Clinical associations of prenatal ischaemic white matter injury

Geraldine Gaffney, Marian V Squier, Ann Johnson, Valerie Flavell, Susan Sellers

Abstract

Neuropathological examinations were carried out at necropsy on 274 cases of intrauterine death or neonatal death at or before three days after birth. Fifty six (20.4%) subjects had evidence of prenatal ischaemic brain damage. On review of the maternal case notes to ascertain antenatal clinical associations there was an increased incidence of intrauterine growth retardation, either based on birth weight for gestational age (odds ratio (OR) 2.0; 95% confidence interval (CI) 1.1 to 3.7) or diagnosed antenatally (OR 2.7; 95% CI 1.3 to 5.6). Oligohydramnios was also more common (OR 2.9; 95% CI 1.2 to 7.0). The association of intrauterine growth retardation and white matter damage remained after excluding fetuses with a major congenital anomaly (OR 2.4; 95% CI 1.1 to 5.1). The findings suggest that chronic intrauterine hypoxia may be associated with damage to cerebral white matter among fetuses and infants who die. The relation between ischaemic white matter damage and cerebral palsy among survivors remains speculative. (Arch Dis Child 1994; 70:F101-F106)

It is well known that ischaemic lesions of the cerebral white matter may develop during the prenatal period and it has been suggested that such lesions may be associated with later neurological impairment, particularly cerebral palsy. Adverse events occurring at any time throughout the prenatal period and during or after birth may interfere with the development of the brain, and the distribution and extent of cerebral injury may vary considerably with the timing of these events. Traditionally, events during the intrapartum period were thought to be responsible for the development of cerebral palsy in many children, but it is now appreciated that only about 13% of cases of cerebral palsy can be attributed to intrapartum injury. Although other aetiological subgroups of cerebral palsy can be identified, such as congenital malformation of the brain, postnatal infection and genetic factors, at present ‘we probably do not know what causes the majority of cerebral palsy’. There is some evidence to support the idea that a proportion of cases of cerebral palsy may be determined antenatally. For example, it has been shown that the mothers of children who develop cerebral palsy have an increased frequency of adverse antenatal events. The association of cerebral palsy and intrauterine growth retardation (IUGR) suggests that long term intrauterine placental insufficiency may have a role in the origin of cerebral palsy in some children, whereas intrauterine vascular accidents leading to focal intracerebral damage may account for some spastic hemiplegia. Hypoxic or ischaemic white matter damage may occur in several forms. These range from diffuse white matter damage, either gliosis to more severe damage characterised by reactive astrocytosis, endothelial proliferation, nuclear karyorrhexis, and macrophage infiltration, probably representing early infarction, to the more widely recognised periventricular leukomalacia where there are small foci of cystic infarction in the deep white matter, usually associated with some degree of diffuse change. The term periventricular telencephalic leukoencephalopathy has been coined to describe diffuse white matter damage which may precede or coexist with periventricular leukomalacia. Widespread cystic degeneration of the white matter, cystic leukoencephalopathy, represents the most severe form of white matter damage. The clinical correlation between cystic periventricular leukomalacia detected by neuroimaging and later cerebral palsy is high, with 60–100% of survivors having a motor impairment. The relation between less extreme forms of white matter damage and later cerebral palsy is not so clear. The observation that only 28% of non-haemorrhagic hypoxic and ischaemic lesions detected at necropsy have been identified by ultrasound during life suggests that neuroimaging may not be sufficiently sensitive to detect minor lesions. This means that it is not yet possible to study the association of minor forms of ischaemic white matter damage and later cerebral palsy using clinical imaging techniques. An alternative approach to studying the possible clinical significance of prenatal ischaemic white matter damage is to identify the antenatal, intrapartum, and neonatal clinical factors found more often among fetuses with such lesions than those without. If these factors were the same as those known to be associated with the prenatal and perinatal periods of children with cerebral palsy this would support the hypothesis that prenatal ischaemic brain lesions have a role in the origin of cerebral palsy. Furthermore, the identification of factors associated with prenatal brain damage may allow the development of preventive measures. Since 1981 a large series of fetal and neonatal brains has been examined systematically.
at necropsy and about a fifth were found to have white matter ischaemic lesions. An earlier report described the neuropathological findings in detail.24 In this study, using a larger series of brains, we have attempted to identify the antenatal and perinatal factors which occur more often among those who are found to have ischaemic white matter damage at necropsy than among those who do not.

Subjects and methods
Two hundred and seventy-four fetuses and infants who had a detailed pathological examination at necropsy in Oxford between 1984 and 1991 were included in the study. The mothers of 164 (60%) of the fetuses were residents of one health district; the remainder were referred from perinatal pathologists from other health districts. It was therefore a highly selected series. The cases included those who had either died in utero (139 fetuses) or in the first three days after birth (135 infants). Infants surviving longer than three days were not included as the evolution of pathological reactions in the brain would not allow clear identification of prenatal damage after this time. Terminations of pregnancy and cases where the pathology of coexisting disorders, such as cytomegalovirus infection or arteriovenous malformation, could be confused with a prenatally ischaemic lesion were excluded.

Neuropathological examination was performed by a single observer (MVS). The diagnosis of intracerebral ischaemic damage was based on finding evidence of cerebral infarction; in the more severe and longstanding cases this was readily recognised as the changes of periventricular leukomalacia. Four criteria were used to establish a diagnosis of diffuse mild or early ischaemic white matter damage.24 These criteria were reactive astrocytosis, macrophage infiltration, karyorrhexis, and endothelial swelling or reduplication. The grey matter was rarely affected in the subjects with mild ischaemic damage.

Variables such as socioeconomic group, ethnic group, maternal smoking habits, maternal age, and past obstetric history were recorded for all 274 subjects. A poor obstetric history was defined as previous intrapartum or neonatal death, previous delivery of a child with motor impairment, or late or recurrent miscarriage. Information on intrapartum events such as the findings on fetal monitoring in labour and mode of delivery was recorded for only those cases where the fetus was still alive at the onset of labour; neonatal information was recorded only for those alive at delivery.

Gestational age was estimated using a combination of accurate menstrual data or an ultrasound scan performed before 20 weeks’ gestation. Where there was a discrepancy of more than 14 days between the menstrual data and the ultrasound estimate of gestation, the ultrasound estimate was used. The presence of intrapartum growth retardation based on an antenatal ultrasound diagnosis was recorded as “antenatal diagnosis of IUGR”. Birth weight at delivery was recorded for all subjects based on standard centiles for gestational age for the Oxford region;25 those with a birth weight at or below the 10th centile were identified. In 75% of those with a birth weight of less than the 10th centile for gestational age there had been an antenatal diagnosis of IUGR.

Cardiotocographic data was classified using the criteria of the Dublin trial of intrapartum monitoring.26 These data were used only if monitoring had been performed continuously throughout labour and the original recording was available to the researcher.

The maternal antenatal and neonatal case notes were reviewed by a single observer (GG) blind to the presence or absence of lesions. In the first analysis the frequency of all demographic, antenatal, intrapartum, and neonatal factors were compared between the two groups (those with and those without lesions). The results of all comparisons are given as odds ratios (ORs) and 95% confidence intervals (CIs). Continuous data were analysed using the Mann-Whitney U test. A p value of less than 0·05 was taken as statistically significant.

A third of the case series had a major congenital anomaly either of the brain or elsewhere. As some of the antenatal factors being considered, such as IUGR, are known to be associated with congenital anomaly and as it is plausible that some congenital anomalies, such as congenital heart disease, might predispose to cerebral ischaemia, the presence of a congenital anomaly is a potential confounding factor. Further analysis was therefore performed to study the clinical associations of white matter lesions in those with a congenital anomaly and in those without.

Results
The case series consisted of 139 cases of intrapartum death, which included 11 cases of intrapartum intrapartum death, and 135 neonatal deaths. There were 56 cases of prenatally intracerebral ischaemic damage (20%); 34 (24%) of the 139 intrapartum deaths and 22 (16%) of the 135 neonatal deaths had lesions. Among those with lesions, only six (11%) had cystic lesions of 1 cm or greater in diameter. There was no difference at the 5% level between those with and without intracerebral lesions in maternal age or in the frequency of most demographic factors and characteristics related to maternal health and previous obstetric history (table 1). When single mothers were compared with married mothers there was a greater chance that the infants of the single

<table>
<thead>
<tr>
<th>Variables</th>
<th>Lesions (n=56)</th>
<th>No lesion (n=218)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father non-white</td>
<td>7 (13)</td>
<td>22 (10)</td>
<td>1·3 (0·5 to 3·2)</td>
</tr>
<tr>
<td>Mother non-white</td>
<td>8 (14)</td>
<td>17 (8)</td>
<td>2·0 (0·8 to 5·0)</td>
</tr>
<tr>
<td>Socioeconomic group &gt;5</td>
<td>11 (20)</td>
<td>33 (15)</td>
<td>1·4 (0·6 to 3·0)</td>
</tr>
<tr>
<td>Unmarried mother</td>
<td>18 (32)</td>
<td>34 (16)</td>
<td>2·5 (1·3 to 5·0)</td>
</tr>
<tr>
<td>Primigravida</td>
<td>19 (34)</td>
<td>77 (35)</td>
<td>0·9 (0·5 to 1·7)</td>
</tr>
<tr>
<td>Maternal illness</td>
<td>3 (5)</td>
<td>29 (13)</td>
<td>0·4 (0·1 to 1·3)</td>
</tr>
<tr>
<td>History of infertility</td>
<td>6 (11)</td>
<td>15 (7)</td>
<td>1·7 (0·6 to 4·5)</td>
</tr>
<tr>
<td>Poor obstetric history</td>
<td>2 (4)</td>
<td>18 (8)</td>
<td>0·4 (0·1 to 1·8)</td>
</tr>
<tr>
<td>Smoking during pregnancy</td>
<td>13 (23)</td>
<td>36 (17)</td>
<td>1·5 (0·7 to 3·0)</td>
</tr>
</tbody>
</table>
Clinical associations of prenatal ischaemic white matter injury

Table 2 Comparison of frequency of antenatal factors in subjects with and without ischaemic white matter damage; values are number (%)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Lesions (n=57)</th>
<th>No lesion (n=218)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induced conception</td>
<td>3 (5)</td>
<td>12 (6)</td>
<td>0.9 (0.3 to 3.6)</td>
</tr>
<tr>
<td>Increased maternal serum α fetoprotein</td>
<td>4/42 (10)</td>
<td>4/125 (3)</td>
<td>3.2 (0.8 to 13.4)</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>6 (11)</td>
<td>33 (15)</td>
<td>0.7 (0.3 to 1.7)</td>
</tr>
<tr>
<td>Severe</td>
<td>2 (4)</td>
<td>13 (6)</td>
<td>0.6 (0.1 to 2.7)</td>
</tr>
<tr>
<td>Antepartum haemorrhage</td>
<td>10 (18)</td>
<td>27 (12)</td>
<td>1.5 (0.7 to 3.4)</td>
</tr>
<tr>
<td>Intrapartum growth retardation</td>
<td>15 (27)</td>
<td>26 (12)</td>
<td>2.7 (1.3 to 5.6)</td>
</tr>
<tr>
<td>Oligohydramnios</td>
<td>10 (18)</td>
<td>15 (7)</td>
<td>2.9 (1.2 to 7.0)</td>
</tr>
<tr>
<td>Polyhydramnios</td>
<td>7 (13)</td>
<td>29 (13)</td>
<td>0.9 (0.4 to 2.3)</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>2 (4)</td>
<td>8 (4)</td>
<td>0.9 (0.2 to 4.7)</td>
</tr>
<tr>
<td>Premature rupture of membranes</td>
<td>7 (13)</td>
<td>25 (11)</td>
<td>1.1 (0.5 to 2.7)</td>
</tr>
<tr>
<td>Prolonged rupture of membranes</td>
<td>7 (13)</td>
<td>18 (8)</td>
<td>0.6 (0.2 to 2.6)*</td>
</tr>
<tr>
<td>Maternal infection during pregnancy</td>
<td>11 (20)</td>
<td>25 (11)</td>
<td>1.3 (0.6 to 3.0)</td>
</tr>
</tbody>
</table>

Table 3 Comparison of frequency of intrapartum factors in subjects with and without ischaemic white matter damage. Based on 135 neonatal deaths and 11 intrapartum intraterm deaths; values are number (%)

<table>
<thead>
<tr>
<th>Intrapartum characteristics</th>
<th>Lesions (n=24)</th>
<th>No lesion (n=122)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breech presentation</td>
<td>3 (13)</td>
<td>33 (27)</td>
<td>0.4 (0.1 to 1.4)</td>
</tr>
<tr>
<td>Induction of labour</td>
<td>3 (13)</td>
<td>16 (13)</td>
<td>1.0 (0.3 to 3.5)</td>
</tr>
<tr>
<td>Augmentation of labour</td>
<td>4 (17)</td>
<td>12 (10)</td>
<td>1.3 (0.3 to 5.6)</td>
</tr>
<tr>
<td>Episiotomy</td>
<td>4 (17)</td>
<td>18 (15)</td>
<td>1.2 (0.4 to 3.8)</td>
</tr>
<tr>
<td>Meconium stained amniotic fluid</td>
<td>7 (29)</td>
<td>7 (6)</td>
<td>6.8 (2.1 to 21.7)</td>
</tr>
<tr>
<td>Ominous/suspicous first stage cardiocograph</td>
<td>6/10 (60)</td>
<td>16/42 (38)</td>
<td>1.2 (1.4 to 107.7)</td>
</tr>
<tr>
<td>Ominous/suspicous second stage cardiocograph</td>
<td>5/6 (83)</td>
<td>12/27 (44)</td>
<td>6.3 (6.0 to 60.9)</td>
</tr>
<tr>
<td>Delivery type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVD</td>
<td>11 (46)</td>
<td>40 (40)</td>
<td>1.3 (0.5 to 3.0)</td>
</tr>
<tr>
<td>Forceps</td>
<td>3 (13)</td>
<td>7 (6)</td>
<td>2.4 (0.6 to 9.8)</td>
</tr>
<tr>
<td>Breech</td>
<td>2 (8)</td>
<td>22 (22)</td>
<td>0.3 (0.1 to 1.5)</td>
</tr>
<tr>
<td>All caesarean sections</td>
<td>7 (29)</td>
<td>38 (31)</td>
<td>0.9 (0.4 to 2.4)</td>
</tr>
<tr>
<td>Emergency caesarean sections</td>
<td>7 (29)</td>
<td>32 (26)</td>
<td>1.2 (0.4 to 3.1)</td>
</tr>
</tbody>
</table>

SVD = spontaneous vaginal delivery.

mothers would have lesions (OR 2.5; 95% CI 0.9 to 7.2). Continuous intrapartum fetal monitoring was performed in the first stage of labour on 13 (54%) of those with lesions and 51 (42%) of those without and in the second stage in nine (38%) of those with lesions and in 38 (31%) of those without. Further analysis was confined to those in whom the complete cardiotocograph was available to the authors. An ominous or suspicious first stage cardiotocograph as defined by the criteria used in the Dublin trial,26 occurred more often among those with lesions (OR 12.4; 95% CI 1.4 to 107.7) (table 3). Ominous or suspicious second stage cardiotocography also occurred more often among those with lesions (OR 6.9; 95% CI 0.6 to 60.9), but the numbers were small and the difference is not significant at the 5% level. The mode of delivery, rates of induction of labour or augmentation, and the rate of monitoring did not differ between the two groups.

ANTENATAL FACTORS

Antenatal diagnosis of IUGR (OR 2.7; 95% CI 1.3 to 5.6) and the presence of oligohydramnios (OR 2.9; 95% CI 1.2 to 7.0) were more common in the group with lesions. Although an increased maternal serum α fetoprotein was uncommon, it did occur more often among mothers of infants with lesions, but was not significant at the 5% level (OR 3.2; 95% CI 0.8 to 13.4). The frequency of the other antenatal factors examined did not differ between the two groups (table 2).

INTRAPARTUM FACTORS

Analysis of intrapartum factors was performed only on those 146 cases who were alive before delivery. Meconium stained liquor was found more often among the group with lesions (OR 6.8; 95% CI 2.1 to 21.7). Continuous intrapartum fetal monitoring was performed in the first stage of labour on 13 (54%) of those with lesions and 51 (42%) of those without and in the second stage in nine (38%) of those with lesions and in 38 (31%) of those without. Further analysis was confined to those in whom the complete cardiotocograph was available to the authors. An ominous or suspicious first stage cardiotocograph as defined by the criteria used in the Dublin trial,26 occurred more often among those with lesions (OR 12.4; 95% CI 1.4 to 107.7) (table 3). Ominous or suspicious second stage cardiotocography also occurred more often among those with lesions (OR 6.9; 95% CI 0.6 to 60.9), but the numbers were small and the difference is not significant at the 5% level. The mode of delivery, rates of induction of labour or augmentation, and the rate of monitoring did not differ between the two groups.

NEONATAL DATA

Mean and median birth weight and gestational age at delivery did not differ between the two groups (table 4). Analysis of the birth weight for gestational age showed that a birth weight at or less than the 10th centile was twice as frequent among those with lesions (OR 2.0; 95% CI 1.1 to 3.7) (Table 4). There was no difference between the frequency of major congenital anomaly between the two groups (OR 1.5; 95% CI 0.8 to 2.7).

One hundred and thirty five infants were alive at delivery (table 4). A five minute Apgar score of 2 or less was recorded with increased frequency among infants with lesions (OR 3.2; 95% CI 1.2 to 8.5). Six infants with lesions (27%) had their cord blood pH measured at delivery as did 35 (31%) of those without lesions. There was an increased likelihood of an umbilical cord pH value of 7.20 or less among those with lesions, but the numbers were small and this is not significant at the 5% level (OR 4.2; 95% CI 0.7 to 25.1).

PLACENTAL HISTOLOGY

Placental histology was performed in 49 (88%) of those with lesions and 171 (78%) of those without. The median placental weight was 394 g for those with lesions and 400 g for those without. There was no difference at the 5% level in the frequency of acute infarction, chronic infarction, the presence of a retroplacental clot, chorioamnionitis, funisitis, and vascular anastomoses between infants with and without lesions.

Table 4 Comparison of frequency of characteristics in subjects with and without ischaemic white matter damage

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Lesions</th>
<th>No lesion</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range) gestation (weeks)</td>
<td>34 (23–41)*</td>
<td>34 (17–42)+</td>
<td></td>
</tr>
<tr>
<td>Median (range) weight (g)</td>
<td>1934 (572–4139)*</td>
<td>1840 (1064–4390)+</td>
<td></td>
</tr>
<tr>
<td>No (%) with congenital abnormality</td>
<td>22 (39–2)*</td>
<td>67 (31)+</td>
<td>1.5 (0.8 to 2.7)</td>
</tr>
<tr>
<td>Birth weight &lt;10th centile</td>
<td>24 (43)*</td>
<td>59 (37)+</td>
<td>2.0 (1.1 to 3.7)</td>
</tr>
<tr>
<td>Characteristic (alive at delivery only)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (%) with Apgar score &lt;2 at 5 min</td>
<td>12/22 (55)</td>
<td>35/133 (31)</td>
<td>3.2 (1.2 to 8.9)</td>
</tr>
<tr>
<td>No (%) with cord pH value &lt;7.20</td>
<td>5/6 (83)</td>
<td>13/35 (37)</td>
<td>4.2 (0.7 to 25.1)</td>
</tr>
</tbody>
</table>

*n=56; fn=274; dp=0.15; sp=0.28.
Table 5 Association of perinatal characteristics with prenatal white matter lesions among those with and without congenital anomaly; values are number (%)

<table>
<thead>
<tr>
<th>Perinatal characteristic</th>
<th>Congenital anomaly absent</th>
<th>Congenital anomaly present</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lesions (n=34)</td>
<td>No lesions (n=151)</td>
</tr>
<tr>
<td>Unmarried</td>
<td>8 (24)</td>
<td>29 (19)</td>
</tr>
<tr>
<td>Mother non-white</td>
<td>6 (18)</td>
<td>10 (7)</td>
</tr>
<tr>
<td>Raised maternal serum α-</td>
<td>3/26 (12)</td>
<td>2/89 (2)</td>
</tr>
<tr>
<td>fetoprotein</td>
<td>9 (26)</td>
<td>16 (11)</td>
</tr>
<tr>
<td>Intrauterine growth retardation</td>
<td>6 (18)</td>
<td>10 (7)</td>
</tr>
<tr>
<td>Oligohydramnios</td>
<td>5/5 (100)</td>
<td>11/19 (58)</td>
</tr>
<tr>
<td>Ominous/suspicious first stage cardiotocograph</td>
<td>3/3 (100)</td>
<td>8/13 (62)</td>
</tr>
<tr>
<td>Meconium stained amniotic fluid</td>
<td>3/12 (25)</td>
<td>4/71 (6)</td>
</tr>
<tr>
<td>Birth weight &lt;10th centile</td>
<td>4/9 (44)</td>
<td>25/61 (41)</td>
</tr>
</tbody>
</table>

**FURTHER ANALYSIS BY PRESENCE OF CONGENITAL ANOMALY**

No major congenital anomaly

One hundred and eighty five (68%) of the 274 subjects had no major congenital anomaly; 34 (18%) of these non-malformed infants had a white matter lesion and 151 (82%) did not. There was an increased incidence of an antenatal diagnosis of IUGR (OR 3.0; 95% CI 1.2 to 7.6), oligohydramnios (OR 3.0; 95% CI 1.0 to 9.0), meconium stained liquor (OR 5.6; 95% CI 1.1 to 29.1), and birth weight less than the 10th centile (OR 2.4; 95% CI 1.1 to 5.1) among non-malformed infants with white matter lesions than those who did not have white matter lesions (table 5). Five (42%) of 12 of those with lesions and 19 (27%) of 71 of those without lesions were monitored continuously during labour. Of those in whom the cardiotocographs were available for analysis, an ominous or suspicious cardiotocograph was found in all five (100%) of those with lesions and 11 (58%) of 19 of those without.

Major congenital anomaly

Eighty nine (32%) of the 274 subjects had a major congenital anomaly; 22 (25%) of these had white matter lesions and 67 (75%) did not. A diverse range of congenital anomalies was found in this group. Most were lethal anomalies such as Potter’s syndrome, holoprosencephaly, and trisomy 13, 18, and 21. Some anomalies such as trisomy 21 were not lethal and the cause of death was either unrelated or death occurred as a consequence of prematurity. When antecedent factors were compared for those with and without lesions in the group with major congenital anomalies (table 5), the association of single maternal marital status and lesions remained at the 5% level among those with lesions (OR 10.3; 95% CI 3.0 to 35.7). Oligohydramnios (OR 2.8; 95% CI 0.7 to 11.4) and an antenatal diagnosis of IUGR (OR 2.1; 95% CI 0.7 to 6.8) were also more common in those with lesions but the difference was not significant at the 5% level.

For those who survived until the intrapartum period the presence of meconium stained liquor was increased at the 5% level (OR 8.0; 95% CI 1.5 to 42.7), as an ominous cardiotocograph in the first stage of labour (OR 11.2; 95% CI 1.0 to 125.6). An ominous or suspicious cardiotocograph in the second stage of labour was not more frequent. For those who survived delivery there was an increased incidence of an Apgar score of 2 or less at five minutes (OR 10.1; 95% CI 2.3 to 45.3).

**Discussion**

The main finding in this study was the increased frequency of IUGR and oligohydramnios among infants in whom there was pathological evidence of prenatal white matter damage. These observations are similar to those of Gilles et al1 and Sims.3 We did not, however, show associations between prenatal white matter lesions and maternal infection, particularly urinary tract infection, antepartum haemorrhage, and polyhydramnios, which were found in these previous studies.13 Increased maternal serum α fetoprotein is known to be associated with pre-eclampsia and IUGR27 as well as an increased risk of congenital anomalies. The association of increased maternal serum α fetoprotein and white matter lesions in our study was stronger among non-malformed infants and we presume that this is largely due to the increased frequency of IUGR in the group with lesions. We are unable to explain the association of white matter lesions and unmarried status (particularly in the group with congenital anomalies), and the association of lesions and non-white mothers (particularly in the group without a congenital anomaly). In view of the large number of associations sought it is possible that these are chance findings.

It is possible that chronic hypoxia in the fetus which results in growth retardation and oligohydramnios may also be associated with cerebral ischaemia leading to white matter lesions which can be seen pathologically. In general, both under experimental conditions of intrauterine hypoxia and IUGR28 and in the human growth retarded fetus,29–32 cerebral perfusion increases without alteration in the regional distribution of blood flow within the brain.33 When hypoxia is severe, however, cerebral blood flow may decrease and areas of the brain with a high metabolic rate such as developing white matter may be compromised. This eventual decrease in cerebral blood flow has been shown using Doppler ultrasound
techniques in severely growth retarded fetuses
with oligohydramnios.24 35

The relation of prenatal white matter lesions
and later cerebral palsy in infants who survive
is not clear. In life, the natural history of such
brain lesions can be studied by repeated scan-
nings using neuroimaging techniques. This type
of longitudinal study can follow the evolution
and later clinical manifestations of severe
extensive white matter damage which is visible
on cranial ultrasound of the fetus or newborn
infant.20 21 Less severe white matter lesions,
however, may not be visible on current
neuroimaging techniques. It then becomes im-
possible to study the relation of these lesions
and cerebral palsy. Indeed it may be that these
mild lesions pose no threat to the neurological
integrity of the child.

There is, however, some other evidence
which suggests that chronic intratuerine
hypoxia, prenatal white matter lesions and
cerebral palsy could be causally linked. Firstly,
fetal growth retardation and oligohydramnios
have previously been found to be associated
with cerebral palsy22 14 15 and our own work
supports this finding (G Gaffney et al, un-
published data). Secondly, a proportion of
children with neurological impairment show
delayed or abnormal myelination on magnetic
resonance imaging.36 37 Thirdly, in vitro studies
have shown that hypoxia has adverse effects on
immature glial cell proliferation and leads to a
proportional decrease in oligodendrocyte
numbers (S Marret et al, presented at the
International Symposium on Fetal and Neonatal
Neurology, Tours, October 1991). These cells are
responsible for myelination and if this effect
also occurred in vivo there may be a
reduced capacity for myelin synthesis, result-
ing in permanent neurological damage and
signs of cerebral palsy.

Of considerable clinical interest were the
observations that the intrapartum passage of
meconium, abnormal cardiocographs, and
low five minute Apgar scores occurred more
often in infants with prenatal white matter
lesions than in those without. Indeed, nine of
the 10 infants with prenatal lesions who were
continuously monitored had ominous or suspi-
cious changes on the cardiocograph in the
first stage of labour. It is often assumed that
such signs reflect an acute hypoxic intrapartum
episode; in this study, however, it is likely that
signs of fetal distress also reflected existing
prenatal lesions.

Major congenital anomalies were common in
this case series and the presence of a con-
genital anomaly is potentially confounding.
Antenatal characteristics, such as growth
retardation, which occur with increasing
frequency in fetuses and infants with white
matter lesions are also more frequent in
infants with a congenital anomaly. It is also
likely that some congenital anomalies may
increase the risk of white matter lesions; for
example, an infant with a cardiac malforma-
tion may have cerebral hypoperfusion.
The association of prenatal white matter
lesions and IUGR persisted, however, after adjusting
for the presence of congenital anomaly in the
analysis. This supports the hypothesis that in
non-malformed infants chronic hypoxia is an
important contributory factor to white matter
damage.

Furthermore, the presence of a congenital
anomaly may confound the association of
prenatal white matter lesions and fetal distress.
Not only may major brain anomaly be
associated with an abnormal cardiocograph,26
but signs of fetal distress may be
prolonged if it has been decided that no
resuscitation will be offered to an infant with a
severe anomaly. The association of white
matter lesions and fetal distress persisted after
adjusting for the presence of congenital
anomaly.

Prenatal lesions were remarkably common
in this series of brains studied neuropathologi-
cally. The series was highly selected but the
frequency was consistent with other reported
studies.1 3 4 The frequency and distribution of
lesions suggests that from 23 to 24 weeks' ges-
tation onwards the white matter of the fetal
brain is particularly susceptible to hypoxia or
ischaemia. It remains to be determined
whether or not the fetus who survives with
lesions will have identifiable changes using
newer techniques of neuroimaging and the
clinical signs of cerebral palsy.

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