Headache
© 2015 American Headache Society
ISSN 0017-8748
doi: 10.1111/head.12690
Published by Wiley Periodicals, Inc.

Resident and Fellow Section

Headache Rounds: Sudden, Transient Neurologic Symptoms in a Woman With Migraine

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The following article is a Graham Headache Center headache rounds presentation at the Brigham and Women's Faulkner Hospital by fellows Roni Sharon and Melissa Rayhill with special guest Tobias Kurth. It summarizes the case of a 36-year-old female with no history of migraine in the past, presenting with several transient neurological episodes associated with headache. Her history, symptoms, imaging workup is reviewed. Following the case is a discussion of the differential diagnosis for the patient's symptoms along with a review of the association of migraine with and without aura with vascular neurological insult such as stroke. The article also discusses the clinical implications of migraine as a risk factor for stroke along with possible treatment recommendations.

Key words: migraine, headache, TIA

(*Headache* 2015;55:1274-1282)

PRESENTATION OF CASE – melissa rayhill, md, and roni sharon, md, fellows in headache medicine, john r. graham headache center, brigham and women's faulkner hospital, boston, ma

The patient is a 36-year-old woman with a history of intermittent headaches beginning in her teenage years. Headaches were initially infrequent and had a strong menstrual association with no other known triggers. They typically lasted 12 to 24 hours, although recently she experienced episodes of pain lasting for up to 2 days. Her headaches were either unilateral or bilateral and were frontal and temporal. If untreated, they could reach an intensity of 8 on a 0–10 pain scale, and were associated with photophobia and nausea. There was no positional component, and they were not exacerbated by coughing or sneezing. She would occasionally experience mild left facial "numbness and tingling" of unclear duration during her headaches but not preceding them.

During a pregnancy 2 years prior to presentation, the patient had more pronounced neurological

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Accepted for publication June 16, 2015.

Section Editors: Morris Levin, MD and Matthew Robbins, MD

Conflict of Interest: None.

Funding: None.

Disclosures: Roni Sharon, MD: No disclosures; Melissa Rayhill, MD: No disclosures; Tobias Kurth, MD: TK has received honoraria for editorial services to Cephalalgia and the BMJ; Elizabeth Loder, MD, MPH: Acting head of research for the British Medical Journal, and receives salary support from the BMJ paid to the Brigham and Women's Hospital.

symptoms preceding some, but not all, of her headaches. She reported that her vision "became narrow" and that she saw "squiggly lines." This lasted for up to 20 minutes and was followed by one of her typical headaches. The patient had undergone a hysterectomy following an episode of heavy uterine bleeding in 2012. Her ovaries were not removed. Prior to that, she used a hormone-eluting intrauterine device for contraception. The patient denied any history of miscarriage or blood clots. She was otherwise healthy, with no history of head trauma. She drank alcohol socially, had never smoked and denied use of illicit drugs.

When the patient was 34 years old she sought emergency evaluation at an outside hospital due to sudden onset of a "head rush" followed immediately by "numbness" and a cold, tingling sensation in her left arm and leg. These symptoms gradually resolved 20 to 30 minutes after onset. The patient noted that her left hand felt particularly cold during the episode. She denied any weakness, chest pain, vertigo, nausea, or vomiting in association with this episode. She did note that she might have had a "floater" moving around in her left eye for about 3 weeks prior to the episode, but she had otherwise been well.

The patient reported that her maternal aunt, an identical twin of her mother, had multiple sclerosis. Her maternal grandmother had strokes in "old age" but there was no family history of premature cardiac events or cerebrovascular disease. Information obtained later in the patient's course, however, revealed that the grandmother had been just 55 at the time of her first stroke. A neurological examination performed in the emergency department was reported as normal.

Comment and Query by Discussant Dr. Tobias Kurth (TK), Research Director at the French National Institute of Health and Medical Research (Inserm) and the University of Bordeaux, Bordeaux, France; Adjunct Professor of Epidemiology at the Harvard T.H. Chan School of Public Health.—This is a very interesting case. There are several diagnostic considerations, including transient ischemic attack (TIA), ischemic stroke or migraine aura. What additional tests were done, if any, and what were the results?

Response by Dr. Sharon.—A magnetic resonance imaging study and magnetic resonance angiogram (MRI/MRA) of the brain, head, and neck were performed at this emergency department visit but the images and official radiology report are not available. The attending physician note remarked that the imaging studies were consistent with "acute to subacute infarct of the right body of the caudate nucleus." No aneurysm or other abnormalities were noted. The patient was admitted and underwent a transesophageal echocardiogram with a bubble test to assess the possibility of a patent foramen ovale (PFO). This was negative. A typical laboratory workup for stroke was performed and was reportedly normal. She was started on oral aspirin 81 mg daily and discharged.

Three days after discharge she presented again to the same emergency department. She reported that while tying her 2-year-old daughter's shoe and talking to the child, she had begun to stutter and experienced difficulty speaking. She described "only saying half sentences" at first, and then was unable to form words properly, although she knew what she wanted to say. Her brother was present at the time and said that he could understand only a few words and the rest was "gibberish." This episode lasted 45 minutes before completely resolving. The patient had no alteration of consciousness and her comprehension was preserved. She reported no weakness or sensory symptoms. Following the episode her neurologic examination was normal. In the emergency department, she was given aspirin and clopidogrel and transferred to this hospital.

Repeat MRI and MRA were performed (see Fig. 1). The official radiology report stated that "A tiny 3 mm focus of low diffusivity nonenhancing T2 prolongation is noted within the right caudate nucleus adjacent to the right lateral ventricle body." The report of the MRA described "an early take off of a right frontopolar artery from the right A1 segment." Repeat neurologic examination was normal with the exception of a right hypertropia, most apparent on left gaze. A cover-uncover test revealed a vertical skew deviation most noticeable on right gaze. A right wider than left palpebral fissure was also noted.

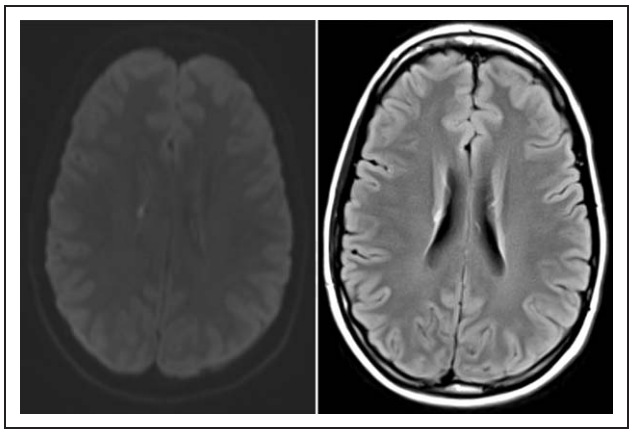

Fig. 1.—MRI brain, DWI left and axial flair right. A small focus of low diffusivity on DWI and nonenhancing T2 prolongation on axial flair is seen within the right caudate nucleus adjacent to the right lateral ventricle body.

Laboratory testing results of hematologic studies, renal function, and coagulation studies (antithrombin 3, protein C, prothrombin gene mutation) were normal except for a trace ANA titer. LDL was 114 mg/dL. A 24-hour Holter monitor and echocardiogram were performed and were unremarkable. The patient was discharged with advice to continue her daily oral dose of 81 mg of aspirin and was started on statin therapy with an LDL goal of less than 100 mg/dL.

Query by Dr. Kurth.—Do you think the first episode was a sensory aura? She had neurologic symptoms followed by a headache. Did she have a headache following the second event? Do you think the MR findings are related to the patient's symptoms?

Response by Dr. Rayhill.—The patient reported a prior history of short-lasting intermittent numbness of the face and arm before some headaches as well as a history of intermittent headaches with migrainous features. During her pregnancy she described episodes consistent with typical visual aura in association with her headaches. In view of this history, some might think that her first presentation to the ED was consistent with sensory aura and required no further evaluation. The physicians in the emergency department, however, did perform an additional workup. They may have been disturbed by the abrupt onset of symptoms, which many experts would say is a "red flag" suggesting that an event is less likely to be aura. Traditional teaching is that aura symptoms come on gradually and that sudden onset is more characteristic of an acute vascular event. Additionally, there is a big difference between "stuttering" and speaking gibberish. The latter is more concerning. Despite this, it is not clear that the MR findings related to the patient's symptoms. For one thing, the MR was read as compatible with a "subacute" infarct but had been performed in response to acute symptoms. In addition, the location of the lesion on restricted diffusion did not correlate with the patient's reported symptoms.

Discussion.—*Discussion of Differential Diagnosis – Dr. Tobias Kurth.*—What is the differential diagnosis in this case, and what are the features of her presentation that support or refute these possibilities? I think the differential diagnosis includes the following: multiple sclerosis (MS), a CNS inflammatory process, seizure, migraine aura, ischemic stroke, or TIA. Let's work through the list.

There are no T2 hyperintensities or so-called "white matter lesions" (WMLs) on the patient's MR scan, so MS is not a satisfactory diagnosis even though there was a family history of MS in a maternal aunt. Some think that MS may be associated with migraine but I do not find the data convincing. The lack of WMLs on imaging also makes it unlikely that some other inflammatory process is occurring. TIAs or stroke can be manifestations of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), for example, but in CADASIL the MRI would show much more dramatic white matter findings. In CADASIL, MRI findings typically precede other symptoms, so their absence is a strong argument against that as a diagnosis. Even if we did see a few white matter lesions, it would not help us much as we know that WMLs are associated with migraine and they are a common finding in such patients. Seizures can cause episodes of transient neurologic deficit, but neither episode sounds like a seizure. They were not stereotyped as one might expect.

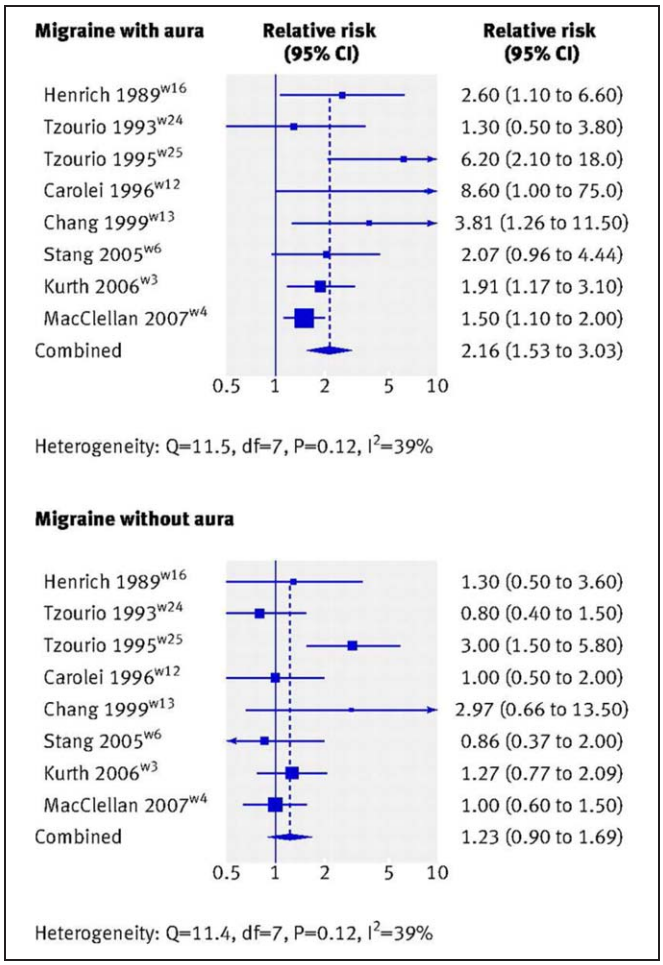

Fig. 2.—Association between migraine with and without aura and ischemic stroke. Reproduced with permission from Kurth.[13]

I would not diagnose aura as the cause of the patient's two sudden episodes of transient neurologic symptoms. The patient does have a history of migraine and describes temporary neurologic events that seem consistent with aura, particularly the episodes during her pregnancy. The high estrogen levels of pregnancy are known to predispose to aura. The two events that brought her to the emergency department, however, were distinct from her previous symptoms. In both of the episodes, the onset of symptoms was very sudden, which points to a vascular etiology. In summary, I think the most likely explanation for her episodes is that they were transient ischemic attacks (TIAs).

Sudden onset of symptoms is the strongest distinguishing factor between migraine aura and vascular etiologies of transient neurologic symptoms. Unlike most cases of migraine aura, this patient's symptoms were not stereotyped. With one episode she had sensory symptoms and with the other she had an expressive aphasia. It is also unclear whether the second episode preceded a headache. An additional feature that steers one away from aura is that the patient does not report a succession of different neurologic symptoms during these episodes. The occurrence of diverse symptoms in succession is useful in distinguishing aura from vascular problems such as TIA or stroke.[1] Finally, this patient reported only "negative" symptoms such as loss of sensation and aphasia. The most common positive symptoms are visual events such as seeing geometric patterns or flashing or

shimmering lights. Aura is still a possibility, of course. Perhaps the history of abrupt symptom onset is inaccurate or perhaps the headache following the second episode was mild and unreported. Still, aura seems less likely than other possibilities.

Dr. Tobias Kurth.—We know there is a strong association between migraine and the vascular system; this seems strongest for migraine with aura. Studies consistently show that migraine roughly doubles risk of ischemic stroke (Fig. 2).[2–4] The combination of migraine with oral contraceptive use boosts the risk and if you then look at the interaction with smoking, it may be even stronger although the effect estimate is very uncertain (4.22 to 19.34) because of the very small number of events. We see the roughly twofold increased risk in women but not men. There also appears to be an increased risk of hemorrhagic stroke as well.[5]

What is the relative contribution of migraine with aura to the risk of other cardiovascular outcomes? In particular, how does the risk conferred by migraine with aura compare to that associated with other major vascular risk factors such as smoking or hypertension?

The increased risk of ischemic stroke in those who have migraine with aura is most apparent in young women who have few or no additional risk factors for ischemic stroke.[3] I suspect the risk also is increased in men who have migraine with aura although it is probably hard to pick up this signal in studies due to the lower prevalence of migraine in men. Clinically, we see strokes in migraine patients with an absolutely "clean" vascular system. My group published a paper showing the interaction between having migraine with aura and the Framingham risk score (as a marker of the risk factor profile).[3] We only picked up a signal for migraine with aura and stroke in those subjects who had the lowest Framingham risk scores. As the Framingham risk score increased the signal disappeared. So if having a high Framingham risk score is associated with a reduced ability of blood vessels to react and constrict, you may actually take away a mechanism that produces stroke once you develop less elastic arteries. The arteries do not allow that mechanism to happen. However, these stiff vessels may produce an increased risk of myocardial infarction. Now, there isn't much evidence for this statement because we are looking at this question in a population setting that lacks detailed vascular work up. So the paradox is that stroke risk may be elevated in young people who have high aura activity and a low Framingham risk score, and as they age the opposite becomes true. That is, as they develop vascular risk factors and an increased Framingham risk score, and migraine aura activity goes down, the risk of myocardial ischemia and infarction increases. An obvious question is whether, if you take the migraine away and take aura away (perhaps with effective preventive treatment), does that reduce the risk of stroke? The reason I think it might go away is you only observe aura as a risk marker for stroke in young people, mainly women. It might also be occurring in men but they are underrepresented. I think there is probably no gender difference, just a stronger signal in women because we have more power in studies to see the effects. With increasing age the signal completely goes away, paralleling the reduction of migraine disease activity. However, what goes away are the painful manifestations of migraine. We do not know that migraine itself, that is, the underlying central nervous system abnormalities that predispose to migraine, goes away. I think a migraine patient is a migraine patient for life. It's still present but they just don't have the headache anymore. If painful migraine attacks go away that may actually be a strong marker of increased risk for coronary events. But you don't pick up the stroke risk. It's not because other RFs go up because you can control for these. How do we know who is going to get a stroke? Impossible to say at this point.

I am quite confident that these increased risks are confined to people who have migraine with aura; the vascular risk in migraineurs without aura is similar to that of the general population. Why is aura a vascular risk factor if the events of aura occur in the cortex? It is not so obvious. When I saw the data from the Women's Health Study showing the increased risk of coronary events I called a few colleagues and said "if I tell you that migraine aura is linked to the heart would you be able to give me a mechanism? How does something in the brain affect

heart attack risk?" The answer was that they could not easily think of a mechanism. But now there are more and more studies showing endovascular (endothelial) dysfunction, which may be stronger in migraineurs with aura than in those without aura.[6,7] Thus, it appears that something linked to the migraine aura mechanism itself may play a role. Or perhaps there is a common mechanism that triggers both aura and produces an increased susceptibility to vascular problems.

I believe these data point to a very interesting possibility, which is that if you are young and have active migraine you likely have a very healthy vascular system. You probably have hyper-reactivity of the vascular system to many stimuli, not only the events that produce migraine. This vascular hyper-reactivity is not the cause of the aura but it is strongly linked with it. The arterial walls, for whatever reason, are more affected and are working harder. This could explain why at some point you might be more susceptible to not only cerebrovascular disease but also cardiovascular disease. We know that arterial hyper-reactivity is not limited to brain arteries in those who have migraine with aura.

Is this phenomenon all or nothing, or is there a spectrum of risk? In other words, is the risk of vascular events the same in someone who has only occasional auras and someone who has frequent, prolonged or complex auras? We simply do not know. Another thing we do not know is whether this increased vascular risk is present in people who only have migraine aura and not headache. It really depends on what the mechanism is. Some emerging data hint that abnormalities of the capillary system might be present in people who have migraine with aura and not in those who have migraine without aura.[6] At present, this is mostly speculative. If we think of migraine attack frequency as a rough proxy for aura frequency, then I can say that we do pick up a signal that stroke risk increases as the number of attacks you have.

Question by Huma Sheikh, MD, attending physician, John R. Graham Headache Center, Instructor in Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA: How do you fit in the changes in hormones? That might be a confounder.

Response by Dr. Kurth: The problem is we cannot really say what is going to happen. There are enormous interactions with migraine with aura: this is a high vascular risk patient now. There is a study from Bushnell in *BMJ* showing clear signal of peripartum stroke, preeclampsia.

Question by Paul Mathew, MD, attending physician, John R. Graham Headache Center, Instructor in Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA: What about elderly men who never had migraine and then start having migraine auras?

Response by Dr. Kurth: You have to do testing. It could be a plain migraine aura but there are secondary inducible aura linked to other things like dissection that you have to rule out. Every single migraine shouldn't get an MRI but that would certainly be an indication in such a case. It's a diagnosis of exclusion.

Comment by Dr. Mathew: So assuming that has been done and all normal then very tricky. Marie Germaine Bousser is very strict and says before she calls aura she wants to exclude other causes.

Question by Dr. Sharon: Have we been able to look at the DNA in women with migraine with aura presenting with stroke at a young age?

Response by Dr. Kurth: With regard to genetic markers at the population level, there will be a study coming out in *Neurology* and this study will report some common genes. What does it mean? Nothing, really. The problem is that in these genetic studies you have to pool different datasets. So you compare genetic hits in a migraine cohort to those in a stroke cohort; however, we are not talking about the same persons having migraine and stroke. If you wait long enough and there are even larger datasets you will always see more "hits," and more "hits," and so on. Are you surprised? No. What does it mean? Nothing; for patients for sure. A large amount of fundamental

research will be necessary to understand the influence of these genes in migraine pathophysiology. This will take years, if we ever are able to make the connection from the gene to the mechanisms.

TREATMENT RECOMMENDATIONS – DR. TOBIAS KURTH

Question by Elizabeth Loder, MD, Chairman, John R. Graham Headache Center, Brigham and Women's Faulkner Hospital, Associate Professor of Neurology, Harvard Medical School Boston, MA: Do you recommend aspirin therapy for people who have migraine with aura?

Response by Dr. Kurth: In the case we discussed I would give aspirin because of a potential TIA, not because she has migraine with aura. I would not treat patients who have migraine with aura with aspirin in general. In the Women's Health Study we see no suggestion in participants who have migraine with aura taking aspirin having additional reduced risk of ischemic stroke.[8] In fact, what we found was that those who had migraine with aura and were randomized to aspirin had an increased risk of myocardial infarction. Now, I cannot think of a biological explanation for this observation. The finding may simply be due to chance, especially given that this is a subgroup analysis. But the data are out there and this was unexpected. The analysis showed a two to threefold increased risk, so I do not think it can be completely ignored until data disprove it.

Use of some, not all nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with an increased risk of stroke. When I say NSAIDs I mean anything other than aspirin. So what do you give? The dose of aspirin needed to relieve pain is relatively high, 1000 mg or so. Migraine has also been linked with increased risk of hemorrhagic stroke. But you have to treat. What is the best choice? What is missing to begin with is the evidence that taking the migraine away removes the increased risk of stroke in these women. That is another study question which we have not done. Should you treat with a statin? I don't know. Should we put people who have migraine with aura on a statin? I don't know. I personally don't think so based on current understandings.

Question by Paul Rizzoli, MD, Director, John R. Graham Headache Center, Brigham and Women's Faulkner Hospital, Assistant Professor of Neurology, Harvard Medical School, Boston, MA: What about triptan use in people with basilar-type or hemiplegic migraine?

Question by Rebecca Burch, MD, attending physician, John R. Graham Headache Center, Instructor in Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA: If the patient in this case did have clear evidence of a stroke on MRI, would you feel comfortable giving her a triptan?

Response by Dr. Kurth: It is technically contraindicated but the evidence is close to nil on the issue. There is no clear increase in vascular events with triptan use though potentially there is with ergot overuse. However, you have to realize when looking at evidence that those are observational registries and there is a prescription bias. You are not as likely to give triptans to patients with migraine with aura or other characteristics that make you worry about increased vascular risk. So we don't truly know. So if you have a patient with frequent migraine who responds well to triptans, and you believe migraine is a risk factor for stroke you should probably treat the attacks with an effective drug.

Question by Dr. Rizzoli: Normally when thinking about risks and benefits of triptans we say potential risks are vasospasm, increased risk of stroke, and the benefit is your pain goes away. But if you are balancing pain relief with a potential of stroke then obviously the risk of stroke is more important than pain reduction from a legal standpoint. But I keep hearing you allude to the possibility that decreasing migraine with a triptan or other drugs might actually be beneficial from the standpoint of risk. That changes the equation a bit. What is your opinion on this? What kind of research could help answer this question?

Response by Dr. Kurth: To evaluate this question we would need to start with a good registry or go back into insurance data and analyze things slightly differently. There hasn't been funding to do this research yet. Ideally a randomized controlled trial with migraine with aura patients who are randomized to treat attacks with triptans or nontriptans, followed for 20 years and then you have the answer.

Question by Dr. Burch: I have a patient who had menstrual migraine with aura and had been put on combined estrogen-containing contraceptives before being diagnosed with migraine with aura. Her history was that her headaches had been nearly completely suppressed, including aura, on the contraceptive pills. When we found her history of migraine with aura she was taken off these and she began to have more frequent aura. What would you say? Should we put her back on or not? What does that mean?

Response by Dr. Kurth: We know estrogen-containing contraceptives increase the risk of stroke in all women and we know that in women with migraine with aura it may further increase this risk. How stable is this estimate? There are not many events (we are talking maybe 30–40 or so over all these publications) so this is a fairly imprecise estimate. We are just getting concerned and want to remove risk. But I think a general statement that women who have aura should not get any estrogen-containing contraceptives is too strong. You could argue there are alternatives that should be discussed. For me, if someone is smoking and has aura they should not be on any estrogen-containing contraceptives. For progesterone only contraception there is no evidence either way. We know that if you give hormones sometimes it increases or decreases symptoms. Still today we cannot link any hormonal mechanism strictly to migraine with aura so you cannot predict what happens. But if you have the situation that with estrogen-containing contraceptives the migraine with aura goes away then you may want to leave it on board. But it is still technically contraindicated. The risk of stroke is low to begin with but if she has a future stroke everyone is blaming you. There are no easy answers.

SUMMARY OF CASE AND LEARNING POINTS – matthew s. robbins, md, section co-editor

The authors present an instructive case of a young woman who has had established migraine without aura who later had the onset of migraine with aura during pregnancy, and at age 34 developed episodic focal neurological symptoms without any accompanying headache that were at variance with her previous attacks. The differential diagnosis for such transient events generally includes transient ischemic attack, seizure, migraine aura, and demyelination. A subacute infarct on MRI was felt to be quite relevant but not necessarily correlating with the timing of her symptoms, and expert opinion yielded the diagnosis of transient ischemic attacks.

The mechanism for cerebrovascular risk in migraine may relate to a number of factors including shared vascular comorbidities, inciting factors, and a postulated susceptibility to spreading depolarization.[9]

Dr. Mathew questions about aura occurring de novo in the elderly. He may be referring to the phenomenon termed "migrainous late-life accompaniments," described by C. Miller Fisher.[10] This phenomenon has been recently revisited in the headache literature.[11,12] The recent work emphasizes that this phenomenon is not actually rare, often occurs without any past migraine history and is unaccompanied by headache, most often features visual symptoms and a gradual evolution of transient neurological symptoms with sequential progression, though requires exclusion of symptomatic causes.

The authors also review controversies related to migraine and the risk of cerebrovascular disease, including risk according to aura status, type of aura, use of triptans and estrogen-containing oral contraception.

SELF-ASSESSMENT QUESTIONS

1. What is the differential diagnosis for transient, focal neurological deficits?
2. Aside from migraine, what disorders that feature headache are also accompanied by white matter lesions on MRI?

3. What form of migraine and what other factors contribute to an elevated relative risk of stroke in a young person?
4. Should aspirin be routinely prescribed for primary stroke prophylaxis in women who have migraine with aura?
5. Can triptans be prescribed to patients who have migraine with brainstem, motor, or prolonged aura?

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