SD is associated with a transient but pronounced CBF increase, presumably in response to increased demand of neurons attempting to repolarize. This transient hyperemia has not been observed until recently in migraine patients, possibly because most studies have relied on indirect measures of CBF and patients were not studied until well into the aura. Clinical studies of the early seconds to minutes of an attack are of interest, since the vasodilation seen in the earliest stage of SD may be linked to the mechanisms of the headache.

Our own studies employing the fMRI-BOLD technique (which measures relative changes in oxygenation of brain circulation) have shown hyperoxygenation of the occipital cortex occurring early in the course of visually activated headache and in one case of spontaneous migraine aura.[3] We also observed activation and subsequent hyperoxia of the red nucleus (RN) and substantia nigra (SN). Experimental SD directly alters RN function via subcortical projection neurons in the guinea pig, and stimulation of the RN in the rat induces analgesia. [4,5] Abnormal function of the RN therefore may be relevant to the head pain experienced by the patient. Nigrostriatal dysfunction may be associated with the pain, nausea, vomiting and other dysautonomic features of the migraine attack. [6]

The mechanisms of bilateral RN and SN involvement in the migraine attack remain to be determined. Hyperoxia of these structures does not determine if their function is activated or suppressed. These studies do suggest that brainstem structures involved in pain and associated symptoms of the migraine attack may be involved through direct neuronal pathways that are activated in the wave of depolarization and subsequently suppressed. Dysmodulation of these brainstem centers could alter the nociceptive aspects of their function and alter the appreciation of pain via central trigeminal structures.

Enhanced excitability of occipital cortex neurons has been proposed as the basis for the spontaneous or triggered onset of the migraine aura.[7] In a study using transcranial magnetic stimulation (TMS), 11 of 11 migraineurs with aura visualized phosphenes (luminous sensations) on occipital cortex stimulation, compared to 3 of 11 controls.[8] The patient with the lowest threshold level experienced her typical migraine aura in response to TMS.

The reasons for increased neuronal excitability in migraine patients remain to be determined and may be multifactorial. Calcium channel abnormalities have been inferred following the discovery of mutations in a P/Q type neuronal calcium channel gene (CACNL1A4) found in several families with a rare migraine subtype called familial hemiplegic migraine.[9] Disorder of mitochondrial energy metabolism, deficiency of systemic and brain Mg2+, and abnormalities of glutamate metabolism may also be implicated.[10-12] In addition to contributing to the excitability of neurons, these same factors may be involved in propagating SD.

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MIGRAINE PROPHYLAXIS

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One-quarter of migraine patients in the general population have > 4 migraine attacks a month, and one-third have very disabling episodes. Migraine treatment is complicated by the fact that attacks can vary in frequency, severity, duration and associated symptoms. Cycles of frequent headache can occur from time to time. Patients differ in comorbidity, coping abilities, response to abortive medications and treatment preferences.

Indications for prophylactic pharmacotherapy include, but are not limited to:

1. Two or more attacks a month that produce disability that lasts 3 or more days
2. Contraindication to, or ineffectiveness of, abortive medications
3. Use of abortives more than twice a week

Goals of prophylaxis include: (1) reducing the frequency and severity of the attacks, (2) making acute attacks more responsive to abortive therapy, and (3) improving quality of life.

Steps before prophylactic therapy is initiated include recognition of comorbidity such as depression, panic attacks, anxiety and bipolar disorder. Overuse of symptomatic medications, including analgesics, ergotamine, and triptans, with resulting drug-rebound headache must be recognized. Such patients have to be detoxified from analgesic/narcotic medications. Pharmacotherapy should always be combined with non-pharmacological approaches including dietary adjustments, reducing triggers, physical exercise, and relaxation training. Ensuring adequate contraception for women with potential to become pregnant is extremely important prior to beginning prophylactic treatment.

Practical Considerations

1. **Start low, go slow.** It is extremely important to start small doses of prophylactic medications initially and gradually build up the dosage as the patients tolerate the medications better by this strategy. Migraineurs frequently require a lower dose of a preventive medicine than is needed for other conditions.

Continued on next page.

2. **Give adequate trial with optimum dose** for at least 3 months before the medication is pronounced ineffective.
3. **Withdraw the medications gradually.** This is particularly important with beta-blockers, calcium channel blockers, and SSRIs. If the headaches are well controlled, a drug holiday can be undertaken following a slow taper program. Many patients experience continued relief after discontinuing the medication or may not need the same dose. A dose reduction may provide a better risk-to-benefit ratio.

The Role of Comorbidity

Comorbidity may result in certain therapeutic opportunities, and/or it may impose therapeutic limitations in using certain medications. Both principles are illustrated by the case vignette, where the patient has been prescribed a beta blocker that may exacerbate her depressive symptoms. A tricyclic antidepressant such as amitriptyline could be tried; selective serotonin reuptake inhibitors such as fluoxetine (Prozac) are sometimes used for migraineurs with comorbid depression; however, their efficacy has not been well studied to date.

Long-term Management

Generally, prophylactic treatment is given for at least 6 months. It is very important to let the patient understand that prophylactic medications take a number of weeks to begin to show the desired effect. In many, the medications may have to be resumed after a while and many patients with chronic migraine need continuous prophylactic therapy. Clinical experience has indicated that tachyphylaxis becomes a problem in long-term management with prophylactic agents. Therefore, it is important to monitor the patient over a period of time and medications may have to be changed.

Migraine Prophylactic Agents

Class	Agent	Dosage
Beta-adrenergic Blocking Agents	*Propranolol (Inderal)	40-240 mg/day in divided doses
	*Propranolol long-acting (Inderal LA)	60-160 mg once daily
	Nadolol (Corgard)	40-160 mg once daily
	*Timolol (Blocadren)	Up to 20 mg twice daily
	Metoprolol (Lopressor)	50-100 mg/day
Tricyclic Antidepressants	Amitriptyline (Elavil & others)	10-200 mg/day
	Nortriptyline (Pamelor, Aventyl)	10-75 mg/day
	Protriptyline (Vivactil)	10-40 mg/day
Calcium Channel Blockers	Verapamil (Calan, Isoptin)	80-360 mg/day
	Diltiazem (Cardizem)	up to 200 mg/day
5-HT2 Antagonists	*Methysergide (Sansert)	4-8 mg/day
	Cyproheptadine (Periactin)	4-16 mg/day
NSAID	Naproxen sodium (Anaprox)	500-1000 mg/day
Antiepileptic Agents	*Divalproex sodium (Depakote)	500-1500 mg/day
	Gabapentin (Neurontin)	600-2400 mg/day

*Approved by the FDA for migraine prophylaxis.

Choice of Agent

Based on a combination of the published literature and personal experience, Tfelt-Hansen and Welch developed a comparated rating using a scale from + to ++++.

Drug	Clinical efficacy	Scientific proof for efficacy	Side effect potential	Examples of side effects (contraindications)
Beta blockers	++++	++++	++	Tiredness, cold extremities, vivid dreams, depression (asthma, brittle diabetes, A-V conduction defects)
Divalproex	++++	++++	++	Nausea, asthenia (liver disease)
Gabapentin	++++	+++	++	Fatigue, sleepiness, dizziness, ataxia
Methysergide	++++	++	+++	Hair loss; chronic use 1/2500 patients—fibrotic disorders (cardiovascular diseases, renal disease)
Naproxen	++	+++	++	Dyspepsia, peptic ulcers (active peptic ulcers)
Amitriptyline	++	++	++	Sedation, dry mouth, weight gain (glaucoma)
SSRIs	++	+	+	
Verapamil	+	+	+	Constipation (bradycardia, A-V conduction defects)

SSRI = selective serotonin reuptake inhibitor. Modified from Tfelt-Hansen & Welch, 1993.

Reasons for Failure

Some reasons for prophylactic treatment failure include wrong diagnosis, not recognizing comorbidity, inadequate dosage of medications, inadequate treatment period, and unrealistic expectations. Agents that may interfere with effective prophylaxis include concomitant use of excess analgesics particularly combination analgesics, excess ergotamine, excess triptans, oral contraceptives, and vasodilator drugs such as nitroglycerine and nifedipine.

Suggested Reading

Tfelt-Hansen P, Welch KMA. Migraine: Prioritizing prophylactic treatment. In: Olesen J, Tfelt-Hansen P, Welch KMA (eds.): The Headaches. New York, Raven Press, 1993:403-404.

Silberstein SD, Lipton RB, Goadsby PJ. Headache in clinical practice. Oxford, ISIS Medical Media, 1998.

Ramadan NM, Schultz LL, Gilkey SJ. Migraine prophylactic drugs: proof of efficacy, utilization, and cost. Cephalalgia 1997;17:73-80.

POSTTEST—TRUE OR FALSE

1. Headache must follow or accompany the aura in order for the diagnosis of migraine with aura to be made.
2. Preventive treatment, when indicated, should be given a trial of at least 3 months at optimal dosing before the decision is made to discontinue as ineffective.
3. Use of acute agents (e.g., triptans, ergotamine) should be avoided in patients on prophylactic medication.
4. Brief, sudden auras are more likely to be benign in origin than prolonged auras.
5. In the presence of other unusual findings, aura symptoms that always occur on the same side may suggest the possibility of underlying disease.

Answers—Pretest

1. Migraine with aura. She requires further evaluation for comorbid depression/anxiety.
2. Imaging would not be considered necessary by most experienced clinicians. Her aura and migraine symptoms are quite typical; the condition is long-standing; and she reports no recent change in symptoms or the pattern of the attack.
3. The diagnosis can be made on the basis of a, b, c, d, and j; e is a frequent aura symptom but not required for the diagnosis; h and i are typical of migraine, providing additional support for the diagnosis.
4. Controlling the pain and associated symptoms of her rapid-onset attacks so that she can continue to function or at least rest more comfortably. Providing cost-effective treatment for her depression/anxiety (avoiding her insurance problems). Offering stress management strategies that may aid in controlling both her anxiety and her migraines.

Answers—Posttest

1. F 2. T 3. F 4. F 5. T