Acute and massive bleeding from placenta previa and infants' brain damage

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Abstract

Background: Among the causes of third trimester bleeding, the impact of placenta previa on cerebral palsy is not well known.

Aims: To clarify the effect of maternal bleeding from placenta previa on cerebral palsy, and in particular when and how it occurs.

Study design: A descriptive study.

Subjects: Sixty infants born to mothers with placenta previa in our regional population-based study of 160,000 deliveries from 1998 to 2012. Premature deliveries occurring at < 26 weeks of gestation and placenta accreta were excluded.

Outcome measures: Prevalence of cystic periventricular leukomalacia (PVL) and cerebral palsy (CP).

Results: Five infants had PVL and 4 of these infants developed CP (1/40,000 deliveries). Acute and massive bleeding (> 500g within 8 hours) occurred at around 30-31 weeks of gestation, and was severe enough to deliver the fetus. None of the 5 infants with PVL underwent antenatal corticosteroid treatment, and 1 infant had mild neonatal hypocapnia with a PaCO2 < 25 mmHg. However, none of the 5 PVL infants showed umbilical

arterial acidemia with pH < 7.2, an abnormal fetal heart rate monitoring pattern, or neonatal hypotension.

Conclusions: Our descriptive study showed that acute and massive bleeding from placenta previa at around 30 weeks of gestation may be a risk factor for CP, and requires careful neonatal follow-up. The underlying process connecting massive placental bleeding and PVL requires further investigation.

Key words. Cerebral palsy, placenta previa, periventricular leukomalacia, third trimester bleeding.

Introduction

Third trimester bleeding is a risk factor for cerebral palsy (CP) [1-4]. Among the causes, placental abruption is more frequently associated with a poor neurological outcome. On the other hand, placenta previa may or may not be a significant risk factor for CP [1-2]. For example, a univariate analysis showed a significant increase in the incidence of CP, while this was not the case with a multivariate analysis. It was also shown that maternal bleeding from placenta previa was a significant risk factor only in low-birth-weight infants, suggesting that prematurity or growth restriction is a contributing factor.

Thus, this study describes the neurological outcome of infants born to mothers with placenta previa and attempts to delineate some of the risk factors associated with CP. For this purpose, we used our regional population-based database relating to perinatal outcome.

Materials and Methods

We performed a retrospective observational study on infants' short-term and long-term neurological outcome born to mothers with placenta previa. For this purpose, we used our database from a regional population-based study relating to perinatal outcome, and approved by the Ethics Committee of the University of Miyazaki.

Perinatal deaths and infants with neurological damage have been registered since 1998 in the Miyazaki district, when the population was 1 million and annual births totaled 10,000. Details have been described elsewhere [5-7]. Among the registered infants with CP, 5 infants were born to mothers with placenta previa. For a comparison, we enrolled another 55 consecutive women with placenta previa who gave birth at the University of Miyazaki during the study period. Women with placenta accreta, increta or percreta, and preterm deliveries at < 26 weeks of gestation were excluded. Antepartum recognition of placenta previa was accomplished with abdominal and vaginal ultrasonography.

During the study period, women with placenta previa were prophylactically hospitalized by 26 to 32 weeks of gestation depending on the women's choice, or were hospitalized for bed-rest when warning bleeding or preterm labor occurred. Tocolytic

agents (magnesium sulfate and ritodorine hydrochloride) were used if sensitive uterine contractions occurred, if insensitive but repetitive uterine contractions occurred at less than 10-min intervals, or if any uterine contractions with significant genital bleeding occurred. Tocolytic agents were continued until the aforementioned clinical signs subsided for greater than 24 hours.

We performed elective Cesarean section (CS) when pregnancies became term, or near-term at $\geq$ 35 weeks following amniocentesis confirmation of fetal lung maturity. Otherwise, emergency CS was performed when acute and massive bleeding occurred, where 'acute' was defined as a relatively short period (several to 8 hours) and 'massive bleeding' was defined as > 300 g hemorrhage with active bleeding or > 500 g hemorrhage at once.

General anesthesia was applied to emergency CS, otherwise, combined spinal and epidural anesthesia was employed. Preterm infants were resuscitated by neonatal specialists and admitted at our neonatal intensive care unit when necessary, and systolic blood pressures were maintained at > 50 mmHg with fluid loading and catecholamine supplementation [8].

Intracranial ultrasonography was performed on admission and at every 2 to 3 week intervals to look for cystic PVL and intracranial hemorrhage. Infants born at < 35 weeks of gestation were examined by magnetic resonance imaging at discharge or when the corrected weeks of gestation reached 40 to 44 weeks. These infants were monitored by our pediatric neurologists and CP was diagnosed at 2 years of age or older.

Numerical values were compared using an unpaired student t-test. Chi-square and Fisher exact tests were used for contingency table analysis. P values < 0.05 were considered statistically significant. Data are expressed as mean $\pm$ SD.

Results

From 1998 to 2012, 158,713 deliveries had occurred in our district. The 60 women enrolled with placenta previa were 33.5 $\pm$ 4.6 years old at delivery. Among these, 28 were nulliparous. Tocolytic agents were administered to 41 women; magnesium sulfate (n=2), ritodorine hydrochloride (n=12), or both (n=27). Thirty-five women underwent emergency CS; 8 women progressed into active labor without massive bleeding, 4 women had fetal indication (2 for recurrent late decelerations and 2 for

moderate to severe variable decelerations), 9 women had other obstetrical indications, and the remaining 14 women had acute and massive bleeding. All of the latter 14 women showed reassuring fetal heart rate patterns except for one, who showed a non-reactive pattern after 500 mg of bleeding, but gave birth to an intact infant. Although these 14 women had acute and massive bleeding, they showed stable circulatory conditions until emergency CS was initiated.

Of the 60 infants born, 5 had cystic PVL on ultrasonography. All 5 PVL infants were born by emergency CS (Table 1), and 4 of these had developed CP (1/40,000 deliveries). There was a significant difference in the occurrence of CP between the acute and massive bleeding group and the others (4/14 versus 0/46, $p<0.01$, Fisher test). Average pH values were also compared between the cystic PVL infants (n=5) and intact infants (n=55), and no statistically significant differences were observed (Figure 1). All 60 infants had umbilical pH values > 7.20.

The 5 PVL infants showed reassuring fetal heart rate patterns immediately prior to birth (Table 1). These infants were born at 30 or 31 weeks of gestation and weighed appropriate-for-date according to Japanese standard curves. None of the 5

infants underwent antenatal corticosteroid prophylactic treatment given the occurrence of sudden bleeding. All 5 infants required respiratory assists and surfactant supplementation due to respiratory distress syndrome, and 1 infant (case 3) experienced mild hypocapnia with a PaCO2 of 23.0 mmHg for several hours. Although none of the infants had intraventricular hemorrhage, 4 had bilateral cystic PVL leading to CP. MRI findings were compatible with PVL, including dilatation of the lateral ventricles. No infant had leukocytosis > 30,000/mm^3 or positive C-reactive protein > 0.3 mg/dl at birth.

During the neonatal period, systolic blood pressures were almost maintained at > 50 mmHg, although the lowest systolic blood pressure recorded was 42.0 $\pm$ 4.3 mmHg (range; 39-47 mmHg) on average, and these infants subsequently developed cystic PVL (n=5). For a comparison, we selected 5 infants matched for gestational age (at 30–31 weeks of gestation) among the remaining 55 infants who did not have PVL. The lowest systolic blood pressure (43.4 $\pm$ 4.5 mmHg, range; 40-51 mmHg) of these infants was not significantly different from that of the PVL infants.

The hemorrhagic volume during the last bleeding episode was 500 g or more

(Figure 2) that caused PVL. These 5 infants were born in a relatively narrow time window between 30 and 31 weeks of gestation.

Discussion

Third trimester bleeding is a risk factor for CP [1-4]. Previous reports on placenta previa showed controversial results. A univariate analysis revealed that placenta previa was a significant risk factor for CP (relative risk; 4.9), although no such significance was revealed in a multivariate analysis [1,2]. Additionally, it is significantly related to CP only in low-birth-weight infants, suggesting that prematurity is a contributing factor towards the development of CP [1,2]. Spinillo *et al.* studied 22 low-birth-weight infants born to women with placenta previa (31.6 $\pm$ 4.3 weeks of gestation and birth weight of 1641 $\pm$ 570 g). Although there was no incidence of cystic PVL or CP among these infants, hemorrhagic episodes were not precisely detailed. Matsuda *et al.* investigated 72 infants with placenta previa (33.4 $\pm$ 2.4 weeks of gestation and birth weight of 2117 $\pm$ 501 g), and only 2 infants had a poor outcome; 1 infant death and 1 infant with CP. However, detailed clinical characteristics were not

reported. Compared to these previous studies, our regional population-based study showed that maternal massive and acute bleeding from placenta previa is associated with cystic PVL and CP when it occurs at around 30-32 weeks of gestation.

Cystic PVL is the major pathological lesion significantly associated with neurological damage in premature infants [9]. Takashima *et al.* showed that since vessels to the periventricular white matter in the cortex had not developed sufficiently, watershed areas were vulnerable to various cardiovascular changes that can lead to cystic PVL [10]. Furthermore, regulatory mechanisms that control cerebral blood flow are also maturation-dependent [11]. Thus, premature infants born at around 28-32 weeks of gestation are vulnerable to circulatory disturbances which could lead to cystic PVL.

Several clinical factors are known to be associated with PVL. For example, hypocapnia with a PaCO2 < 25 mmHg is associated with PVL in premature infants [12, 13]. In this study, 1 infant showed hypocapnia with a PaCO2 of 23 mmHg for several hours, which may be a contributing factor for PVL in this case. Hypotension is also associated with PVL since autoregulation of the cerebral blood flow is premature [11]. In our management protocol, we maintained systolic blood pressure at > 50 mmHg.

However, for a relatively short period, this decreased in the 5 PVL infants (range; 39-47 mmHg), which were still within 95% confidence limits of systolic blood pressure of healthy infants (40–60 mmHg for 1.5 kg birth weight infants) [14]. One prospective study used 209 consecutive premature infants (average gestational age; 31.1 $\pm$ 3.2 weeks and birth weight; 1423 $\pm$ 419 g) to investigate the association between fetal heart rate pattern and cystic PVL [15]. Although women with placenta previa were not included, cystic PVL occurred in 6 infants (2.9%), all of whom had severe variable deceleration or prolonged deceleration, suggesting that sudden severe circulatory disturbance such as cord compression may be associated with cystic PVL. In our study, all 5 infants showed reassuring fetal heart rate patterns when mothers experienced acute and massive bleeding from placenta previa. Other known confounding factors for PVL such as low umbilical arterial pH values, neonatal sepsis, or a low Apgar score were not detected in this study.

As shown in Table 1, none of the 5 PVL infants were subjected to antenatal corticosteroid therapy given the sudden onset of massive bleeding. Since neonates whose mothers receive antenatal corticosteroid therapy have a significantly lower risk

of neonatal death, respiratory distress syndrome, intracranial hemorrhage and necrotizing enterocolitis [16], the lack of antenatal corticosteroid therapy in the current study may play a contributing role in the development of PVL. A retrospective study on the time interval from diagnosis of preterm labor to a 1-dose administration of antenatal corticosteroid was on average 7.6 hours [17], suggesting that acute and massive bleeding that necessitates emergency delivery is not an eligible candidate for antenatal corticosteroid therapy.

The present descriptive study showed that acute and massive bleeding from placenta previa that occurred during the vulnerable period was more likely associated with CP through formation of bilateral cystic PVL. The mechanisms associated with maternal bleeding from placenta previa and neonatal PVL are unknown. We speculate that massive placental bleeding, even though insufficient to cause maternal shock, may cause subtle decreases in uteroplacental perfusion, leading to cystic PVL and CP. Although the prevalence of CP due to placenta previa is low (1/40,000), careful neonatal management is required when acute and massive bleeding occurs to deliver the fetus at around 30-32 weeks of gestation.

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Acknowledgements: This study was supported by a grant (＃79-258) from the Ministry of Education, Culture, Sports, Science and Technology, Japan, a grant from the JAOG Ogyaa Donation Foundation, and a Grant-in-Aid for Scientific Research(C) （No. 24592476）from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Conflict of interest: All authors declare no conflict of interest.

Figure legends

Figure 1. Umbilical arterial pH values were compared between 5 infants with cystic PVL (CP/PVL group) and the remaining 55 infants (Intact). There was no significant difference. (mean $\pm$ SD)

Figure 2. Gestational weeks at delivery (X-axis) and blood loss volume during the last bleeding episode (Y-axis) are depicted. Open circles represent elective CS, and other markers represent emergency CS. Closed circles represent CP with bilateral cystic PVL (n=4), and a closed rectangle represents an intact infant with unilateral cystic PVL (n=1). Five infants with cystic PVL congregated at 30-31 weeks of gestation with blood loss > 500 g during the last episode.

Table 1. Characteristics of the five infants with periventricular leukomalacia

Case	Admission GA (wks)	Delivery GA (wks)	BW (Kg)	Tocolysis	A/N steroid	1-min Apgar Score	RDS	Respirator Support	DOA Support	IVH	Cystic PVL	Outcome
1	26	31	1.67	Rit+Mg	-	4	+	+	+	-	bil	CP
2	27	31	1.79	Rit+Mg	-	9	+	+	+	-	rt	normal
3	26	31	1.60	Rit	-	8	+	+	+	-	bil	CP+E
4	26	30	1.65	Rit	-	9	+	+	+	-	bil	CP
5	30	30	1.44	Rit	-	9	+	+	+	-	bil	CP

GA; gestational age in weeks, BW; birth weight, tocolysis; ritodorine (Rit) and magnesium (Mg), A/N; antenatal, RDS; respiratory distress syndrome, DOA; dopamine, IVH; intraventricular hemorrhage, PVL; periventricular leukomalacia, bil and rt; bilateral and right, and CP and E; cerebral palsy and epilepsy.

Figure 1. Umbilical arterial pH values in CP/PVL and intact infants

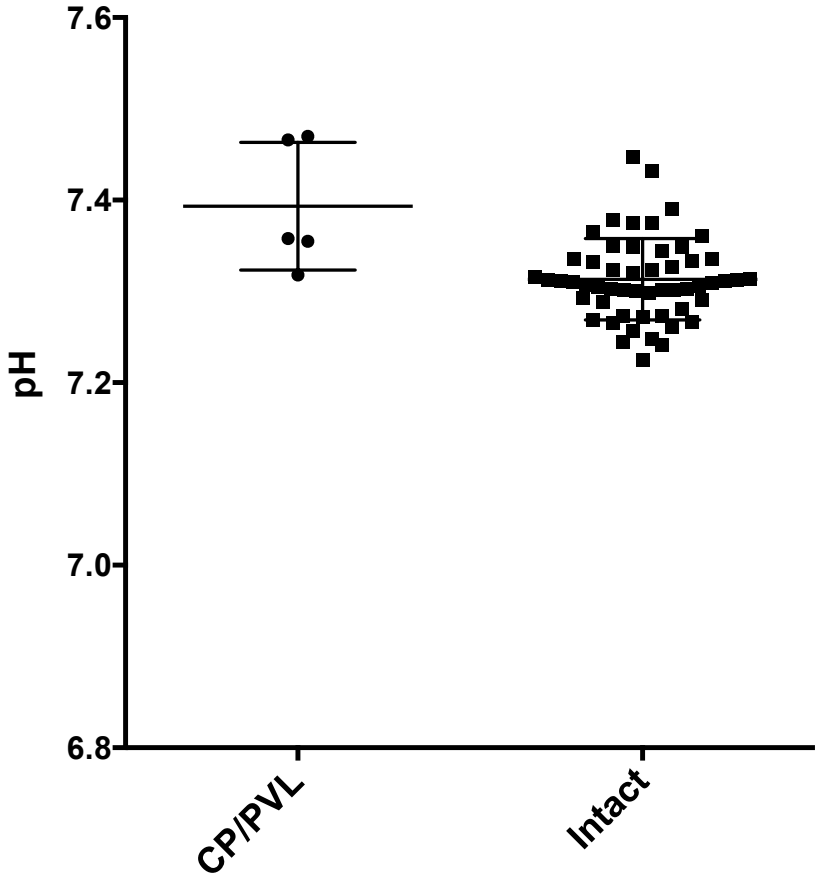

Figure 2. Relationship between blood loss volume and gestational week to cause PVL and CP