Migraine With Persistent Visual Aura
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Migraine with persistent visual aura is a rare but fascinating entity with symptoms that may be similar or dissimilar to migraine visual aura.

CLINICAL HISTORIES

Case 1.—This 74-year-old woman was referred by an ophthalmologist with an 8-week history of squiggles in her left field of vision of both eyes inferior more than superior. During the day, if her eyes were closed, she would see kaleidoscope-type letters with a colored background. The visual symptoms were constant except for several hours in the evening when there was total resolution after her daily vodka and white wine.

There was a history of recurring headaches since the age of 20 occurring about once a week or sometimes more often consistent with migraine without aura, relieved by acetaminophen. Perhaps 10 years ago, she believes that she may have had similar visual symptoms once or twice for a brief time. No other history of visual aura. During the time that she has had the persistent visual symptoms, she has had her usual headaches about once a week, relieved by acetaminophen in about 1 hour.

A magnetic resonance imaging (MRI) of the brain and magnetic resonance angiogram (MRA) of the brain and erythrocyte sedimentation rate were normal. Evaluations by her cardiologist, ophthalmologist, and retina specialist were all normal except for age-related macular degeneration.

A prior neurologist had started her on divalproex sodium which was discontinued due to nausea.

Over the next 4 weeks, the symptoms persisted with only a slight decrease in intensity despite treatment with 60 mg of prednisone daily for 3 days, topiramate 100 mg daily, intravenous valproic acid 500 mg every 8 hours for 2.5 days, 20 mg of intravenous furosemide, and 10 mg of intravenous promethazine.

Case 2.—A 25-year-old woman has had recurring headaches since the age of 7. The headaches have increased in frequency, becoming almost daily for the last couple of months, with a bilateral aching with an intensity of 6/10, present most of the time with light and noise sensitivity and occasional nausea. She has been taking no medications for the headaches.

Since the age of 7, she rather constantly sees what she describes as television static that is getting worse and more noticeable. She sees tiny air molecules, also described as rain on a window, which are most noticeable if she is looking at the sky or a white background, present in both eyes and with the eyes closed. The symptoms can interfere with reading. There is a past history of attention deficit disorder on amphetamine—dextroamphetamine. Her sister has migraine. Neurological exam was normal. Examination by a
neuro-ophthalmologist including visual fields was normal. An MRI of the brain was normal.

Case 3.—A 39-year-old man was referred by his neurologist for a second opinion for persistent visual phenomena. The visual phenomena consisted of small “fuzzy holes.” The holes slowly became larger over several minutes, eventually encompassing half of the man’s visual field. This was followed by a severe headache associated with nausea and vomiting. The visual symptoms lasted a few hours and resolved before the start of the headache. The headaches partially responded to a butalbital combination, but the subject was always left with a mild headache, similar to a 24-hour hangover. He had headaches approximately once or twice a month, and the usual trigger was stress or the “letdown” following stress. The subject occasionally experiences head pain triggered by light.

The patient noticed with each headache that, although his visual symptoms resolved, he was left with faint squiggly lines and a slight haze in his entire visual field. He would usually notice this while looking at the sky or a flat white wall. His headaches were effectively prevented with propranolol or verapamil, and the frequency was reduced to only once or twice a year. However, the haze/visual phenomena were persistent when headaches did occur.

The visual disturbance worsened with every headache. Over the next few years, the visual phenomenon was described as “snowy vision,” which was present all the time and would worsen episodically, unassociated with pain. The subject described the visual phenomenon as like looking at a television with bad reception. It moved and swirled, and covered his entire visual field. When he looked at the sky or a white wall, the snowy effect was dark gray. He also saw constant “sparks,” “shooting stars,” and “floaters.” When the patient closed his eyes or looked at a dark surface, he saw the same effects, except that all of the visual phenomena were white, similar to looking at a sky full of moving and shooting stars.

The visual phenomena were least noticeable when the man looked at surfaces or objects that had middle tones mixed with textures, shadows, and colors, or had dull, rough surfaces. The visual phenomena then seemed to blend into objects (e.g., a textured wall). The visual phenomena were also less noticeable when he was watching television or movies and most profound when he was looking at flat or shiny, 1-color surfaces.

His past medical history was negative. His mother had migraine with visual aura. Neurological examination was normal.

The patient had tried various medications for the visual phenomena, including anti-epileptic drugs such as divalproex sodium (oral and intravenous), lamotrigine, gabapentin, carbamazepine, and topiramate. Other prophylactic agents utilized were cyproheptadine, methylphenidate, sertraline, acetazolamide, baclofen, coenzyme Q10, magnesium oxide, and feverfew. The only medication that produced an improvement, albeit mild, was baclofen. This was at high doses, however, and also produced sedation, making it difficult for the patient to participate in normal activities.

Case 4.—This 36-year-old woman was initially seen with a history of headaches since the age of 10 that had been daily for 1 month and previously every 1 to 2 days for a number of years intermittently with an intensity ranging from 1-10/10 described as a behind the eyes pressure associated with nausea, light, and noise sensitivity. Ibuprofen or an isometheptene combination medication would dull the pain. She would take a few doses of an isometheptene combination medication, and the headache was gone in about 12 hours. Alcohol and her menses were triggers. Sumatriptan, rizatriptan, eletriptan, and almotriptan were not effective. Over 1 year ago, she was taking topiramate 100 mg daily for about 1 year, and the headaches decreased to about once a month, but she discontinued the medication on her own and the frequency increased.

Since the age of 15 years, she had seen circles of light in the center of vision which were bluish intermittently without a scotoma lasting about 40 minutes once every 1 to 2 months without associated headaches. Since the age of 15, she also reported seeing afterimages or tracers which were rather constant and more noticeable in average light rather than in a darker room. Also, since about that time, she had seen clear little circles and fat lines or little bugs or television snows which were present all of the time if she was looking at a white wall. In a dark room, she saw blotchy shadows. She had no scotoma. She also saw shadowy swirling lights all of the time.
She saw a neuro-ophthalmologist 10 years previously and reportedly had a normal exam. An MRI and MRA of the brain 2 years ago were normal. She had seen 2 other neurologists in the prior several years. Propranolol and divalproex sodium did not decrease the frequency of the headaches or visual symptoms, and the topiramate did not affect the visual symptoms.

Past Medical History of Depression.—Neurological examination was normal.

Examination by a neuro-ophthalmologist was normal. Her visual symptoms and headaches were unchanged on topiramate 100 mg daily but, when titrated up to 200 mg daily, after 2 months, she had 1 headache in the prior month, the palinopsia decreased to 2-3 episodes in the prior month, she saw occasional blush lights, and the television snow was less noticeable. The topiramate was decreased to 100 mg daily because of cognitive side effects and desvenlafaxine 50 mg daily was added. When seen again 2 weeks later, the headaches were daily and the visual symptoms just as noticeable as previously. Because of persistent cognitive side effects, topiramate was discontinued, and she was placed on verapamil sustained release 240 mg daily. She was next seen 14 months later. The headaches had decreased to 2 per month but had increased to 6 per month for the prior 3 months. The television snow was less noticeable, but the tracers were constant, and she was having a visual aura of blush lights 15 days per month with or without headache (usually without) lasting up to 1 hour.

Questions.—What is the diagnosis and pathophysiology of these patients’ visual symptoms? What treatments are available? What is the prognosis?

EXPERT OPINION

Migraine Aura and Persistent Migraine Visual Aura.—The aura associated with migraine is a fascinating phenomenon and has been a puzzle to migraine sufferers, clinicians, and scientists alike.1,2 About 20% of migraineurs experience migraine with aura; 99% are visual.3 Even then, the aura is not present with every migraine attack.

Migraine aura without headache is a less common phenomenon. In one study, the lifetime prevalence of migraine without aura, migraine with aura, and migraine aura without headache, respectively, were as follows: 16%, 7%, and 3% in women; and 8%, 4%, and 1% in men.4 In a study from an optometry service, risk factors for migraine aura without headache were female gender, migraine headache, and a history of childhood motion sickness.5 For most patients, the migraine aura without headache is episodic and lasts 15 to 30 minutes.

These cases are examples of an extreme and rare end of the spectrum, prolonged or persistent visual aura without migraine headache. According to the International Classification of Headache Disorders Second Edition description, “Aura symptoms persist for more than 1 week without radiographic evidence of infarction.”6 The diagnostic criteria are the following: the present attack in a patient with migraine with aura is typical of previous attacks except that one or more aura symptoms persists for more than 1 week and is not attributed to another disorder.

San-Juan and Zermeño summarized the 29 previously reported cases of persistent aura and reported a new case.7 The duration of symptoms ranged from 11 days to 28 years and the age of the patients ranged from 9 to 70 years.8-17 The aura is variably described as follows: a pinwheel of bright yellow and red in the left homonymous hemifield; scintillating geometric figures in the right visual hemifield; flickering photopsias, flashing lights and circles; snow and television static over the entire visual field and palinopsia; snow and flickering; rain-like heat waves with flickering lights; scintillating scotomas just to the left of center in both eyes; and shimmering points of light. Only one of the patients reported persistent unilateral numbness without visual or other symptoms,13 although 2 other patients had associated unilateral numbness with the visual symptoms.8,14 MRI scans of the brain were performed in 16 patients and reported as normal or showing non-specific or incidental findings.

Wang et al18 reviewed 23 previously reported cases of persistent visual aura (which include cases summarized by San-Juan and Zermeño7 and one additional case19 and excluded some cases for incomplete descriptions) and presented 6 new cases with a duration of less than 1 to 24 years. The mean age of onset of symptoms was 33.9 years (range 9-67 years), and the
mean duration of symptoms was 46.4 months (range 11 days to more than 20 years). Thirteen patients (44.8%) had headache worsening with the persistent visual aura of whom 11 had daily or very frequent headaches. Sixteen patients (55.2%) reported fluctuations in their visual symptoms such as chromatic changes, persistence, or discreteness. Six patients (20.7%) had superimposed migraine visual auras in addition to the baselines visual disturbance.

Eriksen et al rated the visual symptoms of each case using the Visual Aura Rating Scale (VARS), which includes the following 5 items: duration 5 to 60 minutes (3 points), develops gradually 5 minutes (2 points), scotoma (2 points), zigzag lines (2 points) and unilateral/homonymous (1 point), with the weighted sum as the VARS score (range 0-10 points) involvement.20 Eight patients (27.6%) had complete resolution of their visual symptoms, and a higher VARS score predicted a better outcome. Other predictors for complete resolution included scotoma, unilateral/homonymous involvement, and shorter duration of illness. Wang et al propose using the term “persistent visual aura” for those who have typical migraine visual aura symptoms and persistent visual disturbance for those whose symptoms are unlike typical migraine visual aura symptoms (eg, diffuse particles or granules).

Peatfield et al reported the prognosis of an additional 10 cases of persistent visual aura present for at least 2 months without permanent physical signs or scan abnormalities.21 The symptoms in 4 of the patients had resolved after a mean of 7 months, while 6 had continuing symptoms for between 2 months and 10.5 years. It was difficult to assess whether treatments including acetazolamide, topiramate, valproate, phentoyin, flunarizine, and chlorpromazine were of benefit. None of the patients came to any long-term harm.

Case number 4 also had persistent palinopsia, which is a rare migraine aura (as well as due to multiple other causes excluded in this case) and perhaps never before reported with such long duration.22 There are 2 case reports of topiramate causing reversible palinopsia.23 In this case, topiramate caused significant improvement in her palinopsia, which recurred when topiramate was discontinued.

Pathophysiology of the Aura.—The cause of the migraine aura has long been a source of intense interest and controversy. Wolff, a pioneer of the vascular theory of migraine, proposed that the neurologic symptoms of the migraine aura were caused by cerebral vasoconstriction24 and the headache by vasodilatation of the arteries of the scalp.25

Lashley’s experience of his own visual aura led to his proposal that the aura was due to a spreading abnormality that migrated over the visual cortex at a rate of 3-5 mm per minute.26 Based upon animal experimental evidence, Leão first described what he called spreading depression of activity in the cerebral cortex or cortical spreading depression (CSD).27 This promulgated a neural rather than a vascular cause for migraine aura.28

Abnormal cortical or neuronal excitability has been suggested as a possible factor predisposing to the phenomenon of CSD. The pathophysiologic basis of the migraine aura appears related to firing of excitatory nerves in the occipital cortex, which initiates CSD that moves anteriorly over the cortex. This, in turn, produces the aura.

In a rare form of inherited migraine with prolonged hemiplegic aura (familial hemiplegic migraine), the genes for about half of affected families have been cloned and found on chromosome 1 or 19. These mutant genes code for abnormal calcium channels, which may lead to firing of hyperexcitable neurons and result in severe aura. This is further evidence of a neuronal basis for aura.

The unpredictable and elusive nature of migraine has prevented many investigators from systematically studying migraine aura until advances in non-invasive technology. Research by Cao et al in which migraine was reliably visually triggered in 50% of subjects, enabled immediate measurement of early events of the migraine aura attack.29 One case of spontaneous migraine was also reported by Hadjikhani et al.30 Using newly developed functional MRI techniques, the investigators were able to show in some patients with aura a slow neuronal change in the occipital cortex, moving forward at a rate of 3 to 6 mm per minute. Contrary to what would have been expected with Wolff’s vascular theory, these patients showed vasodilatation and tissue hyperoxygenation at the
spreading edge of the aura, suggesting increased neuronal activity. This demonstrated that the brain was not ischemic during the aura.

There is little information on advanced imaging in persistent migraine visual aura. Jager et al describe 4 cases of persistent migraine visual aura where diffusion- and perfusion-weighted MRI imaging studies were normal. Relja et al describe a 43-year-old woman with a persistent migraine visual aura in her right hemifield with decreased left fronto-parieto-occipital and right occipital blood perfusion on perfusion MRI and single photon emission computerized tomography which was later normal on perfusion MRI when the symptoms had almost resolved. Cortical spreading edema, with restricted diffusion which spontaneously resolved, has been noted in a 58-year-old man with persistent migraine aura (right homonymous hemianopsia) without infarction on MRI. The cause of persistent migraine visual aura is not known but might be similar to a typical aura but with impaired cortical neuronal inhibition. Wang et al suggest that those with persistent visual disturbances which lack a moving quality and consist solely of positive phenomena may be a manifestation of sustained cortical neuronal dysfunction rather than reverberating waves of CSD. Chen and colleagues performed magnetoencephalography on 6 patients with migraine with persistent migraine aura, 39 patients with episodic migraine, 18 patients with chronic migraine, and 24 healthy controls. The visual cortex in patients with persistent visual aura maintained a steady-state hyperexcitability without significant dynamic modulation and differed from episodic and chronic migraine. This study also suggests a pathophysiologic link to sustained excitatory links possibly related to reverberating CSD.

**Diagnosis.**—The diagnosis is made from the history and a normal neurological and neuro-ophthalmological examination. Obtaining an MRI of the brain is certainly reasonable. However, the yield is probably low as MRI scans of the brain were performed in 16 patients and reported as normal or showing non-specific or incidental findings. Whether MRA scans of the brain and neck provide additional diagnostic information is not known from published cases. Internal carotid or vertebral artery dissection can mimic migraine with aura with a visual aura only or a march of symptoms (such as visual then sensory then dysphasia) associated with a migraine-like headache, but the reported duration of the visual aura is up to 3 days, and not 1 week or more. There is a case report of a 34-year-old woman with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy presenting with migraine with persistent visual aura without infarct, resolving after administration of intravenous lorazepam and mannitol. Vasculitis and coagulopathy testing may also be considered if loss of vision is a prominent part of the aura. However, the yield is not known from published cases where the prognosis is benign.

**Treatment.**—As there have been no medications shown effective in double-blind, placebo-controlled studies in persistent migraine aura without headache, the selection of treatment is necessarily empirical and anecdotal. Most patients elect no treatment if the disorder is episodic.

Medications reported as effective include cyproheptadine, dihydroergotamine, divalproex sodium, (mono- and polytherapy) furosemide intravenous 20 mg once and verapamil, fusosemide intravenous 20 mg once, lamotrigine (mono- and polytherapy), and nimodipine. In Dr. Aurora’s experience, low doses of divalproex sodium, gabapentin, and topiramate have been effective. In case 4, the persistent visual aura was less intense on topiramate 200 mg daily, and the palinopsia resolved. The time from starting treatment and complete response varied from several hours to 2 months and was typically 2 to 4 weeks. Of the cases reviewed by Wang et al, 17/29 reported headache improvement after treatment. In 10, the headache improved despite persistent visual symptoms, and in 2, the headache improved before complete resolution of the visual symptoms.

Most patients were reported as unresponsive to numerous medications including aspirin, ibuprofen, naproxen, carbamazepine, phenytoin, phenobarbital, divalproex sodium, lamotrigine, topiramate, diazepam, flunarizine, nimodipine, citicoline, verapamil, fluoxetine, sertraline, amitriptyline, nortriptyline, dothiepin, nefedipine, baclofen, propranolol, metoprolol, atenolol, sumatriptan, methylprednisolone, magnesium, acetazolamide, and pizotifen.
The treatment for persistent migraine aura is based on the neuronal theory of hyperexcitability. As suggested by case reports, calcium channel blockers such as verapamil and nimodipine may be effective. Familial hemiplegic migraine, as noted earlier, is caused by mutant voltage-gated P/Q-type calcium channel genes, which likely influence presynaptic neurotransmitter release, possibly of excitatory amino acid systems. Currently, there are no drugs designed as blockers for the P/Q calcium channel. Verapamil, which is an L-type calcium channel blocker, may be effective for basilar-type migraine and familial and sporadic hemiplegic migraine.

Acetazolamide, a carbonic anhydrase inhibitor, may work at doses of 500-1000 mg per day. Furosemide may be effective by inhibiting CSD through its effects on potassium.

Other treatments might be tried. Using nuclear magnetic resonance spectroscopy, low magnesium levels have been found in the brain, and magnesium deficiency has been associated with cortical spreading deficiency in an animal model. Although case reports have been negative so far, magnesium supplementation, at doses of 600 mg per day or 1000 mg intravenously, which may be effective for migraine with and without aura, might be effective in some patients.

Vitamin B2 or riboflavin is effective for migraine prevention, at a dose of 400 mg per day, maintained for 3 months, and could also be tried. Riboflavin’s effect may be due to increasing mitochondrial energy metabolism in the electron transport chain in aura, which may also lead to increased neuronal firing. Treatment with intranasal ketamine (a potent antagonist of N-Methyl-D-aspartic acid-glutamate receptor activation that blocks CSD), which reduces the severity of prolonged migraine aura, has also not been reported but might be effective.

Non-invasive investigations such as functional MRI and magnetoencephalography may allow us to further elucidate causative mechanisms and, hopefully, develop more effective targeted treatments.

REFERENCES
migraine can be stopped by intranasal ketamine. *Neurology*. 2000;55:139-141.

