Vascular and Degenerative Processes Differentially Affect Regional Interhemispheric Connections in Normal Aging, Mild Cognitive Impairment, and Alzheimer Disease

Dong Young Lee, MD, PhD; Evan Fletcher, PhD; Oliver Martinez, BS; Natalia Zozulya, BS; Jane Kim, BS; Jeannie Tran, BS; Michael Buonocore, MD, PhD; Owen Carmichael, PhD; Charles DeCarli, MD

Background and Purpose—Despite the critical importance of the corpus callosum (CC) to the connection between brain hemispheres, little is known about the independent contribution of degenerative and vascular processes to regional changes in the microstructural integrity of the CC. Here, we examine these changes in subjects with mild cognitive impairment, with Alzheimer disease, and in cognitively normal elderly adults.

Methods—We used 3-dimensional brain MRI with diffusion tensor imaging in 47 Alzheimer disease, 77 mild cognitive impairment, and 107 cognitively normal subjects, and we calculated mean fractional anisotropy (FA) values for 4 CC regions corresponding to 4 homologous regions of cortical gray matter (GM). To assess vascular and degenerative processes, we also measured cortical GM and white matter hyperintensity (WMH) volume in corresponding regions and evaluated their vascular risk.

Results—We found that GM volumes in anterior and posterior regions were significantly related to FA values in the corresponding regions of the CC for all 3 diagnostic groups. Independent of GM volume, frontal WMH volume was also associated with FA values in the corresponding CC regions, but posterior WMH volume was not. Vascular risk was associated with FA of most CC regions, whereas diagnosis of cognitive state was associated only with FA of the anterior and posterior CC regions.

Conclusions—We found differential region-specific associations between degenerative and vascular processes and the structural integrity of the CC across the spectrum of cognitive ability. Based on these results, we propose a model to explain regional disruption in the interhemispheric connection. (Stroke. 2010;41:1791-1797.)

Key Words: Alzheimer disease ■ cerebrovascular disorders ■ corpus callosum ■ diffusion tensor imaging ■ mild cognitive impairment

The corpus callosum (CC) is the major white matter structure involved in interhemispheric cortico-cortical communication and is critical to multiple cognitive functions.1 The fibers of the CC arise predominantly from large pyramidal neurons in cortical layers III and V.2 These same neuron populations are selectively affected by Alzheimer disease (AD) pathologies.3,4 In support of this relation, several MRI studies have reported microstructural alteration of the CC as measured by fractional anisotropy (FA) derived from diffusion tensor imaging in AD and even mild cognitive impairment (MCI),5,6 a transitional state between normal cognitive function and dementia, especially AD. Knowledge about region-specific relationships between CC microstructural alteration and cortical degenerative process in AD and MCI, however, remains limited.

Vascular processes are also hypothesized to affect the integrity of the CC in normal aging, MCI, and AD.6–8 Subcortical vascular white matter damage, grossly reflected by white matter hyperintensities (WMH) seen on MRI, is common to aging, MCI, and AD, as well as cerebrovascular disease.7 Such white matter damage could also alter CC integrity through direct injury to subcortical axonal fibers. Nevertheless, little is known about regional associations between cerebrovascular pathology and CC alteration in normal aging or cognitive impairment.

Previous work in our laboratory has found regional patterns in WMH7 and white matter FA8 that are distinct for both cerebrovascular disease and AD processes, suggesting that both processes might independently affect CC integrity. Given the importance of the CC to integrative cognitive processes, further investigation of the influence of AD and cerebrovascular disease processes on CC integrity may lead important insights relating to the pathobiology of cognitive impairment attributable to these 2 pathologies individually or in combination.
Therefore, this report seeks to further delineate the complicated region-specific associations between degenerative and vascular processes and CC microstructural integrity. To accomplish this, we first investigated the neuroanatomical relationships of regional cortical gray matter (GM) and WMH volumes with homologous CC subregional FA among a group of subjects with normal cognition, MCI and AD. Secondly, the associations of diagnosis (cognitively normal [CN], MCI and AD) and vascular risk with each of regional cortical GM volume, WMH volume, and CC FA were evaluated. Combining the results from these 2 steps of investigation, we proposed a possible patho-anatomic model to explain regional CC disruptions by AD degenerative and vascular processes.

Subjects and Methods
Subjects included 47 AD, 77 MCI, and 107 CN individuals. The AD group consisted of 78.7% patients with probable AD. 19.1% patients with possible AD, and 2.1% patients with AD and sufficient cerebrovascular disease, defined as ≥2 strokes, at least 1 of which is outside cerebellum on MRI, or single stroke with clearly documented temporal relationship to the onset or aggravation of cognitive impairment9 for the diagnosis of mixed dementia; 83.6% of MCI patients are amnestic and 16.4% are nonamnestic subtype. No subjects except those with mixed dementia had clinical stroke. The diagnosis of AD was made according to the National Institute of Neurological and Communication Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association criteria.9 The diagnosis of mixed dementia was according to the criteria of the State of California Alzheimer’s Disease Diagnostic and Treatment Centers.9 MCI was diagnosed according to current consensus criteria.11 CN was diagnosed if there was no clinically significant cognitive impairment.

Subjects were recruited from the Alzheimer’s Disease Center at the University of California, Davis. All participants received a comprehensive clinical evaluation and neuropsychological testing with a standardized test battery. In addition, all subjects received a standardized MRI scan of the brain at the baseline evaluation. The Institutional Review Boards at all participating institutions approved this study, and subjects or their legal representatives gave written informed consent.

Vascular Risk Assessment
The presence or absence of stroke, diabetes, hyperlipidemia, transient ischemic attack, hypertension, and coronary artery disease was systematically assessed to create a composite score for vascular risks, which was the sum of the factors present, ranging from 0 to 6, and reported as a percentage.6

Image Acquisition and Processing
All brain imaging was performed at the University of California at Davis Imaging Research Center on a 1.5-T GE Signa Horizon LX Echospeed system. Three sequences were used: a 3-dimensional T1-weighted coronal spoiled gradient-recalled echo acquisition, a fluid-attenuated inversion recovery sequence, and a diffusion tensor imaging sequence. Diffusion tensor imaging was performed according to an in-house procedure that has been previously described.7,16

Regions of Interest
For determination of regional GM, WMH volumes, and CC FA, we drew 3 different sets of regions of interest (ROI) on a minimal deformation template (Supplemental Figure I available online at http://stroke.ahajournals.org). The first set consisted of 4 GM ROI labeled as GM I, GM II, GM III, and GM IV, corresponding to prefrontal cortex, premotor and supplementary motor cortex, sensory motor cortex, and parieto-temporo-occipital cortex without postcentral gyrus, respectively. GM IV was additionally divided into 3 subregions for more detailed comparison (IV-p for parietal cortex, IV-t for temporal cortex, and IV-o for occipital cortex). Both left and right GM of each region were combined to create each GM ROI. The second set consisted of 2 white matter ROI, ie, frontal white and posterior white matter ROI. The cerebral white matter was divided into frontal and posterior white matter ROI by an arbitrary curved plane containing the bilateral central sulci. The third set included 4 CC subregion ROI specifically identified as homologous to the 4 cortical regions as previously determined.14 The CC was outlined on mid-sagittal and 4 adjacent sagittal slices (ie, 2 right and 2 left slices to the mid-sagittal one; 1 slice thickness=0.938 mm) and divided into 4 subregion ROI, ie, CC I, CC II, CC III, and CC IV. The proportions for division were determined according to a recently proposed CC subdivision based on cytoarchitectonic cortical topography and advanced diffusion tensor imaging tractography.14

Image Analysis
Image analysis was performed to obtain subject tissue volumes and FA values among the predefined ROI drawn on the minimal deformation template. This was accomplished in 4 stages.

Image Registration
The method of image registration has been previously described.6 Native space T1 spoiled gradient-recalled echo acquisition brain images were first stripped of the skull using an in-house semiautomatic algorithm. Next, they were linearly aligned to the template image using a 12-parameter affine transformation. These aligned images were then warped onto the template using a high-dimensional B-spline deformation.

Four-Tissue Image Segmentation
Segmentation of GM, white matter, WMH, and cerebrospinal fluid was performed on native space T1 spoiled gradient-recalled echo acquisition images by an in-house computer program using Bayesian maximal-likelihood expectation-maximization computation.15 Tissue probabilities used a combination of Gaussian intensity distributions combined with a Markov random field component for modeling the tissue classification of voxel neighborhoods. Two in-house enhancements included automatic initialization of the expectation-maximization step via a high-dimensional B-spline warp in which template-based tissue probability maps are fitted to the native T1 spoiled gradient-recalled echo acquisition images and edge detection to dictate the appropriate neighborhood clique structure of the Markov random field for locations in homogeneous tissue or at tissue boundaries. The segmentation of WMH was determined by WMH maps derived from subject fluid-attenuated inversion recovery images according to an in-house procedure that has been previously described.7,16

Automatic Fitting of Template ROI
The linear alignment followed by B-spline warp, performed to register the native T1 spoiled gradient-recalled echo acquisition image with the template, were reversed to fit each ROI back into native space. Each ROI was transformed using the inverse of the warp, followed by the inverse of the affine transformation. Accurate ROI tissue volumes then can be achieved in conjunction with the native space tissue segmentations.

ROI Volume and Tissue Calculation
Volumetric calculations were made using ROI transformed onto native space images. For every CC region mask on a subject native brain, volume and mean FA were calculated. Mean FA values were obtained by averaging FA values over every voxel within the mask. GM and WMH volumes inside an ROI were obtained by counting GM or WMH voxels of the segmented image within the desired ROI.

Statistical Analysis
Demographic, clinical, and overall MRI volume data for the 3 cognitive groups were compared by 1-way analysis of variance with Tukey post hoc comparisons. To investigate independent, region-specific association of GM and WMH volume with CC FA, we first tested multiple linear regression models with CC FA as the dependent variable, and corresponding GM and WMH volume (frontal WMH volume for CC I and CC II FA, and posterior WMH volume for
for CC III and IV FA), and age as independent variables for each CC region across AD, MCI, and CN groups. The associations of diagnosis and vascular risk with any regional brain volume or FA were tested by analyses of covariance with age as a covariate using Tukey post hoc comparison. Values with \( P < 0.05 \) were regarded as significant when otherwise not specified.

### Results

#### Subject Characteristics

Demographic, clinical, and overall MRI volume description of all the subjects are summarized in Table 1.

![Figure 1](http://stroke.ahajournals.org/)

**Figure 1.** Graphic displays of regional volume and fractional anisotropy (FA) according to diagnostic group. A, Regional gray matter (GM) volume. B, Regional white matter hyperintensity (WMH) volume. C, FA of subregions of the corpus callosum (CC). White columns indicate cognitively normal older individuals; gray columns indicate patients with mild cognitive impairment; black columns indicate patients with Alzheimer disease. TCV indicates total cranial volume. Error bars indicate SD. \( *P < 0.05, **P < 0.01 \) by Tukey post hoc diagnostic group comparison.
Regional GM and WMH Volumes and CC FA

Before investigating the relationships among the target variables, we first compared regional cortical GM and WMH volumes and CC FA between diagnostic groups. There were significant diagnostic group differences in volume for each of GM I, GM II, and GM IV-t (F=6.92, P=0.001 for GM I; F=14.73, P<0.001 for II; F=28.31, P<0.001 for IV-t; Figure 1A). A strong trend toward significant group differences was also found for GM IV-p (F=2.93; P=0.054). We also found a significant group difference in whole GM IV volume (F=9.80; P<0.001). In contrast, there were no significant diagnostic group differences in GM III and GM IV-o volume. Furthermore, there were significant diagnostic group differences in both frontal and posterior WMH volume (F=5.85, P=0.003 for the frontal WMH; F=4.13, P=0.017 for the posterior WMH; Figure 1B). The results of post hoc comparisons for each analysis are presented in Figure 1A and 1B. Significant group differences were found for FA measures in all CC regions (F=3.90, P=0.022 for CC I; F=3.90, P=0.022 for II; F=4.18, P=0.017 for III; F=6.87, P=0.001 for IV; Figure 1C). Post hoc analyses showed that AD patients had significantly lower FA values in all the CC regions as compared to CN individuals (Figure 1C). Effect size (i.e., Cohen d(17)) for the difference of FA between CN and AD was 0.591 for CC I, 0.530 for CC II, 0.507 for CC III, and 0.583 for CC IV, indicating that the greatest group differences were at the genu and splenium of the CC. AD also had significantly lower FA in the CC II, CC III, and CC IV than MCI (Figure 1C). There were, however, no significant differences of regional CC FA values between CN and MCI.

Region-Specific Association of GM and WMH Volume With CC FA

Among 4 multiple regression models explaining regional CC FA by corresponding GM and WMH volume that included all subjects, the models for CC I, CC II, and CC IV FA were significant, but the model for CC III FA was not (Table 2). The results for individual independent variables were quite different among each of the significant models. In case of the model for CC I FA, both corresponding GM and WMH volume were statistically significant, whereas only GM volume was significant in the model for CC IV FA. In the model CC II FA, GM volume was significant and WMH volume was marginally significant.

Additionally, to identify any differences in GM and WMH volume vs CC FA relationship among AD, MCI, and CN groups, both GM volume by diagnosis and WMH volume by diagnosis interaction effects were tested with main effects of age, GM volume, WMH volume, and diagnosis for each regional CC FA using general linear model. For CC IV FA, there was an additionally significant posterior WMH volume by diagnosis interaction (F=6.33; P=0.002). Therefore, we tested individual associations between posterior WMH volume and CC IV FA again for each diagnostic group, controlling age and GM IV volume. Posterior WMH volume had a significant negative association with CC IV FA only in AD group, but not in CN and MCI groups, whereas GM IV volume was significantly associated with CC IV FA in all 3 groups (Table 3 and Supplemental Figure II available online at http://stroke.ahajournals.org). No such WMH volume by diagnosis interactions were found for CC I, CC II, and CC III FA. In addition, there were no GM volume by diagnosis interactions for all regional CC FA.

Independent Association of Diagnosis and Vascular Risk With Regional GM and WMH Volume and CC FA

Independent of vascular risk, diagnosis was significantly associated with volumes of GM I, GM II, and GM IV, but not with that of GM III. Vascular risk was not significantly associated with regional GM volumes (Table 4). In contrast, both diagnosis and vascular risk were significantly associated with frontal and posterior WMH volume. Contribution of vascular risk to regional WMH volumes, however, was relatively greater in the frontal region than in the posterior region (Table 4). Finally, with regard to regional CC FA, diagnosis was significantly related only with CC I and CC IV FA showing relatively greater contribution to CC IV compared to CC I. In contrast, vascular risk showed significant association with CC I, CC II, CC III FA, and marginally significant association with CC IV FA.

Discussion

Our ROI-based approach revealed that microstructural integrity, as measured by FA, differed significantly by degree of cognitive impairment in all CC subregions with greater effect sizes in the anterior (ie, CC I) and posterior regions (IV) compared to the middle region (II and III). The volume of cortical GM I, GM II, and GM IV was significantly related to the FA of topographically homologous CC subregions across the spectrum of cognitive ability. Independent of GM vol-
We found significant AD-associated FA changes in all CC regions, whereas other ROI-based studies reported significant FA deficits only in the splenium, but not in the genu of the CC.\(^5\) Our analytic method may be one reason for the differences. Although most previous studies focused only on the genu and splenium utilizing relatively small ROI,\(^5\) we investigated regional FA across the entire CC based on cytoarchitectonic cortical topography.\(^{14}\) In support of our findings, a voxel-based study\(^{18}\) reported prominent FA differences between AD and CN in the anterior CC, encompassing both the genu and anterior body.

To delineate regional patho-anatomic associations between degenerative and vascular processes and CC integrity, we first investigated region-specific associations between cortical GM and WMH volumes and CC FA using topographically corresponding ROI pairs.\(^{14}\) Although 1 previous study reported correlation between GM change and regional CC integrity in AD, it focused only on small regions in the genu and splenium and did not take into consideration the topographically organized regions of the entire CC.\(^9\) The FA of the CC I, CC II, and CC IV were significantly associated with the volume of the corresponding cortical GM regions within the entire subject group. These findings suggest that CC microstructural integrity is closely associated with secondary degenerative changes of axonal fibers attributable to primary GM injury. This is further supported by significant processes on CC integrity across the spectrum of cognitive ability.

### Table 3. Multiple Regression Models for Corpus Callosum Region IV Fractional Anisotrophy in Each Diagnostic Group

<table>
<thead>
<tr>
<th>Variables</th>
<th>CN (n=107)</th>
<th>MCI (n=77)</th>
<th>AD (n=47)</th>
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<tbody>
<tr>
<td>GM IV volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\beta)</td>
<td>0.283</td>
<td>0.260</td>
<td>0.328</td>
</tr>
<tr>
<td>(\Delta R^2)</td>
<td>0.074</td>
<td>0.059</td>
<td>0.129</td>
</tr>
<tr>
<td>(P)</td>
<td>0.005</td>
<td>0.036</td>
<td>0.017</td>
</tr>
<tr>
<td>Posterior WMH volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\beta)</td>
<td>0.053</td>
<td>0.109</td>
<td>-0.406</td>
</tr>
<tr>
<td>(\Delta R^2)</td>
<td>0.002</td>
<td>0.009</td>
<td>0.156</td>
</tr>
<tr>
<td>(P)</td>
<td>0.621</td>
<td>0.416</td>
<td>0.008</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\beta)</td>
<td>-0.044</td>
<td>-0.121</td>
<td>0.020</td>
</tr>
<tr>
<td>(\Delta R^2)</td>
<td>0.002</td>
<td>0.010</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(P)</td>
<td>0.677</td>
<td>0.490</td>
<td>0.899</td>
</tr>
<tr>
<td>Overall model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(R^2)</td>
<td>0.081</td>
<td>0.095</td>
<td>0.271</td>
</tr>
<tr>
<td>(P)</td>
<td>0.033</td>
<td>0.064</td>
<td>0.004</td>
</tr>
</tbody>
</table>

### Table 4. Independent Effect of Age, Vascular Risk, and Diagnosis on Regional Gray Matter Volume, White Matter Hyperintensity Volume, and Corpus Callosum Fractional Anisotrophy

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Independent Variable</th>
<th>Statistics</th>
<th>GM I</th>
<th>GM II</th>
<th>GM III</th>
<th>GM IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>GM volume</td>
<td>Diagnosis</td>
<td>(F)</td>
<td>9.90</td>
<td>3.49</td>
<td>0.77</td>
<td>20.40</td>
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<tr>
<td></td>
<td>(P)</td>
<td>&lt;0.001</td>
<td>0.032</td>
<td>0.465</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td>Vascular risk</td>
<td>(F)</td>
<td>0.14</td>
<td>0.21</td>
<td>&lt;0.001</td>
<td>1.85</td>
</tr>
<tr>
<td></td>
<td>(P)</td>
<td>0.713</td>
<td>0.650</td>
<td>0.962</td>
<td>0.175</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>(F)</td>
<td>11.04</td>
<td>2.06</td>
<td>15.95</td>
<td>14.72</td>
</tr>
<tr>
<td></td>
<td>(P)</td>
<td>0.001</td>
<td>0.153</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>WMH volume</td>
<td>Diagnosis</td>
<td>(F)</td>
<td>4.96</td>
<td>5.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(P)</td>
<td>0.007</td>
<td>0.007</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vascular risk</td>
<td>(F)</td>
<td>7.73</td>
<td>3.89</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(P)</td>
<td>0.006</td>
<td>0.049</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>(F)</td>
<td>40.31</td>
<td>69.19</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>(P)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC FA</td>
<td>Diagnosis</td>
<td>(F)</td>
<td>3.58</td>
<td>2.35</td>
<td>2.45</td>
<td>6.10</td>
</tr>
<tr>
<td></td>
<td>(P)</td>
<td>0.030</td>
<td>0.098</td>
<td>0.089</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vascular risk</td>
<td>(F)</td>
<td>5.79</td>
<td>12.24</td>
<td>4.42</td>
<td>3.76</td>
</tr>
<tr>
<td></td>
<td>(P)</td>
<td>0.017</td>
<td>0.001</td>
<td>0.037</td>
<td>0.054</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>(F)</td>
<td>14.03</td>
<td>0.05</td>
<td>&lt;0.01</td>
<td>2.24</td>
</tr>
<tr>
<td></td>
<td>(P)</td>
<td>&lt;0.001</td>
<td>0.820</td>
<td>0.956</td>
<td>0.136</td>
<td></td>
</tr>
</tbody>
</table>

Data are \(F\) and \(P\) by analysis of covariance including diagnosis as a factor and age and vascular risk as covariates.
diagnosis–CC and diagnosis–GM associations in similar regions. Interestingly, however, a similar GM–CC association was also observed in CN, as well as in AD and MCI (Table 3). Although this is a preliminary finding from a secondary analysis, it does suggest the possibility that some of these elderly individuals may have considerable, but asymptomatic, AD pathology.20 and this requires further study, particularly with direct pathological examination and longitudinal evaluation.

When analyzed across diagnostic groups, the regional association of WMH with CC FA was significant only in the most anterior CC subregion (CC I). In contrast, vascular risk had meaningful associations with most CC regions. This regional discrepancy between WMH–CC and vascular risk–CC relationships appears to be related to relatively different etiologies of WMH between the frontal and posterior WMH.7 As shown in Table 4, posterior WMH are most strongly related to degenerative processes, whereas frontal WMH are equally related to both vascular process and degeneration. When we analyzed each diagnostic group individually, the posterior CC was associated with posterior WMH in AD group, but not in CN and MCI groups. This also may be explained by strong association of WMH with AD degeneration in this region.

Based on the results of the current study, we propose an explanatory model of patho-anatomic mechanism for the microstructural disruption of the CC in CN, MCI, and AD (Figure 2). Briefly, both AD degenerative and vascular processes contribute to a similar degree to the alteration of the anterior CC ( genu and anterior body; Figure 2A), whereas the influence of degenerative process is prominent compared to vascular process for the posterior CC (splenium; Figure 2C). In case of the middle CC (middle and posterior body), vascular impact remains substantial, but the impact of degenerative process appears less (Figure 2B). In this model, subcortical WM damage, grossly measured by WMH, mediates not only the direct impact of vascular injury process but also the indirect influence of cortical GM degeneration that, in combination, contributes to the microstructural alteration of the CC. Future work will examine the cognitive consequences of these CC differences.

Conclusion

We found differential, region-specific associations of degenerative and vascular processes with CC microstructural alteration in a cohort of subjects with a spectrum of cognitive ability. Based on the results of the current study, a patho-anatomic explanatory model for regional disruptions of the interhemispheric connection is proposed. Our results are also consistent with the evolving literature that suggests that both AD and cerebrovascular disease additively affect brain structure, leading to increased risk for dementia late in life.

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Disclosure

None.

References

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