Axonal Injury in the Internal Capsule Correlates With Motor Impairment After Stroke

S.T. Pendlebury, MRCP; A.M. Blamire, PhD; M.A. Lee, MRCP; P. Styles, DPhil; P.M. Matthews, DPhil

Background and Purpose—Magnetic resonance spectroscopy (MRS) in ischemic stroke has shown a correlation between N-acetylaspartate (NAA) loss from the infarcted region and disability. We tested the hypothesis that NAA loss in the descending motor pathways, measured at the level of the posterior limb of the internal capsule, would determine motor deficit after a cortical, subcortical, or striatocapsular stroke.

Methods—Eighteen patients with first ischemic stroke causing a motor deficit were examined between 1 month and 5 years after stroke. T2-weighted imaging of the brain and localized proton (voxel, 1.5×2×2 cm³) MRS from the posterior limb of each internal capsule were performed and correlated to a motor deficit score.

Results—Mean internal capsule NAA was significantly lower in the patient group as a whole compared with the control group (P<0.001). Reductions in internal capsule NAA on the side of the lesion were seen in cases of cortical stroke in which there was no extension of the stroke into the voxel as well as in cases of striatocapsular stroke involving the voxel region. There was a strong relationship between reduction in capsule NAA and contralateral motor deficit (log curve, r²=0.9, P<0.001).

Conclusions—Axonal injury in the descending motor pathways at the level of the internal capsule correlated with motor deficit in patients after stroke. This was the case for strokes directly involving the internal capsule and for strokes in the motor cortex and subcortex in which there was presumed anterograde axonal injury. (Stroke. 1999;30:956-962.)

Key Words: cerebrovascular disorders • nuclear magnetic resonance • outcome

In stroke, destruction of a given part of the brain causes a deficit of function. The type and severity of the deficit is determined by the magnitude of neuronal loss and the location of the lesion, together with the mitigating effects of adaptive recovery mechanisms. The development of MRI has enabled visualization of infarcts in the brain in vivo. However, lesion volume measured with T2 changes on MRI may not accurately assess neuronal damage, because lesions may be patchy and edema may contribute to T2 signal hyperintensity. Recently, magnetic resonance spectroscopy (MRS) has been used to attempt better quantification of the brain damage caused by stroke. Proton MRS allows in vivo measurement of N-acetyl-containing compounds, creatine, choline, and lactate. The majority of the N-acetyl signal comes from N-acetyl aspartate (NAA), which is present in high concentrations in the brain.1 Much smaller contributions to the N-acetyl signal come from other N-acetyl groups, including N-acetylglutamate.2 The function of NAA is unclear, although suggestions include initiation of protein synthesis, neurotransmission, and deactivation of glutamate. NAA is of particular interest in studies of the brain because it is located almost exclusively in neurons in the adult.3 Initially, it was suggested that decreases in NAA represented neuronal loss;4 recently, however, reversible decreases in NAA have been shown to occur in acute lesions in multiple sclerosis and in stroke-like episodes in MELAS.5 Further, NAA synthesis in vitro has been shown to occur in an energy-dependent manner and to be reduced by mitochondrial inhibitors.6 Therefore, decreases in the NAA resonance peak in vivo must be interpreted as an index of neuronal or axonal injury rather than a marker of neuronal or axonal loss. Decreases in NAA have been shown to correlate with disability in multiple sclerosis,7 suggesting that axonal injury is responsible for chronic functional impairment in this disease.

Early studies of MRS in stroke showed increased lactate and decreased NAA within the stroke lesion.8–11 Subsequently, attempts were made to determine whether the magnitude of neuronal damage as measured by NAA loss from the infarcted region, correlated with disability and impairment in stroke patients. Ford et al12 found that the patients who made the complete recoveries were those in whom NAA levels were relatively well preserved. In contrast, Gideon et al13 found no clear relationship between level of NAA and clinical outcome. Graham et al14 found that NAA reduction correlated with the Barthel Index score at discharge.

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From the Centre for Functional MRI of the Brain (FMRIB), John Radcliffe Hospital, and the Department of Clinical Neurology, The Radcliffe Infirmary (S.T.P., M.A.L., P.M.M.), and the MRC Magnetic Resonance Spectroscopy Unit, John Radcliffe Hospital (A.M.B., P.S.), Oxford, UK.
Correspondence to Dr Sarah Pendlebury, Centre for Functional Magnetic Resonance of the Brain (FMRIB), The John Radcliffe Hospital, Oxford, OX3 9DU, UK, E-mail stpendle@bioch.ox.ac.uk
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The study.

local ethics committee, and informed consent was obtained prior to similar mean age were recruited. The study was approved by the were not excluded from the study. Ten healthy control subjects of a have hemorrhagic or brain stem stroke, history of prior symptomatic with stroke, and other coexistent neurological disease or cognitive impair-

ment were excluded from the study. Patients subsequently found to from general practitioners and from the local stroke unit. Patients entry into the study that resulted in a motor deficit, were recruited

in the internal capsule containing the descending motor pathways and were correlated with motor impairment at the time of the MRS study. Our hypothesis was that the magnitude of axonal injury in the internal capsule would correlate with the motor deficit experienced by the patient. We proposed that this injury in the internal capsule would correlate with the motor deficit secondary to a cortical, subcortical, or capsular stroke.

Subjects and Methods

Patients and Controls

Eighteen patients (12 males, 6 females) who had suffered a stroke, as defined by the WHO criteria,16 between 1 month and 5 years before entry into the study that resulted in a motor deficit, were recruited from general practitioners and from the local stroke unit. Patients with hemorrhagic or brain stem stroke, history of prior symptomatic stroke, and other coexistent neurological disease or cognitive impairment were excluded from the study. Patients subsequently found to have >1 T2 hyperintense lesion on MRI consistent with infarction were not excluded from the study. Ten healthy control subjects of a similar mean age were recruited. The study was approved by the local ethics committee, and informed consent was obtained prior to the study.

MRI and Spectroscopy

MRI and spectroscopy were performed using a 2-T whole-body magnet interfaced with a Bruker Avance spectrometer (Bruker Medical). Care was taken to standardize head positioning across subjects by placing the subject’s head in a foam head localizer, with the orbitomeatal line positioned perpendicular to the long axis of the magnet. A forehead strap and side padding were used to immobilize the head. All images and spectra were obtained with a quadrature birdcage coil tuned to 85.2 MHz. A sagittal scout image was performed to confirm correct subject head alignment, followed by axial fast spin-echo T2-weighted imaging with the following parameters to provide 30 contiguous slices: TR = 3100 ms, TE = 82 ms, slice thickness = 5 mm with nominal in-plane resolution of 1 mm, matrix = 256×196 with zero filling = 2562, field of view = 25.6 cm, and averages = 2.

Proton spectra were acquired from a 1.5×2×2 cm3 volume of interest (voxel) that was positioned visually on screen using the T2 axial images and was centered on the posterior limb of the internal capsule at the level of the third ventricle (Figure 1). Symmetrical placement of the voxel on the right and the left capsules was confirmed by 2 observers. Volume selection was performed with a point-resolved spectroscopy sequence (PRESS).17 Preliminary experiments on control subjects showed that a TE of 90 ms produced 20% more signal than the conventional TE of 135 ms, while minimizing problems arising from macromolecular resonances with very short T2 values. The other volume of interest acquisition parameters were TR = 1500 ms, data points = 2048, spectral width = 2500 Hz, and acquisitions = 256. Water suppression was produced using a chemical shift selection (CHESS)18 sequence. A non–water-suppressed spectrum was collected with 16 averages with no offset frequency from the same voxel.

The voxel dimensions were selected to include the whole of the posterior limb of the internal capsule with the minimum of partial volume effects. To avoid significant chemical shift displacement of the signal of interest (NAA), an offset frequency of −228 Hz relative to the water frequency was applied to all 3 pulses of the PRESS sequence. This ensured that the NAA signal was collected from precisely that volume of tissue enclosed by the voxel defined on the T2-weighted axial image. Spectral analysis was performed with the operator blinded to the patient’s clinical details and side of motor deficit. Four hertz of exponential line broadening was applied prior to Fourier transformation. Automatic line fitting and integration was done with the software package 1D WIN-NMR (Bruker Fransen Analytik GmbH).

The apparent NAA concentration was calculated relative to the water concentration for each internal capsule using the ratio of the areas under the NAA and water peaks. The water concentration for each internal capsule was calculated from the water peak, because the protocol was already at the limit of patient tolerance. However, the parallel increases in T1 and T2 relaxation times that are expected in chronic stroke19 will tend to self-compensate, making significant errors occurring as a result of T1 and T2 relaxation effects unlikely. Reduction in capsule NAA was calculated for each patient by taking the difference in apparent NAA concentration between the right and left capsules and expressing this as a percentage of the higher capsule NAA concentration. In patients in whom T2-weighted hyperintense regions were seen in both hemispheres, the same calculation was

Figure 1. Axial T2-weighted image showing location of the spectroscopy voxel over the posterior limb of the internal capsule of each hemisphere together with the spectra obtained from the right and left internal capsules of patient 7. ppm indicates parts per million.
TABLE 1. Patient Clinical Data and Infarct Characterization From T2-Weighted MRI

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>Handedness</th>
<th>Time Since Stroke, mo</th>
<th>Stroke Location on MRI/Hemisphere</th>
<th>Left Hemisphere Lesion Volume, cm³</th>
<th>Right Hemisphere Lesion Volume, cm³</th>
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<td>84/M</td>
<td>R</td>
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<td>R</td>
<td>30</td>
<td>Frontoparietal/L</td>
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<td>Striatocapsular/R</td>
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<td>Striatocapsular/frontoparietal/L</td>
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</table>

applied to obtain a measure of capsular NAA asymmetry. The mean, SD, and maximum of the difference in capsule NAA between sides in normal subjects as measured under our experimental conditions were obtained using the same method. Although changes in creatine and choline were seen in some of the patients, they were not analyzed in this study.

Calculation of Lesion Volume

Hyperintense regions seen on the T2-weighted axial scans were assumed to correspond to areas of infarction. Lesion area was measured in each patient with a manually defined thresholding technique (Medx Software, Sensor Systems). Lesion volume was calculated by multiplying the total lesion area by the slice thickness (5 mm). In those patients in whom the stroke was seen to involve the region enclosed by the voxel, the same manual thresholding technique was used to segment out the percentage of the voxel volume occupied by the stroke.

Clinical Assessment

Clinical assessment was carried out at the time of the MRS/MRI examination by a single observer (S.P.). Specific measures of motor function obtained from the patients were the Motricity Index,20 the 9-Hole Peg Test,21 grip strength measured by a modified strain gauge,22 and leg extension power measured by a leg extensor rig dynamometer. A composite motor deficit score was generated by calculating the mean of the percentage performance of the affected arm and leg for Motricity Index, grip strength, 9-Hole Peg Test time, and leg extensor power compared with that of unaffected limbs. Thus, a complete hemiparesis with no function in the arm or leg gave a motor deficit score of 100. A similar score was generated using the average of the right and left internal capsule NAA concentrations for each subject. Comparisons were made between percentage reduction in internal capsule NAA and contralateral motor deficit score and Barthel score, respectively. In cases in which the NAA reduction was seen in the capsule ipsilateral to the motor deficit, the NAA reduction was given a negative value. Lesion volume was also compared with contralateral motor deficit. Comparison between percentage reduction in capsule NAA and ipsilateral lesion volume was made in patients in whom there was a single lesion on MRI (n=12); patients with multiple lacunes were excluded from this analysis because it was not possible to determine which of the lesions lay within the motor outflow tract where they might have been expected to affect the NAA level in the descending motor pathways.

Statistics

Null hypotheses were tested using the Mann-Whitney U test. Correlations were tested with Spearman’s rank test. A curve-fitting approach was used to find the optimal description of the relationship between NAA reduction and motor deficit score (SPSS 7.5 for Windows, SPSS Inc).

Results

Clinical details for the patients are shown in Table 1. There was no significant difference between the mean ages of the patients and those of the control subjects (patients: 70.6 [range, 31 to 84] years; controls: 69.7 [range, 57 to 82] years). Table 2 shows the MRS data and functional assessment scores for all the patients. NAA levels in the internal capsule in controls showed a mean±SD difference of 9.2±5.4% (range, 0% to 17%) between hemispheres. Mean internal capsule NAA was significantly lower in the patient group compared with the control group (40±9 versus 51±9, NAA/ H₂O×10⁻³, P=0.009).

NAA loss from the internal capsule was associated with motor deficit. The relationship between NAA reduction and combined motor deficit score was better described by a log plot (r²=0.89, P<0.001; Figure 2) than other standard curves or a linear plot. There was a similar relationship between reduction in NAA and upper limb motor deficit score (log
The relationship between motor deficit and NAA loss was significant whether patients were examined between 1 and 2.5 months or after 2.5 months poststroke. There was no significant relationship between reduction in NAA and Barthel Index score (Spearman $r = 0.3$, $P = 0.3$).

Seven patients (7, 9, 11, 12, 13, 16, and 18) showed a reduction in NAA in the internal capsule that exceeded the maximum right-left variation seen in control subjects. In each case, the reduced NAA level was seen on the side of the lesion, contralateral to the side of motor deficit. Reduction in NAA in the capsule ipsilateral to the motor deficit was seen in 5 patients (2, 3, 5, 6, and 10). None of these reductions was greater than control right-left capsule NAA differences. Seven patients (1, 3, 4, 5, 6, 8, and 17) had lesions in both hemispheres, and in none of these patients were NAA reductions seen that were greater than control right-left differences. Of the 7 patients in whom there was reduced NAA on the side of the lesion, 3 (patients 7, 16, and 18) had strokes located primarily in the striatocapsular region enclosed by the spectroscopy voxel (mean percentage voxel volume occupied by T2 change, 50%; range, 28% to 70%).

TABLE 2. Patient MRS, Functional Assessment, and Disability Data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Left Internal Capsule NAA*</th>
<th>Right Internal Capsule NAA*</th>
<th>Percentage Reduction in NAA†</th>
<th>% Voxel Occupied by Stroke, Left/Right</th>
<th>Motor Deficit/Affected Side</th>
<th>Upper Limb Motor Deficit/Affected Side</th>
<th>Barthel Index Score</th>
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<td>51</td>
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<td>54</td>
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<td>70/0</td>
<td>77/R</td>
<td>91/R</td>
<td>19</td>
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</table>

*Expressed as the ratio of NAA to water (NAA/H2O×10−5), not corrected for saturation effects.
†Difference between right and left internal capsule NAA levels expressed as a percentage of the higher capsule NAA level. Negative values indicate a reduction in capsule NAA ipsilateral to the motor deficit.

Figure 2. Percentage reduction in internal capsule NAA versus contralateral combined motor deficit score for all 18 stroke patients (log curve, $r^2 = 0.89$, $P < 0.001$). Filled squares indicate patients studied <2.5 months after stroke; open squares, patients studied >2.5 months after stroke.

Figure 3. Percentage reduction in internal capsule NAA versus contralateral combined upper limb motor deficit score for all 18 stroke patients (log curve, $r^2 = 0.91$, $P < 0.001$). Filled triangles indicate patients studied <2.5 months after stroke; open triangles, patients studied >2.5 months after stroke.
and 4 (patients 9, 11, 12, and 13) had strokes that were principally cortical or subcortical with little extension into the voxel region (mean percentage voxel volume occupied by T2 change, 16%; range, 3% to 38%). The percentage of the voxel volume occupied by stroke against reduction in NAA for these 7 patients is shown in Figure 4. The relationship between the extent of NAA reduction and motor deficit was similar regardless of the extent of T2 change seen within the voxel.

Lesion volume was significantly correlated with motor deficit (Spearman \( r = 0.7 \), \( P = 0.001 \); Figure 5) and Barthel Index (Spearman \( r = 0.5 \), \( P = 0.03 \)). Lesion volume was not significantly correlated with reduction in internal capsule NAA (all patients with a single lesion, \( n = 12 \); Figure 6).

**Discussion**

Using MRS, we examined the relationship between axonal injury in the internal capsule, as shown by NAA loss, and functional impairment in patients who had suffered a motor stroke. There was a significant correlation between NAA loss in the capsule and motor deficit. These findings are consistent with the hypothesis that the extent of axonal injury in the descending motor pathways determines the magnitude of motor deficit in patients 1 month or more after stroke. In a recent study of multiple sclerosis patients with asymmetrical impairment, Lee et al.\(^{25} \) found a similar relationship between NAA loss in the internal capsule and motor deficit, although the correlation was not as strong as that observed in the present study of stroke patients. The lack of correlation we observed between axonal injury in the internal capsule and Barthel Index score can be explained by the fact that disability scales do not reflect damage to physiological systems as closely as impairment scales: patients will score well on the Barthel Index if they are independent in such activities as transferring from a wheelchair, regardless of the degree of limb weakness.\(^{23} \) We speculate that lesion volume correlated with Barthel score because larger infarcts are more likely to cause multiple problems, such as limb weakness, neglect, apraxia, and visual impairment, which contribute to disability.

Our study included patients with cortical, corona radiata, and striatocapsular strokes; hence, the extent of stroke extension, as shown by T2 change, into the region of the internal capsule enclosed by the spectroscopy voxel was highly variable (0% to 70%). In the 7 patients who had a reduction in capsule NAA greater than the maximum right-left difference seen in controls, the magnitude of the NAA reduction was independent of the amount of T2 lesion seen in the voxel. This is shown in Figure 4, where it can be seen that although there was a relationship between the percentage of the voxel volume occupied by stroke and the NAA reduction, in general the NAA loss was greater than would have been expected from the amount of lesion within the voxel. In particular, patients 7 and 13 had similar amounts of lesion within the voxel, but patient 13 had over twice the reduction in NAA. Similarly, patients 9 and 16 had similar levels of NAA loss, but the percentage of voxel volume occupied by stroke was 17 times higher in patient 16. Patients in whom NAA loss was closely related to the percentage of the voxel volume occupied by stroke (patients 7, 16, and 18) had strokes located principally in the striatocapsular region, whereas patients in whom the NAA loss was greater than that expected simply from the amount of T2 lesion within the voxel (patients 9, 11,
12, and 13) had cortical infarction. Thus, there were patients in whom the majority of axonal injury in the internal capsule within the voxel occurred as a result of direct involvement in the stroke and patients in whom significant damage to the axons in the internal capsule within the voxel must also have occurred as a result of anterograde degeneration. In other words, NAA loss was observed from normal-appearing white matter. Reduced NAA in normal-appearing white matter has also been shown to occur in patients with multiple sclerosis26 and head injury (M. Garnett, A.M. Blamire, and P. Styles, unpublished data, 1998). The time course of NAA loss from axons undergoing Wallerian degeneration is unclear and may be slower than NAA loss from the core of the infarct. It is possible that in the patients with cortical infarction, NAA losses from the internal capsule could have increased further after the study period.

Thus, NAA loss from the internal capsule would appear to provide a quantitative measure of functional axonal injury whether the injury occurs through direct ischemia to the axon within the spectroscopy voxel or through Wallerian degeneration. We did not see any of the characteristic imaging changes of Wallerian degeneration27 in our patients, but the imaging views normally used to show these changes were not performed. Our results are in agreement with the finding that the extent of Wallerian degeneration after stroke as shown by imaging views normally used to show these changes were not damaged ones.31 Pathway duplication may allow greater ways enables remaining intact pathways to take over from the compromised ones.32 Reversibility of recovery mechanisms after stroke, and one proposed mechanism is that duplication of function in the descending pathways enables remaining intact pathways to take over from the compromised ones.32 Pathway duplication may allow greater potential for recovery for coarse upper-limb function and leg function than for fine upper-limb movements that require integrity of the corticospinal tract from the contralateral hemisphere32 and cannot be controlled by the other descending pathways. This may explain in part why the curve for NAA reduction versus upper limb deficit is displaced to the left with respect to the curve for upper and lower limbs combined, indicating a greater upper-limb motor deficit for a given NAA reduction. Finally, it is possible that some of the acute deficit seen in stroke patients is secondary to potentially reversible metabolic compromise of neurons or axons. Resolution of this compromise could lead to patient recovery. Therefore, some of our patients, particularly those with minor deficits and no observable capsule NAA loss, may have had larger NAA losses acutely than were apparent at the time of the study.

The patients in our study were selected for motor deficit, and thus the infarcts would have involved the motor cortex or its projections in the subcortical white matter and internal capsule. Therefore, one might have expected an association between lesion volume and axonal injury in the capsule ipsilateral to the lesion. Lesion volume as measured by T2 changes on MRI was not correlated with capsule NAA loss when all patients with single lesions were included (n = 12) but was significant for patients with single lesions studied within 1 year of onset (n = 9, P = 0.03). The lack of correlation when more chronic patients were included could be explained by atrophy in the descending pathways causing the NAA loss to be underestimated (see below). It is of note that although lesion volume predicted contralateral motor deficit, the relationship was not as strong as that observed between NAA loss in the capsule and contralateral motor deficit.

There are a number of important points in our study relating to partial volume effects caused by the fact that the spectroscopy voxel included not only the descending motor pathways but also some basal ganglia and thalamus and the thalamocortical projections. First, partial volume effects may explain the fact that the relationship between NAA reduction and motor deficit is better described by a curve rather than a linear plot. Assuming that the descending pathways occupy 60% of the voxel volume, a maximal motor deficit could result from a 60% NAA loss from the voxel region in cases where damage occurred exclusively to the motor pathways, sparing the other structures within the voxel. The graph of NAA reduction against upper limb deficit indicates that a maximal upper limb deficit occurs with a 40% NAA loss, which would be consistent with the fact that the upper limb motor pathways occupy a smaller volume within the voxel than all the motor pathways together.

Second, the partial volume effects could have resulted in insufficient sensitivity in our experiment to detect small NAA losses in the descending motor tracts in patients with minor strokes. Underestimation of NAA loss may also have occurred in the patients studied a year or more after stroke, owing to atrophy in the descending motor pathways. Histological and imaging studies have shown massive shrinkage in the midbrain, pons, and pyramids after hemispheric lesions causing hemiparesis.33,34 One patient,14 examined more than 2 years after stroke, had a large cortical lesion with moderate motor deficit but no NAA loss from the capsule on the side of the lesion. Atrophy of the damaged motor pathways in this patient may have caused the volume originally occupied by the damaged pathways to be replaced by the surrounding normal tissue, resulting in no measured loss of NAA signal from the voxel. Finally, the partial volume effects may have led to an overestimation of NAA loss in the descending motor pathways in patients with damage to the thalamus and basal ganglia as a result of direct ischemia, metabolic depression,35 or retrograde changes from cortical strokes.36 However, given the tight correlation observed between NAA reduction and motor deficit, it would seem that the partial volume effects described are not of major practical significance.
Internal Capsule Axonal Injury and Motor Impairment

In conclusion, we have shown that axonal injury in the internal capsule, as measured by NAA loss, correlates with functional impairment in patients who have suffered a motor stroke. This was the case for cortical strokes in which there was presumed anterograde degeneration of the descending motor pathways passing through the capsule as well as for striatocapsular strokes in which there was direct involvement of the internal capsule in the stroke. MRS allows early assessment of axonal injury after T2-weighted imaging changes of Wallerian degeneration occur and provides a quantitative measure of damage. Future experiments should include longitudinal studies of patients after stroke to determine the time course of NAA loss in the internal capsule and whether there is a reversible component to this loss. This, together with monitoring of motor impairment, would allow assessment of MRS measurement of axonal injury in the internal capsule as a prognostic tool in patients after stroke.

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References

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S. T. Pendlebury, A. M. Blamire, M. A. Lee, P. Styles and P. M. Matthews

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