BRIEF REPORT

Placenta previa as a risk factor for antenatal- and peripartum periventricular leukomalacia resulting in cerebral palsy in Japan: a retrospective study [version 1; peer review: awaiting peer review]

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Abstract

Intrapartum fetal heart rate monitoring abnormalities had been reported to correlate with decreased umbilical artery base excess associated with neonatal seizures. After encountering a child born at 35 weeks of gestation diagnosed with cerebral palsy associated with periventricular leukomalacia (PVL) without fetal heart rate monitoring abnormalities, a review and analysis of summary reports of PVL cases published on the home page of the Japan Obstetric Compensation System for Cerebral Palsy (JOCSC). Based on the case and the review of the reports of PVL cases from JOCSC, placenta previa may be a risk factor for antenatal- and peripartum PVL resulted in cerebral palsy in Japan.

Keywords

periventricular leukomalacia, placenta previa, Japan

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Introduction
Brain injury in premature infants is generally thought to primarily consist of periventricular leukomalacia (PVL), a distinctive form of cerebral white matter injury. PVL occurs most commonly in premature infants born at less than 32 weeks’ gestation. In an earlier study in Japan, frequent moderate variable deceleration on fetal cardiotocogram (CTG) was observed to be a cause of antenatal PVL in premature infants. In the report by Ito et al., frequent moderate variable decelerations on fetal CTG were observed frequently for infants with antenatal PVL (80.0%) than control infants (27.3%, p < 0.05). In addition, in low birth weight infants, intrapartum severe variable deceleration or prolonged deceleration have been suggested to play a causal role in PVL. Although intrapartum fetal heart rate monitoring abnormalities had been reported to correlate with decreased umbilical artery base excess associated with neonatal seizures, recently it has been observed to have no relation to perinatal mortality or pediatric neurologic morbidity. The main factor related to the presence of PVL has been suggested to be gestational age.

We encountered a case of PVL without fetal heart rate monitoring abnormalities. Subsequently, a review and analysis of the summary reports of PVL cases published on the home page (HP) of the Japan Obstetric Compensation System for Cerebral Palsy (JOCSC) was conducted. We conclude that placenta previa may be a risk factor for antenatal- and peripartum PVL resulting in cerebral palsy (CP) in Japan.

Case report
An elective cesarean section was performed at 35 weeks’ gestation because of placenta previa in the mother with warning bleeding of 60 g. A 2346-g, male infant was delivered with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. The mother’s pregnancy had progressed uneventfully until the day before the cesarean section. The preoperative fetal CTG, performed 20 minutes before the cesarean section, showed a reassuring fetal status without any fetal heart rate decelerations. The umbilical artery pH was 7.334. The total blood loss during cesarean section was 1,080 g. The infant had no problems before the cesarean section. The preoperative fetal CTG, showed a hyperkalemia (n = 1). Table 1 shows the clinical characteristics of the 187 cases of antenatal- and peripartum PVL with and without MSDs on fetal CTG. The incidence of neonatal asphyxia in the cases with MSDs was higher than in those without MSDs (p < 0.01); however, the percentage of cases without MSDs was higher than those with MSDs (73.3 vs. 26.7%, p < 0.01). In cases without MSDs, the percentage of neonates born at term was higher than those with MSDs (p = 0.04). These cases might have potentially transient episodes leading to PVL in the uterus between 26 and 32 weeks of gestation. Our case may be same as these cases.

Table 2 shows the perinatal complications in the cases of antenatal- and peripartum PVL with and without MSDs on fetal CTG. The incidence of intrauterine infection and placental abruption in the cases with MSDs was higher than those without MSDs (p < 0.01), while the incidence of placenta previa in the cases without MSDs was higher than those with MSDs (p = 0.04). The former results were as expected, while the latter may be a new finding. The percentage of placenta previa in the cases of PVL was 5.7% (12/209), which seemed to be higher than the total percentage of placenta previa reported in Japan (0.3-0.5%).

Discussion
To date, some possible mechanisms leading to PVL in cases of placenta previa has been discussed in Japan. Oda et al. reported that the main risk factor for PVL in preterm placenta previa is an initial antepartum hemorrhage <28 weeks of gestation and they speculated that decreased placental perfusion in the second trimester of pregnancy is associated with the developmental window of vulnerability for PVL. However, Furuta et al. observed that acute and massive bleeding from placenta previa at around 30 weeks of gestation is a risk factor for PVL and CP requiring careful neonatal follow-up.

Findings
There were 209 cases of PVL published in the HP of JOCSC retrieved in January 2020. We examined the presence or absence of moderate/severe decelerations (MSDs) on fetal CTG in 187 cases. Cases excluded were 13 cases of monochorionic twins and 9 cases of postnatal PVL due to late circulatory collapse (n = 6), neonatal hypoglycemia (n = 2) and neonatal hyperkalemia (n = 1). Table 1 shows the clinical characteristics of the 187 cases of antenatal- and peripartum PVL with and without MSDs on fetal CTG. The incidence of neonatal asphyxia in the cases with MSDs was higher than in those without MSDs (p < 0.01); however, the percentage of cases without MSDs was higher than those with MSDs (73.3 vs. 26.7%, p < 0.01). In cases without MSDs, the percentage of neonates born at term was higher than those with MSDs (p = 0.04). These cases might have potentially transient episodes leading to PVL in the uterus between 26 and 32 weeks of gestation. Our case may be same as these cases.
Table 1. Clinical characteristics of antenatal- and peripartum periventricular leukomalacia with and without moderate/severe decelerations on fetal cardiotocogram.

<table>
<thead>
<tr>
<th>Moderate/severe decelerations, n (%)</th>
<th>P-value</th>
<th>Odds ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)</td>
<td>( )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>137</td>
<td></td>
</tr>
<tr>
<td>Gestational age at delivery (weeks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>12 (24.0)</td>
<td>29 (21.2)</td>
<td>0.15</td>
</tr>
<tr>
<td>30-31</td>
<td>14 (28.0)</td>
<td>26 (19.0)</td>
<td>0.22</td>
</tr>
<tr>
<td>32-33</td>
<td>15 (30.0)</td>
<td>33 (24.1)</td>
<td>0.46</td>
</tr>
<tr>
<td>34-36</td>
<td>8 (16.0)</td>
<td>29 (21.2)</td>
<td>Ref.</td>
</tr>
<tr>
<td>≥ 37</td>
<td>0 (0)</td>
<td>20 (14.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>21 (42.0)</td>
<td>52 (38.0)</td>
<td>Ref.</td>
</tr>
<tr>
<td>Yes</td>
<td>29 (58.0)</td>
<td>85 (62.0)</td>
<td>0.62</td>
</tr>
<tr>
<td>Apgar score at 1 min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 4</td>
<td>22 (44.0)</td>
<td>27 (19.7)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>4-6</td>
<td>16 (32.0)</td>
<td>44 (32.1)</td>
<td>0.14</td>
</tr>
<tr>
<td>≥ 7</td>
<td>12 (24.0)</td>
<td>66 (48.2)</td>
<td>Ref.</td>
</tr>
<tr>
<td>Urinalysis pH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 7.0</td>
<td>34 (68.0)</td>
<td>115 (99.1)</td>
<td>Ref.</td>
</tr>
<tr>
<td>&lt; 7.0</td>
<td>11 (22.0)</td>
<td>1 (0.9)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Fetal growth restriction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>41 (82.0)</td>
<td>117 (85.4)</td>
<td>Ref.</td>
</tr>
<tr>
<td>Yes</td>
<td>9 (18.0)</td>
<td>20 (14.6)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

However, in the 12 cases of placenta previa in that study, massive bleeding and initial bleeding < 28 weeks of gestation were observed in only 4 (33.3%) and 1 cases (8.3%) Kmisek et al. observed that gross lesions with disturbance of uteroplacental circulation including massive retroplacental hematoma, extensive infarction or thrombosis, and marked basal or perivillous fibrin deposition frequently in placentae in cases of antenatal- and peripartum PVL. They also observed the high frequency of ischemic changes in villi in those placentae. The same findings have been reported to be observed in cases of placenta previa. The same findings may have occurred in our case.
Based on the data from JOCSC, serious abnormal fetal heart rate patterns were not observed in approximately 70% of cases with antenatal- and peripartum PVL on fetal CTG, and placenta previa itself may be associated with the development of antenatal- and/or peripartum PVL.

Data availability

**Underlying data**
The Japan Obstetric Compensation System for Cerebral Palsy (JOCSC) for is a free to access resource. Cause analysis reports (summary reports) for patients with periventricular leukomalacia can be accessed here: [http://www.sanka-hp.jcqhc.or.jp/documents/analysis/index.html](http://www.sanka-hp.jcqhc.or.jp/documents/analysis/index.html), Feb 12, 2020. These reports are in Japanese.


This project contains the following underlying data:


Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

Consent

Written informed consent for publication of the clinical details of the case report was obtained from the mother in the case report.

References

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