Birth Parameters Are Associated With Late-Life White Matter Integrity in Community-Dwelling Older People

Susan D. Shenkin, MD, MRCP (UK); Mark E. Bastin, DPhil; Tom J. MacGillivray, PhD; Ian J. Deary, PhD, FRCPE, FRCPsych, FMedSci; John M. Starr, FRCPE; Joanna M. Wardlaw, FRCR, FRCPE, FMedSci

Background and Purpose—Lower birth weight is associated with increased risk of stroke, but little is known about the mechanism for this association or influence in addition to vascular risk factors. We investigated whether there was an association between birth parameters and imaging markers of white matter integrity in community-dwelling older people.

Methods—One hundred seven volunteers, age 75 to 81 years, had birth parameters (weight, length, placental weight, gestational age) extracted from archives. Neuroimaging included assessment of white matter lesions and diffusion tensor–magnetic resonance imaging parameters in normal-appearing white matter.

Results—Lower placental weight was correlated with increased white matter lesion load ($P<0.05$) and diffusion tensor–magnetic resonance imaging parameters ($P<0.05$). Birth weight and frontal white matter fractional anisotropy were significantly correlated ($P<0.05$). These associations were only slightly attenuated when corrected for gestational age, sex, age at scan, and vascular risk factors.

Conclusions—Lower placental and possibly lower birth weight were associated with sensitive neuroimaging measures of white matter lesions in this cohort, independent of vascular risk factors later in life. Further studies are required to confirm these findings to explore life-long risk factors for age-related white matter changes. (Stroke. 2009;40:1225-1228.)

Key Words: leukoaraiosis ■ magnetic resonance ■ white matter disease ■ birth weight ■ diffusion tensor imaging ■ life course

Studies of early life influences show an association between increased stroke incidence and lower birth weight. Stroke is, however, a heterogeneous condition with a variety of etiologies. Epidemiologic studies may underestimate mild strokes and, depending on the type of neuroimaging (if used), may not accurately distinguish ischemic from hemorrhagic or small- from large-artery strokes. Some large cohort studies suggest that the influence of birth weight may be more important for hemorrhagic than ischemic stroke, whereas others have found the opposite.

To understand whether early life influences increase the risk of stroke, more sensitive and specific outcome measures are required. Appropriate neuroimaging can distinguish ischemic from hemorrhagic stroke and can detect other vascular effects on the brain, such as white matter lesions (WMLs) or alterations in water diffusion parameters. WMLs are associated with vascular risk factors and lacunar stroke and pathologically with small arteriolar wall thickening and disintegration. White matter damage is reflected by increased mean diffusivity ($<D>$) and decreased fractional anisotropy (FA) in diffusion tensor—magnetic resonance imaging (DT-MRI), both within WMLs themselves and in surrounding normal-appearing white matter. No studies have reported early life influences on later-life white matter integrity assessed by neuroimaging.

We therefore investigated the relation between birth parameters and white matter integrity, as detected by structural and DT-MRI, in community-dwelling older people. We hypothesized that lower birth weight would be associated with white matter damage (WMLs, increased $<D>$, and...
decreased FA) and investigated whether the association was accounted for by vascular risk factors.

Subjects and Methods

Subjects

We recruited 115 volunteers who were living independently in the community and who had been born in 1 Edinburgh hospital between 1921 and 1926, by invitation, media appeal, or posters. Exclusion criteria were contraindications to MRI and severe physical or mental illness such that they would not be able to attend or complete the tests. Of 115 subjects recruited, 110 completed the MRI examination. Three scans were excluded owing to incidental findings (pituitary adenoma, meningoima, and temporal cyst), as these may influence WML ratings or DT-MRI parameters; i.e., 107 subjects were included in the analyses. All subjects provided informed consent. The Lothian Regional Ethics Committee approved the study.

MRI Scanning

MRI data were collected on a GE 1.5-T clinical scanner according to a previously described protocol: T1-weighted spin-echo imaging, T2-weighted fast spin-echo and fluid-attenuated inversion recovery fast spin-echo imaging, and DT-MRI based on spin-echo echo-planar imaging.

Image Processing

T2-weighted and fluid-attenuated inversion recovery images were examined for the presence of infarct or hemorrhage and quantified for WML load on the Fazekas scale, which rates periventricular hyperintensities (PVHs) and deep white matter hyperintensities (DWMHs) separately on a scale of 0 to 3. The rater (J.M.W.), an experienced neuroradiologist, was blind to all other data.

Maps of <D> and FA for each subject were generated and converted into Analyze format (Mayo Foundation). Regions of interest were placed in the frontal and occipital white matter and centrum semiovale with the T2-weighted echo-planar images, avoiding WMLs, by an observer (T.J.M.) blind to all other data.

Birth Records

We retrieved birth parameters from the original archival record and converted imperial to metric units. Social class was determined from paternal occupation according to the Registrar General’s classification.

Vascular Risk Factors

We collected data on history of hypertension, diabetes, heart disease, stroke, peripheral or other vascular disease, and smoking status. Blood pressure was measured with the subject in the supine position, after a 2-minute rest, with a Dinamap Compact Monitor automated blood pressure machine (Critikon). Blood samples were taken for glycosylated hemoglobin (HbA1c), cholesterol, and triglycerides.

Statistical Analysis

We used Spearman’s rho to investigate correlations between birth parameters and WMLs and Pearson’s r for correlations between birth parameters and DT-MRI. We explored the influence of potential mediators and confounders on the relation between birth parameters and white matter integrity with the use of partial correlation for DT-MRI and logistic regression for WMLs (missing data excluded listwise).

Results

Table 1 shows demographic data for the 107 subjects (mean±SD age, 78.4±1.5 years). Table 2 shows descriptive data for birth parameters, vascular risk factors, WML load, and DT-MRI parameters. Table 3 shows correlations between birth parameters and neuroimaging data. Birth weight and fronta FA were significantly correlated. Placental weight was correlated significantly with WML load and with 3 of 6 DT-MRI parameters. The associations were in the expected direction: lower placental weight was associated with increased WML score, increased <D> in the frontal and centrum semiovale region, and decreased FA in the frontal region. There was a trend toward a negative association between gestational age and WMLs but not DT-MRI parameters. Adjustment, with partial correlation, for gestational age, age at scan, sex, and vascular risk factors (disease history, smoking status, blood pressure, HbA1c, cholesterol, triglycerides) did not substantially affect the associations between birth parameters and DT-MRI variables.

Because there were so few people with Fazekas scores 0 or 3, we dichotomized both PVH and DWMH scales into minimal (0–1) and present (2–3). Logistic regression was performed including birth parameters, gestational age, vascular risk factors, and social class (these variables were forced into the model because of a priori considerations). Placental weight predicted PVH (β=−4.3, P=0.031), and no other parameters entered the model. Placental weight predicted DWMH (β=−4.5, P=0.033), and no other parameters entered the model.

To establish whether the correlation between birth measurements and DT-MRI parameters were driven by subjects with previous stroke or with higher WML load, we reanalyzed the data after excluding those with MRI evidence of stroke and history of stroke and correcting for WML load. Excluding those with MRI evidence of stroke only slightly attenuated the correlations (within 0.03 of the previous associations; results available from authors), but they conformed to the same pattern. Excluding those with a self-reported history of stroke did not substantially alter the results. Correcting for WML load with partial correlation also did not substantially change the relation. Therefore, placental weight was correlated with deep and periventricular WMLs and with white matter DT-MRI parameters.

Discussion

In 107 community-dwelling people age 75 to 81 years, there was a significant association between placental weight and
Table 2. Descriptive Statistics (Birth Parameters, Vascular Risk Factors, DT-MRI Parameters and WML Load)

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, g</td>
<td>107</td>
<td>3311.6</td>
<td>458.3</td>
<td>2226</td>
<td>4564</td>
</tr>
<tr>
<td>Birth length, cm</td>
<td>107</td>
<td>50.6</td>
<td>2.7</td>
<td>43.2</td>
<td>55.9</td>
</tr>
<tr>
<td>Placental weight, g</td>
<td>81</td>
<td>678.4</td>
<td>146.6</td>
<td>340.0</td>
<td>1077.0</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>98</td>
<td>39.6</td>
<td>2.4</td>
<td>30.3</td>
<td>45.3</td>
</tr>
<tr>
<td>Total serum cholesterol, mmol/L</td>
<td>106</td>
<td>5.5</td>
<td>1.1</td>
<td>3.3</td>
<td>8.8</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>107</td>
<td>158.8</td>
<td>25.9</td>
<td>103</td>
<td>238</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>101</td>
<td>5.8</td>
<td>0.61</td>
<td>4.3</td>
<td>8.7</td>
</tr>
<tr>
<td>Frontal &lt;D&gt; (×10⁻⁶ mm²/sec)</td>
<td>102</td>
<td>839.3</td>
<td>42.6</td>
<td>758.1</td>
<td>994.0</td>
</tr>
<tr>
<td>Occipital &lt;D&gt;, × 10⁻⁶ mm²/s</td>
<td>102</td>
<td>760.6</td>
<td>36.2</td>
<td>676.7</td>
<td>877.4</td>
</tr>
<tr>
<td>Centrum semiovale &lt;D&gt;, × 10⁻⁶ mm²/s</td>
<td>103</td>
<td>766.9</td>
<td>41.7</td>
<td>690.0</td>
<td>940.2</td>
</tr>
<tr>
<td>Frontal FA</td>
<td>102</td>
<td>0.30</td>
<td>0.03</td>
<td>0.23</td>
<td>0.39</td>
</tr>
<tr>
<td>Occipital FA</td>
<td>102</td>
<td>0.41</td>
<td>0.05</td>
<td>0.22</td>
<td>0.55</td>
</tr>
<tr>
<td>Centrum semiovale FA</td>
<td>103</td>
<td>0.39</td>
<td>0.06</td>
<td>0.28</td>
<td>0.56</td>
</tr>
</tbody>
</table>

| WML load: PVH                   | 0   | 56 (52.3%)| 35 (32.7%) | 15 (14.0%) |
| WML load: DWMH                 | 8 (7.5%) | 76 (71.0%)| 16 (15.0%) | 7 (6.5%)   |

Imperial units in original records were converted to metric units: 1 lb=453.6 g; 1 oz=28.3 g; 1 inch=2.5cm.

Table 3. Correlations Among Birth Parameters and Markers of Cerebrovascular Disease (WML and DT-MRI)

<table>
<thead>
<tr>
<th></th>
<th>PVH</th>
<th>DWMH</th>
<th>Frontal &lt;D&gt;</th>
<th>Occipital &lt;D&gt;</th>
<th>CS &lt;D&gt;</th>
<th>Frontal FA</th>
<th>Occipital FA</th>
<th>CS FA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight</td>
<td>−0.11</td>
<td>−0.18</td>
<td>−0.11</td>
<td>0.09</td>
<td>−0.17</td>
<td>0.20*</td>
<td>−0.00</td>
<td>0.05</td>
</tr>
<tr>
<td>Birth length</td>
<td>0.02</td>
<td>−0.11</td>
<td>−0.00</td>
<td>0.10</td>
<td>−0.04</td>
<td>0.17</td>
<td>−0.09</td>
<td>0.10</td>
</tr>
<tr>
<td>Placental weight</td>
<td>−0.24*</td>
<td>−0.33†</td>
<td>−0.25*</td>
<td>−0.06</td>
<td>−0.27*</td>
<td>0.36†</td>
<td>0.00</td>
<td>0.05</td>
</tr>
<tr>
<td>Gestational age</td>
<td>−0.10</td>
<td>−0.19</td>
<td>0.06</td>
<td>0.01</td>
<td>−0.06</td>
<td>0.10</td>
<td>−0.04</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Correlations for WMLs used Spearman’s rho and for DT-MRI parameters, Pearson’s r. CS indicates centrum semiovale.

*P<0.05, †P<0.01.
cance owing to lack of power. Conversely, the positive results may be an artifact of multiple testing, although the consistency of the association between placental weight and WML and both \(<D\) and FA suggests this is not the case. Ethics approval enabled collection of birth data only with individual consent; therefore, we are unable to estimate the degree of selection bias. There is also the possibility of survival bias: ie, that a lack of association between birth parameters and white matter integrity in this cohort is because those with significant cerebrovascular disease had already died. We plan to repeat this study with a younger cohort to investigate this possibility. We did not have data on head size or postnatal growth.\(^1\) Despite detailed information on vascular risk factors, the relation reported could still be due to residual confounding by factors related to both birth weight and MRI changes, eg, maternal nutrition or genetic factors. It is possible that the mothers of babies with low placental weight had worse vasculature themselves, and such intergenerational studies will be an interesting area for future study. We suggest that MRI can be used to further investigate the relation between life course influences and white matter integrity.

**Acknowledgments**

We thank the staff of the SFC Brain Imaging Research Centre for technical support. Margaret M. Rush (funded by the Scottish Office) extracted the birth data from 1921 from the original records. We are grateful to Dr Michael Barfoot, Lothian Health Services Archivist, for facilitating research access to birth records used in this study. We are very grateful to all of the participants in this study.

**Sources of Funding**

This work was funded by a project grant from Chest, Heart and Stroke, Scotland. Susan D. Shenkin was supported by a Medical Research Council Clinical Training Fellowship. MRI was performed in the SFC Brain Imaging Research Centre, University of Edinburgh (www.sbirc.ed.ac.uk). The work was supported by the University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative. Funding from the BBSRC, EPSRC, ESRC, and MRC is gratefully acknowledged.

**Disclosures**

None.

**References**


Birth Parameters Are Associated With Late-Life White Matter Integrity in Community-Dwelling Older People

Susan D. Shenkin, Mark E. Bastin, Tom J. MacGillivray, Ian J. Deary, John M. Starr and Joanna M. Wardlaw

Stroke. 2009;40:1225-1228; originally published online February 12, 2009; doi: 10.1161/STROKEAHA.108.527259

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/40/4/1225

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/