Normal Cortical Energy Metabolism in Migrainous Stroke
A 31P-MR Spectroscopy Study

Ursula G. Schulz, DPhil; Andrew M. Blamire, PhD; Paul Davies, MD; Peter Styles, PhD; Peter M. Rothwell, PhD

Background and Purpose—Previous 31P-magnetic resonance spectroscopy (31P-MRS) studies have shown that cerebral cortical energy metabolism is abnormal in migraine and that cortical energy reserves decrease with increasing severity and duration of aura. Migrainous infarction is a rare complication of migraine with aura, and its pathophysiology is poorly understood. We used 31P-MRS to determine whether migrainous stroke shows similar interictal abnormalities in cortical energy metabolism as severe, prolonged aura.

Methods—We used 31P-MRS to study patients with a diagnosis of either migrainous infarction or migraine with persistent aura without infarction (aura duration >7 days) according to International Headache Society criteria. We compared clinical presentation and metabolite ratios between patient groups. We also studied healthy controls with no history of migraine.

Results—Patients with persistent aura without infarction had lower phosphocreatine-phosphate (PCr/Pi) ratios (mean±SD, 1.61±0.10) compared with controls (1.94±0.35, P=0.011) and with patients with migrainous stroke (1.96±0.16, P<0.0001). These differences were present in cortical tissue only. In migrainous stroke patients, the metabolite ratios did not differ significantly from those of controls without migraine.

Conclusions—The differences in cortical energy reserves between patients with migrainous stroke and in those with migraine with persistent aura suggest that the pathomechanisms of these conditions differ and that migrainous infarction does not simply represent a particularly severe form of migrainous aura. This finding supports the revised International Headache Society criteria, which now distinguish between migrainous infarction and migraine with persistent aura without infarction. (Stroke. 2009;40:3740-3744.)

Key Words: MR spectroscopy ▪ migraine with aura ▪ pathophysiology ▪ migraine pathogenesis

The association between migraine and ischemic stroke is complex. Migraine with aura is a risk factor for stroke,1 a stroke can present with migrainous symptoms,2 and sometimes stroke and migraine are caused by a single underlying cause, such as CADASIL.3 Rarely, migraine may cause a stroke.4,5 However, the pathophysiology of migrainous stroke is poorly understood.

Phosphorus magnetic resonance spectroscopy (31P-MRS) is a noninvasive method that has been used to study cerebral energy metabolism in migraine.5–8 Although early studies found reduced energy reserves in all types of migraine,6 this finding was less consistent in more recent studies.7,8 We have previously shown that there is a dose-response relationship between aura severity and cerebral cortical energy metabolism, in that interictal cortical energy reserves decrease with increasing aura duration and that they are lower in patients with hemiplegic migraine compared with patients with nonmotor aura.8

In the current study, our aim was to study the pathophysiology of migrainous infarction with 31P-MRS. Our question was whether migrainous infarction and severe aura share the same pathophysiologic mechanism. We studied patients with migrainous stroke and compared them with normal controls and with patients with migraine with persistent aura without infarction according to International Headache Classification (ICHD)-2 criteriaa (henceforth referred to as "migraine with persistent aura"). We chose patients with migraine with persistent aura as a comparison group because clinically, this is the most severe, prolonged type of aura, and as we have previously shown, these patients have the lowest cortical energy reserves.8 We hypothesized that if migrainous infarction represents a particularly severe form of migraine with aura and if aura severity is determined by cortical energy reserves, then 31P-MRS abnormalities in migrainous infarction should be similar to or even more marked than those in migraine with persistent aura.

Methods

Patients and Controls
We included consecutive patients with a history of migraine with persistent aura and patients with a history of migrainous infarction.
The diagnosis was made according to the ICHD-2 criteria, which define migraine with persistent aura as “aura symptoms persisting for >1 week without radiographic evidence of infarction” and migrainous infarction as “one or more migrainous aura symptoms persisting for >1 hour, which are associated with an ischemic brain lesion in the appropriate territory demonstrated by neuroimaging.” In both cases, the aura symptoms must be typical of previous attacks of migraine with aura, and other diagnoses must have been excluded.

Each patient underwent a detailed standardized interview. We recorded the frequency of migraine attacks and the usual type and duration of symptoms during an attack. All patients had MR brain imaging, and patients with migrainous infarction had detailed investigations (ECG, echocardiography, vascular imaging with Doppler ultrasound, computed tomography or MR angiography, and laboratory testing) to exclude other causes of stroke. Patients who took part in the study were scanned in the interictal period, at least 4 weeks after resolution of the most recent migraine attack. We also studied a group of age- and sex-matched controls. These study subjects had no history of migraine, and they were free of chronic or recurrent headache and other neurologic illness. The study was approved by the local research ethics committee.

**Imaging and Spectroscopy**

Structural imaging and $^{31}$P-MRS were performed at 2 T (Bruker Avance Spectrometer, Bruker Biospin, Ettlingen, Germany). We used a birdcage head coil to acquire anatomic T2-weighted (repetition time [TR]/echo time [TE]=3 seconds/80 ms) and T1-weighted (TR/TE=0.5 second/10 ms) images and an 8-cm surface coil to collect $^{31}$P spectra.

In preparation for the phosphorus data collection, magnetic field homogeneity was optimized over a $5\times5\times5$\,cm$^3$ volume (point-resolved spectroscopy (PRESS)–localized voxel, TR/TE=1.5 seconds/135 ms) centered on the lentiform nucleus on each side to include as much brain tissue as possible, and shim parameters were stored. The patient bed was withdrawn from the magnet while maintaining the patient position, and the phosphorus surface coil was placed lateral to the left hemisphere centered over the location of the previously imaged voxel. Phosphorus spectra were acquired with a 1-dimensional spectroscopic imaging sequence (adiabatic 90° excitation, TR=2.5 seconds, 32 encode steps to create 1-cm-thick sagittal slices, 16 averages). The patient bed was once again withdrawn and the surface coil relocated over the right hemisphere. Shim parameters for the right hemisphere were recalled, and a second phosphorus data set was collected (the Figure).

**Data Processing and Statistical Analysis**

Phosphorus data sets were quantified with the use of time domain–fitting software (MRUI) with the AMARES algorithm to obtain peak integrals for phosphocreatine (PCr), adenosine triphosphate (ATP), and inorganic phosphate (Pi). Tissue pH was calculated from the difference in chemical shift of PCr and Pi.

We determined the ratios of PCr to Pi, PCr to ATP, and Pi to ATP and the pH in gray matter, white matter, and the total hemisphere (white matter+gray matter+mixed tissue). We compared the mean ratios between controls, patients with persistent aura, and patients with migrainous stroke by ANOVA. We analyzed the metabolite ratios in the symptomatic and contralateral hemispheres and compared the results between hemispheres with the paired t test. All statistical analyses were done with SPSS 15.01 (SPSS Inc, Chicago, Ill).

**Results**

We studied 14 patients (6 men; mean±SD age, 43±12 years) and 14 age- and sex-matched controls (6 men; mean±SD age, 40±15 years) with no history of migraine. Five patients had a migrainous stroke, and 9 had at least 1 episode of migraine with persistent aura between 2 and 6 months before the study. In keeping with the history of visual aura, MR brain imaging showed occipital infarcts in 4 stroke patients, whereas the stroke patient with hemiplegic migraine had an infarct in the internal capsule. The patients with persistent aura and the controls showed no imaging abnormalities.

Table 1 shows the clinical baseline data. The clinical features of the migraine attacks differed between patients with migrainous stroke and patients with persistent aura: 1 of the 5 migrainous stroke patients had motor symptoms, whereas 8 of the 9 patients with persistent aura presented with hemiplegic migraine.

Table 2 shows the results of the $^{31}$P-MRS for the averaged symptomatic and contralateral hemispheres. We combined the findings in both hemispheres to obtain 1 overall value per patient. This appeared valid, as we found no significant differences between hemispheres in patients or in controls and because differences between study groups were also present when the hemispheres were studied individually. Patients with persistent aura had significantly lower PCr/Pi (mean±SD, 1.61±0.10) than controls (1.94±0.35, P=0.011) and patients with migrainous stroke (1.96±0.16, P<0.0001). These differences were present in cortical tissue only. We found no significant differences in metabolite ratios or pH between patients with migrainous stroke and controls without migraine.

In either patient group, there was 1 patient whose aura symptoms differed from those of the other patients in that group: 1 of the migrainous stroke patients had hemiplegic
migraine rather than visual aura, and 1 of the patients with persistent aura had visual aura rather than hemiplegic migraine. To analyze whether energy metabolism in these 2 patients was concordant with the aura symptoms (visual vs hemiplegia) or with the clinical presentation (stroke vs persistent aura), we performed a separate analysis restricted to patients with persistent hemiplegic migraine versus patients with migrainous stroke and visual aura (Table 2). The PCr/Pi in the patient with persistent visual aura was low (1.59), whereas it was normal in the patient with migrainous stroke and hemiplegic migraine (2.02). The cortical metabolite ratios were thus consistent with the clinical presentation rather than the aura symptoms.

Discussion

We found significant differences in cerebral energy metabolism between patients with migrainous infarction and those with migraine with persistent aura. Hemispheric cortical cellular energy reserves, expressed as the PCr/Pi ratio, were significantly lower in patients with persistent aura than in patients with migrainous stroke and in controls, whereas the PCr/Pi ratio in patients with migrainous infarction did not differ from that in controls.

We have previously shown that cortical energy reserves decrease with increasing duration and symptom severity of migrainous aura. Although these associations were present independently, aura duration and type of aura symptoms were closely associated.8 In the current study, our aim was to determine whether migrainous stroke has the same pathomechanism as migraine with aura and whether it is therefore associated with similar or even more marked metabolic abnormalities as persistent aura. Our finding of normal cortical energy reserves in migrainous stroke suggests that the pathomechanisms of migrainous infarction and of migraine with persistent aura differ.

Several studies of migrainous aura have shown that a wave of cortical spreading depression is followed by a wave of reduced cortical perfusion.11–13 The severity of the cortical depression may determine the degree of subsequent hypoperfusion.14 Although it is unclear whether it is sufficient to reach ischemic levels,13,15 hypoperfusion during the aura is a possible mechanism of migrainous infarction.2,3 We have previously suggested that the severity of cortical spreading depression is associated with the degree of reduction of interictal cortical energy reserves.8 If the degree of hypoperfusion during migrainous aura is associated with the severity of cortical depression and if this in turn is associated with the level of reduction of interictal energy reserves, then we would expect patients with migrainous infarction to have reduced cortical energy reserves. However, in the current study, cortical energy reserves in patients with migrainous infarction were normal. This suggests that if hypoperfusion is the mechanism of migrainous infarction, then its severity is independent of interictal energy reserves and it may be unrelated to the degree of cortical depression. Alternatively, a migrainous stroke may be caused by other mechanisms, eg, vasospasm, or hypercoagulability caused by the release of inflammatory mediators.16

Only 1 other 31P-MRS study, done in 1989, included patients with migrainous infarction. It included 4 patients with migrainous stroke and 4 patients with “prolonged aura” according to previous IHS criteria.5,17 Although the authors did not specifically compare the 2 groups, their data showed no difference in energy metabolism between patients with migrainous stroke and those with prolonged aura. In contrast to our findings, all patients had lower energy reserves than did controls.5 There are several possible explanations for the differences between this early study and ours. First, the previous study obtained measurements from the occipital lobes, which may have included the infarct. Metabolism in infarcted tissue may differ from that in normal cortical tissue. We obtained our measurements from the hemispheric cortex and included noninfarcted tissue only. Second, we used a higher field strength with improved signal-to-noise-ratio. We
also used time domain fitting to determine the spectral frequencies, thus abolishing errors that could result from baseline distortions in frequency domain fits. Our methodology was similar to that of other authors, who also did not find an overall abnormality in energy metabolism in migraineurs.7 Finally, in our study, patients with persistent aura differed markedly from controls and from migrainous stroke patients. “Migraine with persistent aura without infarction” is a new diagnostic code in the ICHD-2,4 and it is unclear whether such patients were included in the previous study. Different results in the previous and our study may at least partly reflect differences in patient selection.

We found a high proportion of patients with hemiplegic migraine among our patients with persistent aura. This may reflect the previously described association between persistent aura and hemiplegic migraine.4,18,19 Hemiplegic migraine differs from other types of migraine in that it may be associated with genetic abnormalities. These lead to a “channelopathy,” which may affect ion homeostasis and cause cortical hyperexcitability. Cortical hyperexcitability may facilitate the spreading of cortical depression and lead to a more extensive neurologic deficit. It may also increase cortical energy demands and reduce energy reserves,20 which may lead to prolonged aura. This mechanism would explain the association of hemiplegic migraine and prolonged aura. In patients with migraine with persistent aura without hemiplegia, similar genetic changes have not been found. This suggests that the aura in these patients may have a different pathomechanism and that the finding of low cortical energy reserves in our study may not be generalizable to all patients with persistent aura. However, we found consistently low PCr/Pi values in patients with persistent aura and consistently normal PCr/Pi values in patients with migrainous stroke, regardless of the presence of hemiplegia. Furthermore, our previous study showed an independent association between increasing aura duration and decreasing cortical energy reserves.8 Although this does not prove the generalizability of our findings, it suggests that persistent aura is associated with low cortical energy reserves, regardless of the presence of hemiplegia. It is likely that cortical energy reserves are

<table>
<thead>
<tr>
<th>Table 2. 31P-MRS Data</th>
<th>Controls n=14</th>
<th>Persistent Aura n=9</th>
<th>Migrainous Stroke n=5</th>
<th>P (Persistent Aura vs Stroke)</th>
<th>Persistent Hemiplegic Aura n=8</th>
<th>Migrainous Stroke With Visual Aura n=4</th>
<th>P (Hemiplegic Aura vs Stroke With Visual Aura)</th>
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<tr>
<td>Total</td>
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<td>PCr/Pi</td>
<td>2.04 (0.25)</td>
<td>1.74 (0.21)</td>
<td>2.01 (0.12)</td>
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<td>1.73 (0.23)</td>
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<td>PCr/ATP</td>
<td>1.15 (0.14)</td>
<td>1.04 (0.18)</td>
<td>1.12 (0.09)</td>
<td>0.349</td>
<td>1.03 (0.19)</td>
<td>1.08 (0.19)</td>
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<td>Pi/ATP</td>
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<td>0.60 (0.07)</td>
<td>0.56 (0.05)</td>
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<td>0.60 (0.06)</td>
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<td>pH</td>
<td>7.02 (0.03)</td>
<td>7.00 (0.02)</td>
<td>7.02 (0.02)</td>
<td>0.182</td>
<td>7.01 (0.01)</td>
<td>6.98 (0.04)</td>
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<td>P (vs controls)</td>
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<td>0.108</td>
<td>0.782</td>
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</tr>
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</table>

Grey matter

| PCr/Pi                 | 1.94 (0.35)   | 1.61 (0.10)         | 1.96 (0.16)           | <0.0001                     | 1.60 (0.14)                 | 2.12 (0.08)                         | <0.0001                                       |
| P (vs controls)        |               | 0.011               | 0.944                 |                             |                             |                                      |                                                |
| PCr/ATP                | 1.18 (0.17)   | 1.14 (0.25)         | 1.15 (0.13)           | 0.937                       | 1.15 (0.28)                 | 1.09 (0.18)                         | 0.688                                         |
| P (vs controls)        |               | 0.645               | 0.717                 |                             |                             |                                      |                                                |
| Pi/ATP                 | 0.62 (0.12)   | 0.70 (0.14)         | 0.60 (0.04)           | 0.134                       | 0.72 (0.14)                 | 0.51 (0.08)                         | 0.021                                         |
| P (vs controls)        |               | 0.134               | 0.690                 |                             |                             |                                      |                                                |
| pH                     | 7.04 (0.05)   | 7.01 (0.03)         | 7.04 (0.01)           | 0.06                        | 7.02 (0.02)                 | 7.01 (0.03)                         | 0.151                                         |
| P (vs controls)        |               | 0.115               | 0.989                 |                             |                             |                                      |                                                |

White matter

| PCr/Pi                 | 2.28 (0.53)   | 2.24 (0.39)         | 2.32 (0.42)           | 0.608                       | 2.24 (0.42)                 | 2.30 (0.48)                         | 0.816                                         |
| P (vs controls)        |               | 0.830               | 0.870                 |                             |                             |                                      |                                                |
| PCr/ATP                | 1.08 (0.17)   | 1.08 (0.12)         | 1.05 (0.22)           | 0.803                       | 1.06 (0.13)                 | 1.05 (0.25)                         | 0.901                                         |
| P (vs controls)        |               | 0.806               | 0.705                 |                             |                             |                                      |                                                |
| Pi/ATP                 | 0.50 (0.13)   | 0.50 (0.10)         | 0.45 (0.08)           | 0.386                       | 0.50 (0.11)                 | 0.46 (0.09)                         | 0.622                                         |
| P (vs controls)        |               | 0.861               | 0.508                 |                             |                             |                                      |                                                |
| pH                     | 7.01 (0.03)   | 7.01 (0.03)         | 6.99 (0.04)           | 0.303                       | 7.01 (0.02)                 | 7.00 (0.035)                        | 0.198                                         |
| P (vs controls)        |               | 0.895               | 0.282                 |                             |                             |                                      |                                                |
influenced by other factors in addition to the level of cortical excitability, and therefore aura duration may vary independently of aura symptoms. Given the genetic differences between patients with and without hemiplegic migraine, the mechanism leading to low cortical energy reserves may differ between patient groups.

A potential shortcoming of our study is that we only sampled the frontotemporoparietal regions of each hemisphere. We may therefore have missed regional differences in energy metabolism between patients with visual aura, whose symptoms may arise purely from the occipital lobes, and patients with hemiplegic migraine, whose symptoms show more widespread hemispheric involvement. Such regional differences in cortical energy reserves could explain the differences we found in energy metabolism between patients with migrainous stroke, who mainly had visual symptoms, and patients with persistent aura, all but one of whom had hemiplegic migraine. They might also explain differences between our and previous studies of 31P-MRS in migraine, which sampled the occipital lobes. However, because migrainous infarction commonly involves the occipital lobes, we specifically decided not to obtain measurements from these to avoid including infarcted tissue with potentially abnormal energy metabolism. Furthermore, the changes in energy metabolism in migraineurs are thought to be generalized and have even been shown in muscle tissue and platelets. It appears unlikely that changes that affect several body systems should show regional variation within the brain. This is supported by a previous study of migraineurs that did not find any consistent differences in PCr/PI values between anterior and posterior regions of the brain; by a study of patients with hemiplegic migraine, who had reduced energy reserves in the occipital lobes; and also by our study, which showed no differences in cortical energy metabolism between the symptomatic and asymptomatic hemispheres. All these data suggest that changes in cortical energy metabolism are generalized. We therefore think that the differences we found between patients with migrainous stroke and those with persistent aura are genuine and most likely represent pathophysiologic differences between these two patient groups.

Our study does not clarify the mechanism of migrainous infarction. However, it is the first 31P-MRS study to show that migrainous stroke and migraine with persistent aura may have different mechanisms. This is consistent with MR perfusion and single-photon emission computed tomography (SPECT) studies, which found normal or even increased perfusion in patients with persistent aura. Our results also support the revised IHS criteria, which distinguish between migraine with persistent aura and migrainous infarction. We have shown not only that these patients differ in the presence of infarction on structural imaging but also that there are underlying pathophysiologic differences.

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**Disclosures**

None.

**References**

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