BRIEF REPORT: BILATERAL SPREADING CEREBRAL HYPOPERFUSION DURING SPONTANEOUS MIGRAINE HEADACHE

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ALTHOUGH decreases in regional cerebral blood flow are known to occur in relation to migraine headache, the pattern of the alterations in blood flow has not been precisely delineated. Olesen et al. have described a series of patients who had migraine headaches during serial cerebral blood-flow measurement by the intracarotid xenon-133 technique.[1] They observed a pattern of localized decreases in flow that appeared to spread contiguously along the cerebral cortex. These observations were confirmed in subsequent studies,[2,3] and with very few exceptions[1,4] the pattern of "spreading oligemia" or "spreading hypoperfusion"[5] has been apparent only in patients who have migraine headaches with aura (previously known as classic migraine).[6] The carotid-artery puncture itself was thought to trigger the migraines in these patients,[2] causing concern about the generalizability of these findings to spontaneous migraines.[7]

Areas of hypoperfusion have been demonstrated tomographically with intravenous or inhaled xenon-133 in patients who rushed to the hospital at the onset of spontaneous migraine headaches,[6] but no subsequent spreading of the area of hypoperfusion has been demonstrated, possibly because these patients were studied much later in the course of their headaches. As a general rule, the hypoperfusion is ipsilateral to the headache pain and contralateral to the symptoms of aura.[3] Two unexplained cases of bilateral blood-flow changes have been documented.[3]

Although the presence of hypoperfusion in migraine with aura is well accepted, the spreading nature of the hypoperfusion is controversial, since some investigators argue that the apparent spread is a technical artifact.[8,9] During a recent series of blood-flow measurements with positron-emission tomography (PET) and oxygen-15–labeled water, one of our subjects unexpectedly had a migraine headache. The headache was associated with bilateral hypoperfusion that started in the occipital lobes and spread anteriorly into the temporal and parietal lobes, providing unequivocal high-resolution evidence of the spreading nature of hypoperfusion associated with a spontaneous migraine.

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Supported by a grant (1 K08 NS01646-01) from the National Institute of Neurological Disorders and Stroke, a contract (DE-FCO3-87ER60615) with the Department of Energy, gifts from the Ahmanson Foundation and the Jennifer Jones Simon Foundation, and grants from the International Human Frontier Science Program and the Brain Mapping Medical Research Organization.

CASE REPORT

A 21-year-old right-handed woman was recruited as a normal volunteer for the PET study of cerebral blood flow. As an adult, she had had headaches every one to two weeks, some of which were unilateral and associated with nausea, vomiting, or photophobia. Motion or glare from a computer terminal could cause or aggravate her headaches. She had never had migraine with aura or neurologic deficits, and she had no neurologic deficits before, during, or after the PET study. The only other family member with headache was a cousin who had migraines.

The woman gave informed consent in accordance with the requirements of the UCLA Human Subjects Protection Committee. Twelve serial measurements of blood flow were made at 15-minute intervals with the subject in a darkened room, fixating her vision on a computer screen that presented a series of line drawings at a rate of two per second. A few minutes after the sixth measurement, she noted the gradual onset of a throbbing headache that she described as a sharp pain in the center of the back of her head, "as if someone had hit me there." The headache worsened, with no change in location, during the six subsequent measurements. She also had nausea and photophobia. Interviewed after the study about any symptoms that might be interpreted as those of a migraine with aura, she indicated that during one measurement (the ninth, she thought) she had been unable to focus her vision clearly on the drawings on the screen, although she tried very hard to concentrate on doing so. She indicated that otherwise she had looked fixedly at the screen with her eyes open throughout all the measurements.

The subject continued to have headache, nausea, mild vertigo, and anorexia after returning home from the study and had headache and nausea for the entire next day, before her condition gradually returned to base line.

METHODS

For each measurement of blood flow, the subject received an intravenous injection of 10 mCi (370 MBq) of water labeled with oxygen-15. Data were acquired for two minutes after the injection. As compared with shorter imaging times, this approach improves the signal-to-noise ratio but results in a nonlinear relation between blood flow and counts.[10-12] Three different sets of visual stimuli — A, B, and C — were presented in the order ABCCBAABCCBA during the study. The subject was instructed to view these stimuli passively, maintaining visual fixation on a cross in the center of the screen. Visual fixation was verified immediately before and after each measurement.

The scanning procedures and image-reconstruction methods have been described by Cherry et al.[13,14] Each final data set consisted of 15 planes with a distance of 6.75 mm between planes and a full width at half-maximal resolution of 7.2 mm within the plane and 7.5 mm axially. Correction was made for minor head movements.[15] The PET images were registered to T_1-weighted magnetic resonance imaging (MRI) scans as described by Woods et al.[16]

Data analysis began with simple visual inspection of the images. The subject's headache began after the sixth measurement, and large changes in blood flow unrelated to the visual stimuli were obvious in all six measurements made after the onset of headache. Because these changes spared the frontal and inferior cerebellar regions, the images were normalized to one another on the assumption that blood flow to these regions remained constant throughout all 12 measurements; the global normalization process generally used in analyzing PET activation studies was not applied.[17] After normalization, the first five sets of images were averaged to create a pre-headache base-line image (the sixth set of images, acquired immediately before the onset of the headache, was not included). This base-line image was then compared with each subsequent measurement to generate a series of images indicating the percentage of change.

The subdivisions of the images (voxels) that were of potential interest were those in which the blood flow was lowest and de-

creased the most (to a level at least 20 percent below the base-line value) in studies 7 through 12. To eliminate areas of noise, only the largest contiguous region of voxels that met these criteria was analyzed further. Six regions of interest that were not necessarily contiguous were generated within this larger region by categorizing each voxel according to the measurement obtained after the onset of headache that showed the greatest sequential decrease in blood flow. These six regions were used to generate time–activity profiles that included all 12 measurements. Finally, the Pearson correlation coefficient[18] was used to reclassify each voxel meeting the above criteria according to the time–activity profile with which it had the strongest positive significant correlation, with P values less than 0.005 considered to indicate statistical significance.

Results

Figure 1 shows the base-line set of images obtained before the headache, the images showing the percentages of change in measurements 6 through 12, and the corresponding MRI images. Figure 2 shows a graph and a series of anatomical images; the colors used to depict the six time–activity profiles on the graph correspond to the colors used on the images to depict the areas significantly correlated with the various time–activity profiles.

Discussion

Bilateral decreases in blood flow were evident in our subject's occipital regions in the first measurement after the onset of the headache (i.e., the seventh measurement), and the decreases progressed anteriorly with time. Although certain strong neurophysiologic stimuli can produce blood-flow changes of the magnitude seen here,[19,20] the subject's blood-flow changes were unrelated to the stimuli presented, and these same stimuli have produced blood-flow changes of only about 5 percent in other volunteers. Eye closure can cause decreased occipital blood flow, but the subject indicated that she was consistently able to maintain visual fixation despite the headache. The earliest blood-flow changes did not involve the primary visual cortex and so cannot be attributed to eye closure. Given the tomographic nature of the images and the rela-

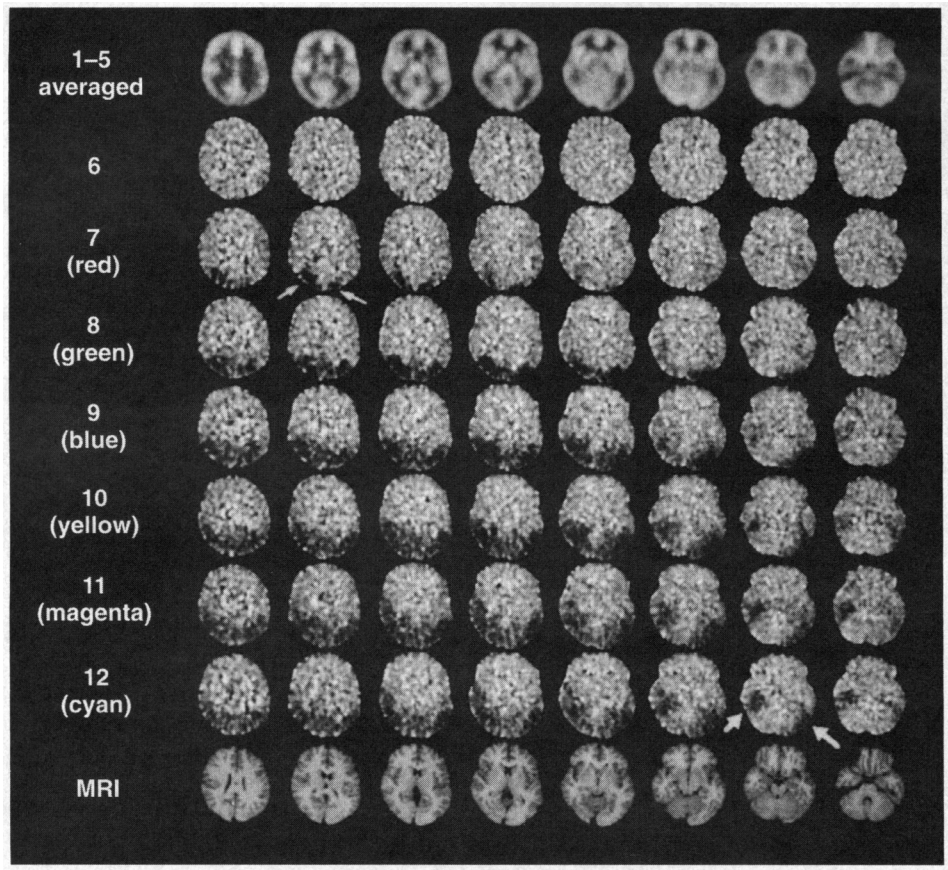

Figure 1. PET and MRI Scans of Blood Flow in the Brain of a Woman with Migraine Headache.

In each row results are shown for 8 of the 15 planes studied. The top row shows the base-line PET images before the headache, derived by normalizing the first five sets of images to one another and then averaging them. The images are oriented with the right hemisphere shown at the left. The middle rows, designated 6 through 12, show the percentage of change in blood flow in the succeeding sets of images; this value was derived by comparing measurements 6 through 12, after normalization, with the base-line image. All the images showing the percentage of change use the same scale of intensity, with darker areas representing decreases relative to the base-line image. The studies shown in rows 7 through 12 are labeled with the colors used to indicate those studies in Figure 2. The thin arrows indicate the areas of earliest decreased blood flow, and the thick arrows distant areas of involvement at the time of the last measurement. The bottom row shows MRI scans corresponding to the PET scans.

tively high spatial resolution, we see no basis for dismissing the changes as methodologic or physiologic artifacts. The involvement spread contiguously across the cortical surface at a relatively constant rate, sparing the cerebellum, the basal ganglia, and the thalamus and ultimately spanning the vascular distributions of four major cerebral arteries.

Given that extensive serotonergic afferent neurons from nuclei of the median and dorsal raphe supply the small blood vessels of the brain,[21,22] we considered the possibility that the changes we observed in cortical blood flow might have been mediated neuronally through projections from these nuclei. However, evidence from a study of macaques suggests that projections from the median raphe have almost no topographic relation to the cortical surface.[23] This lack of a cortical topographic relation is difficult to reconcile with a causative role for these nuclei in generating the organized pattern of blood-flow changes seen in our subject, but it does not exclude a serotonergic role in transducing the physiologic changes associated with migraine into pain.[24]

We believe that the most plausible explanation for the blood-flow changes in our subject is that they were the result of spreading depression. Spreading depression, first described by Leão,[25] is a transient marked reduction in electrical activity in gray matter in animals that advances contiguously across the cortical surface; the rate of advance is consistent with the spread of symptoms during migraine with aura.[26,27] It is associated with decreases in blood flow similar in magnitude and duration to those measured here.[28-30] The hypothesis of spreading depression in migraine has recently been reviewed elsewhere.[31] Spreading depression can move transcallosally to homologous regions of the opposite hemisphere in animals,[25,26,32] and we postulate that transcallosal spread accounts for the bilaterality of the findings in our subject. The regions involved earliest were the visual areas known as Brodmann's areas 18 and 19, which are known to have interhemispheric connections through the corpus callosum.[33,34] Although unilaterality of headache is one of the criteria used in diagnosing migraine,[35] bilateral migraines with aura are well documented.[7,36,37]

Because of our imaging protocol, the decrements in

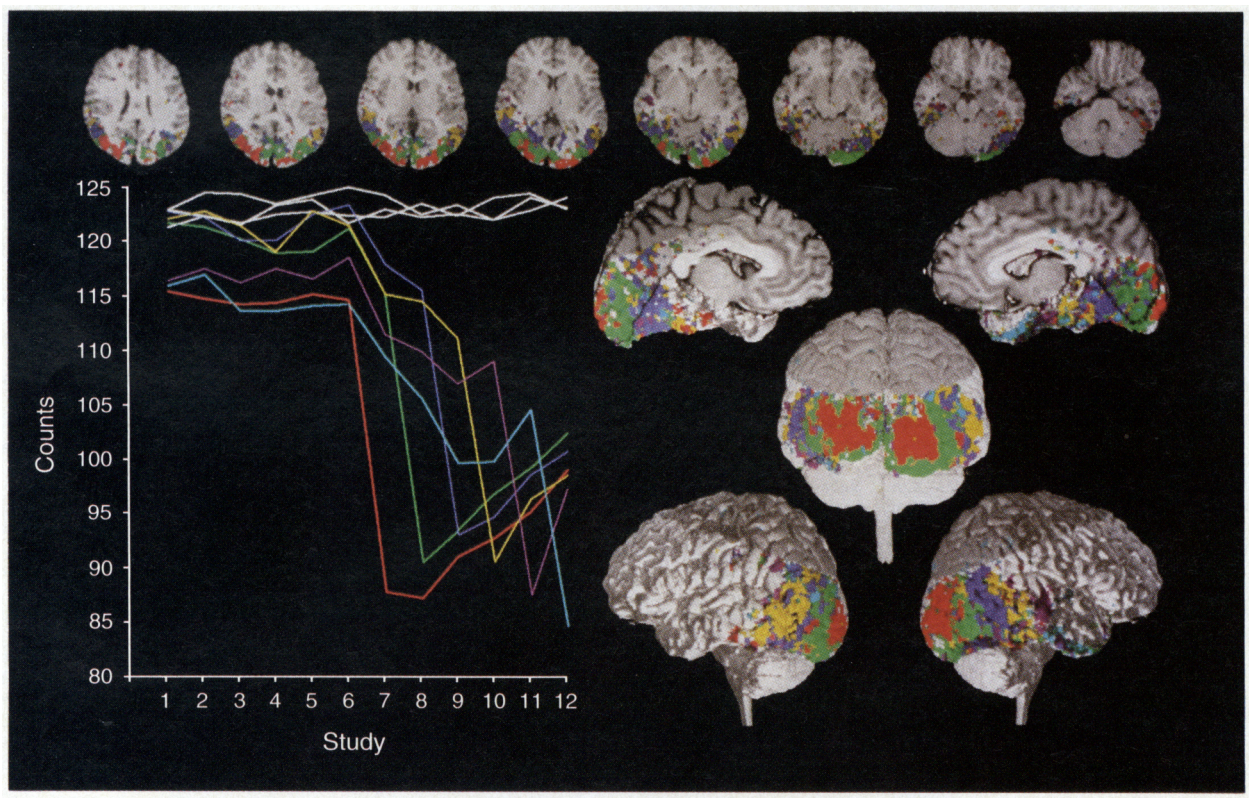

Figure 2. Time–Activity Profiles for the Six Regions of Interest in the Areas with Maximal Serial Decreases in Regional Blood Flow during Measurements 7 through 12.

Regional blood flow was measured in normalized counts, an arbitrary unit. The three regions shown in white on the graph represent the right anterior frontal, left anterior frontal, and inferior cerebellar regions. The gradual decline in some regions after measurement 6 may be due to decreased neuronal input from areas involved earlier, or it may be an artifact related to the limited spatial resolution of the technique. The two-dimensional images at the top correspond to the planes shown in Figure 1. The posterior areas shown in green on the sixth and seventh images are occipital, not cerebellar. In the three-dimensional renderings, the right hemisphere is shown on the right; mesial, posterior, and lateral views are shown (top to bottom). The areas rendered in gray toward the top of the brain were outside the field of view of the PET scanner. The initial involvement (shown in red) occurred in Brodmann's areas 18 and 19.

counts that we measured systematically underestimated the actual decrements in blood flow. We estimate that the actual maximal decreases were on the order of 40 percent, potentially approaching the ischemic range. However, most of these extreme changes were relatively brief, with substantial recovery by the time of the next measurement 15 minutes later. Whether the symptoms of migraine with aura are caused by ischemia is a controversial question[38,39] that cannot be addressed in this case because of the paucity of symptoms of aura in our subject. Her hazy vision, characterized by Olesen as a "less typical" aura symptom, has not generally been associated with blood-flow abnormalities in previous studies.[5] A better understanding of the pathophysiologic features of spreading hypoperfusion would be of obvious clinical importance, since migraine can sometimes lead to ischemic stroke and since stroke can sometimes be aggravated by or associated with the development of migraine.[40]

We are indebted to the volunteer who participated in this study for her extraordinary cooperation; to Deborah Dorsey, R.N., for recruiting the subject; to Diane Martin for photography; to Ron Sumida, Larry Pang, Marc Hulgan, and Der-Jen Liu for technical assistance during the PET study; and to Dr. Simon Cherry for the three-dimensional PET-reconstruction algorithm and for helpful discussions of issues related to the quantitation of the blood-flow changes.

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