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Placental Features in Preterm Infants With Periventricular Leukomalacia

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ABSTRACT. *Objective.* **Evaluation of the placenta provides some important insights into pathophysiologic changes that take place during the prenatal and intrapartum process. We investigated the relationship between placental findings and periventricular leukomalacia (PVL) to obtain a better understanding of its cause.**

Methods. **Thirty-two preterm infants with PVL delivered before 34 weeks' gestation, between 1990 and 1999, were classified into 4 groups according to the onset of brain injury assumed from ultrasonographic presentation and clinical course: 2 Antenatal, 22 Peripartum, 5 Postnatal, and 3 in an unknown time of onset group. We evaluated the gross and histopathologic features of the placentas of each group and compared them with those of a control group matched by birth weight and gestational age in terms of the frequency of major placental findings. Potential confounding factors were controlled in logistic regression analyses.**

Results. **Gross lesions with disturbance of uteroplacental circulation, including massive retroplacental hematoma, extensive infarction or thrombosis, and marked basal or perivillous fibrin deposition, were observed more frequently in the Antenatal + Peripartum combined subgroup than in the controls (41.7% vs 13.7%). Placentas from the Antenatal + Peripartum subgroup also demonstrated a significantly higher frequency of ischemic changes in villi, based on histopathologic examination, as compared with the control group (54.2% vs 13.7%). These associations remained after adjustment for confounding factors in logistic regression analyses (odds ratio: 4.04, 95% confidence interval: 1.40–11.67; and odds ratio: 7.28, 95% confidence interval: 2.50–21.20; respectively). Frequencies of chorioamnionitis and twin placentation tended to be higher in PVL cases than in the controls, although the differences were not statistically significant (46.9% vs 37.9%, 37.5% vs 20.0%, respectively).**

Conclusions. **These results suggest that disturbed placental circulation underlies the development of PVL in the majority of cases with prenatal and peripartum brain injury. In chorioamnionitis cases, certain additional factors were suggested in the genesis of PVL. Thus, placental examination is essential for elucidating the pathophysiologic changes leading to PVL in the perinatal process.** *Pediatrics* **2002;109:650–655;** ***periventricular leukomalacia, placenta, placental circulation, ischemic changes in villi.***

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ABBREVIATIONS. PVL, periventricular leukomalacia; US, ultrasound scan; IVH, intraventricular hemorrhage; GLDC, gross lesions with disturbance of uteroplacental circulation; OR, odds ratio; CI, confidence interval; M-D, monochorionic-diamniotic; D-D, dichorionic-diamniotic; TTTS, twin-to-twin transfusion syndrome.

Despite the greatly improved survival rate of preterm infants in recent years, the incidence of later neurodevelopmental disabilities including cerebral palsy has not been reduced.[1,2] Periventricular leukomalacia (PVL), or necrosis of white matter adjacent to the external angles of the lateral ventricle,[3] is a major cause of cerebral palsy development in preterm infants,[4,5] and its pathogenesis is complex and multifactorial.[6,7] Various prenatal and postnatal risk factors (eg, intrauterine infection, peripartum hemorrhage, hypovolemia, hypocarbia, and so on) have been implicated as potential causes of PVL,[8–15] superimposing on characteristic background features of prematurity including periventricular vascular anatomic factors,[16,17] pressure-passive cerebral circulation,[18] and intrinsic vulnerability of glial cells within the white matter.[19] To identify crucial factors that precipitate PVL, prenatal conditions as well as neonatal course should be considered. Herein, we focused on identifying causative pathophysiologic changes during the antenatal and intrapartum process by placental examination, because to date, only a few epidemiologic studies have related placental features to the development of PVL.[8,9] The present study was designed to evaluate the relationship between placental findings and PVL.

MATERIALS AND METHODS

Study Population

From 1990 to 1999, 1439 preterm infants delivered before 34 weeks' gestation were admitted to the neonatal intensive care unit of our institution. For these preterm infants, cranial ultrasound scans (US) were routinely obtained immediately after birth, more than once a day during days 1 to 4, on days 7, 14, 21, and 28, or more frequently as clinically needed, and thereafter every 2 weeks until discharge. During follow-up, brain magnetic resonance imaging scans were performed at around 12 months' corrected age for infants presenting neurologic abnormalities regardless of their US findings, and scans were read by pediatric radiologists.

PVL was diagnosed in 34 of the 1439 infants: 31 were inborns and 3 were outborn infants. The diagnosis of PVL was made by cranial US in 29 infants: 27 had cysts (>3 mm in diameter) within the periventricular white matter, and 2 showed persistence of

periventricular white matter echogenicity higher than that of the choroid plexus.[3,20–25] Four infants, who developed cerebral palsy without apparent cyst presentation on US, were diagnosed by magnetic resonance imaging[26] after 12 months' corrected age. One was diagnosed by autopsy[6,7] on day 1.

All placentas delivered in our institution before 34 weeks' gestation are routinely submitted for pathologic examination with informed consent, and placentas of some cases delivered at other facilities are also transferred with the infants to our institution with permission from their mothers. Detailed placental reports of gross and microscopic findings, together with preserved slides stained with hematoxylin and eosin, are available for retrospective studies. In this study, placental reports and slides were available in 32 of the 34 PVL cases: 31 inborn cases and 1 of the 3 outborn cases. Those who examined the placentas were blinded to the clinical and ultrasonographic data of the infants.

Control infants without PVL were selected as follows: 3 infants of the same gestational age (within 1 week) and same birth weight (within 150 g) were selected for each PVL case by searching the computerized patient database forward and backward from the date of admission of the case, and infants whose placental reports and slides were available served as controls. The control group consisted of 95 infants.

Infants with intraventricular hemorrhage (IVH; graded according to the criteria of Papile et al[27]) were also included in both the PVL group and controls, whereas cases with porencephaly subsequent to grade IV IVH were excluded from the study.

Methods

We estimated the time of brain injury in the PVL cases from the findings of cranial US and clinical courses based on previous reports.[10,20,26] Briefly, the cases with periventricular cysts detected immediately after birth were assumed to have sustained their injuries in the antenatal period. If bilateral periventricular echodense lesions were present within several hours after birth and cystic lesions were detected around 2 weeks after birth, we presumed the onset of brain injury to be during the peripartum period. If a neonate presented periventricular echodense lesions within a few days after a serious clinical episode and cyst formation was evident about 2 weeks after the event, the time of brain insult was assumed to be mainly postpartum. According to the assumed onset of brain insult, we classified PVL cases into 4 groups, ie, Antenatal, Peripartum, Postnatal, and Unknown. Two of the 32 cases were classified into the Antenatal group, 22 the Peripartum group, and 5 the Postnatal group. Onset of injury was undetermined in 3 cases (Unknown group). The Antenatal and Peripartum groups were combined and presented as the "Antenatal + Peripartum subgroup" in the data analysis, because investigation of the placenta is especially important in these cases.

We evaluated the macroscopic and microscopic placental findings of each group, and compared the frequencies of major findings with those in controls. We also evaluated relevant clinical characteristics of both the PVL cases and controls; such as 1-and 5-minute Apgar scores, duration of mechanical ventilation, evidence of hypotension (lowest systolic blood pressure <30 mm Hg within 7 days of birth), hypocarbia (lowest Pco_2 <25 mm Hg), respiratory distress syndrome requiring surfactant replacement therapy, patent ductus arteriosus requiring either medication or surgical ligation, and IVH (grade≥II).

Classification of Placental Findings

The gross findings were classified into 3 categories as follows: 1) lesions including massive retroplacental hematoma (>5 cm in diameter or ≥2 hematoma >2 cm in diameter, including abruptio placentae), extensive infarction or thrombosis (>5 cm in diameter or multiple lesions >2 cm in diameter), and marked basal or perivillous fibrin deposition[28,29] were grouped into "gross lesions with disturbance of uteroplacental circulation (GLDC)",[29] 2) placentas of twins, and 3) abnormalities of the umbilical cord including marginal or velamentous insertion. The histologic findings were also categorized into 3 groups: 1) abnormal villi such as dysmature villi, immature villi, or villitis of unknown etiology,[29,30] 2) ischemic changes in villi including excessive numbers of syncytiotrophoblastic knots, shrinkage of villi, and accelerated perivillous fibrin deposition: these features indicate either decreased uteroplacental blood flow or decreased fetal blood flow to or through the placenta,[29–32] and 3) chorioamnionitis,[33] many of which also showed inflammation of the umbilical cord. For placentas with ≥2 of the findings mentioned above, all findings were counted for the frequency calculations. In addition to these findings, we also recorded placenta previa, extrachorial placentation, villous edema, chorangiosis, and other even more rare features.

Statistical Analysis

χ^2 or Fisher exact tests were used for comparison of the frequency of each placental feature between PVL cases and controls. A Mann-Whitney *U* test or an unpaired t test was used for comparison of continuous variables. A difference was considered significant when the *P* value was lower than .05.

Logistic regression analyses, adjusting for the potential confounding clinical factors associated with PVL in the univariate analyses ($P < .05$), were conducted to evaluate the independent association of placental findings with PVL. The odds ratio (OR) with 95% confidence interval (CI) extended the interpretation of significant test results.

RESULTS

Demographic and clinical characteristics of the entire PVL group, the Antenatal + Peripartum subgroup, and the control group are shown in Table 1. There were no significant differences in demographic data between any pair of groups. The preva-

TABLE 1. Demographic and Clinical Characteristics

Characteristic	PVL Group		Control Group (n = 95)
	All PVL (n = 32)	Antenatal + Peripartum Subgroup (n = 24)	
Gastational age (wk), mean ± SD	28.6 ± 2.3	28.7 ± 2.2	28.6 ± 2.6
Birth weight (g), mean ± SD	1153 ± 457	1135 ± 456	1159 ± 440
Gender, male (%)	65.7	62.5	53.7
Apgar score at 1 min, median (range)	4 (1–8)	4 (1–8)	6 (1–9)
Apgar score at 5 min, median (range)	8 (1–9)	8 (1–9)	8 (1–10)
Duration of MV (d), mean ± SD	32.2 ± 42.4*	34.5 ± 46.7*	13.0 ± 18.5
Hypotension (lowest SBP <30 mm Hg)	9 (28.1%)	9 (37.5%)	23 (24.2%)
Hypocarbia (lowest Pco_2 <25 mm Hg)	7 (21.8%)	5 (20.8%)	13 (13.7%)
RDS	16 (50.0%)	12 (50.0%)	38 (40.0%)
PDA	12 (37.5%)	8 (33.3%)	26 (27.4%)
IVH (grade ≥II)	12 (37.5%)†	10 (41.7%)†	17 (17.9%)
IVH (grade III–IV)	4 (12.5%)	3 (12.7%)	7 (7.4%)

SD indicates standard deviation; SBP, systolic blood pressure; MV, mechanical ventilation; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage.
* $P < .01$ compared with control group using Mann-Whitney *U* test.
† $P < .05$ compared with control group using χ^2 test.

lences of hypotension, hypocarbia, respiratory distress syndrome, patent ductus arteriosus, and severe IVH (grade III-IV) were slightly higher in PVL cases than in controls, although the differences were not statistically significant ($P > .10$). There were significant differences with regard to the duration of mechanical ventilation and the prevalence of IVH (grade≥II) between the PVL and control groups. Measures of placental weight, umbilical cord length, and umbilical cord diameter were similar in all groups (Table 2).

The number and percentage of placental findings in each of the three groups are presented in Table 3. Compared with the control group, placentas of PVL cases showed a significantly higher frequency of GLDC. The prevalence of GLDC was especially high in the Antenatal + Peripartum subgroup: this relation remained after adjustment for confounding clinical factors [ie, duration of mechanical ventilation and evidence of IVH (grade≥II)] in a logistic regression analysis (OR: 4.04; 95% CI: 1.40–11.67; $P = .010$). Three of the 10 placentas with GLDC in the PVL group were identified as showing abruptio placentae, in which fresh lesions were dominant with or without minor old lesions. Both fresh and old lesions were apparent in the other 7. Ischemic changes in villi were also recognized on microscopic examination of 7 (including 2 abruptio placentae) of the 10 placentas with GLDC (Fig 1).

All multiple pregnancies enrolled in this study were twin. The frequency of twin placentation in PVL cases was higher than in controls, although not significantly. Of the 8 twin placentas in the Antenatal + Peripartum group, 4 were monochorionic-diamniotic (M-D) and the others were dichorionic-diamniotic (D-D) form. Every M-D placenta, 2 from 1 pair and 2 from different twin pairs, had vascular anastomosis and twin-to-twin transfusion syndrome (TTTS) was diagnosed clinically. All D-D placentas, from 4 different twin sets, had associated GLDC and/or ischemic changes in villi. Of all 19 twin placentas in the control group, only 1 M-D placenta showed ischemic change, and none had GLDC.

Marginal or velamentous umbilical cord insertion was seen in 6 PVL cases, 5 of which involved twin placentas. The incidence of abnormal insertion was similar in PVL cases and controls. None of the cases enrolled in this study had extremely short or long cords, excessive torsion, or true knot. The percentages of abnormal villi, such as dismature villi, immature villi, and villitis, were smaller in PVL cases than in controls, although the difference was not significant.

Ischemic changes in villi were significantly more frequent in PVL cases than in controls. The frequency was strikingly high in the Antenatal + Peripartum subgroup, more than half of which was positive. These associations remained after adjustment for confounding factors in logistic regression analyses (OR: 5.67, 95% CI: 2.13–15.04, $P = .0005$; and OR: 7.28, 95% CI: 2.50–21.20, $P = .0003$; respectively). Most ischemic changes in villi were accompanied by GLDC or severe chorioamnionitis.

The frequencies of chorioamnionitis and inflammation of the umbilical cord in PVL cases were slightly higher than in controls, although the differences were not significant. Massive infiltration of polymorphonuclear leukocytes into the chorionic membrane was observed in all chorioamnionitis cases in the Antenatal + Peripartum subgroup, most of which were also accompanied by severe umbilical inflammation. Ischemic changes were also identified in the villi of 7 of the 12 placentas with chorioamnionitis in this subgroup.

With respect to the Antenatal + Peripartum group, all cases had ≥1 of the following findings: GLDC, M-D twin placentas clinically diagnosed as TTTS, or chorioamnionitis with severe inflammation. As to the Postnatal group, 1 placenta had mild and another severe chorioamnionitis. Two others in this group were twin placentas of D-D form with no other findings. Ischemic changes were seen in 2 placentas in this group. There was 1 chorioamnionitis case and 2 cases with M-D twin placentas in the Unknown group.

No differences were found between PVL cases and controls in the percentages of any other findings, eg, villous edema, chorangiosis, placenta previa, and extrachorial placentation.

DISCUSSION

A number of antenatal, perinatal, and postnatal factors have been reported in association with PVL.[8–15,34–38] Some autopsy studies have revealed relatively high prevalences of prenatal white matter injury, ranging from 16% to 31%[39,40]; and some previous reports suggested antenatal[8] or perinatal[10] factors to be more important than postnatal factors in the genesis of PVL. Although placental examination provides various types of information, such as severity and duration of hypoperfusion, degree and duration of intrauterine inflammation, and type of twin

TABLE 2. Measures of Placentas and Umbilical Cords

	PVL Group		Control Group ($n = 95$)
	All PVL ($n = 32$)	Antenatal + Peripartum Subgroup ($n = 24$)	
Placental weight (g)	260 ± 101	232 ± 95	240 ± 91
Umbilical cord length (cm)	37.8 ± 12.3	33.4 ± 8.6	33.8 ± 8.4
Umbilical cord diameter (cm)	1.46 ± 0.50	1.35 ± 0.48	1.46 ± 0.49

Values represent means ± standard deviation.
P value is not significant for all variables compared with control group using unpaired *t* test or Mann-Whitney *U* test.

TABLE 3. Number and Percentage of Placental Findings

Placental Findings	PVL Group		Control Group (n = 95)
	All PVL (n = 32)	Antenatal + Peripartum Subgroup (n = 24)	
Gross findings			
GLDC	10 (31.3)*	10 (41.7)**	13 (13.7)
Twin placentation	12 (37.5)	8 (33.3)	19 (20.0)
Umbilical cord abnormalities	6 (18.8)	6 (25.0)	16 (16.8)
Histopathological findings			
Abnormal villi (DV, IV, VUE)	1 (3.1)	1 (4.2)	13 (13.7)
Ischemic changes in villi	15 (46.9)***	13 (54.2)***	13 (13.7)
Chorioamnionitis	15 (46.9)	12 (50.0)	36 (37.9)
CAM with umbilical cord inflammation	12 (37.5)	10 (41.7)	32 (33.7)

GLDC indicates gross lesions with disturbance of uteroplacental circulation; DV, dysmature villi; IV, immature villi; VUE, villitis of unknown etiology; CAM, chorioamnionitis.
Values represent number positive (% positive).
* $P < .05$, ** $P < .005$, *** $P < .0001$ compared with control group using χ^2 test or Fisher exact test.

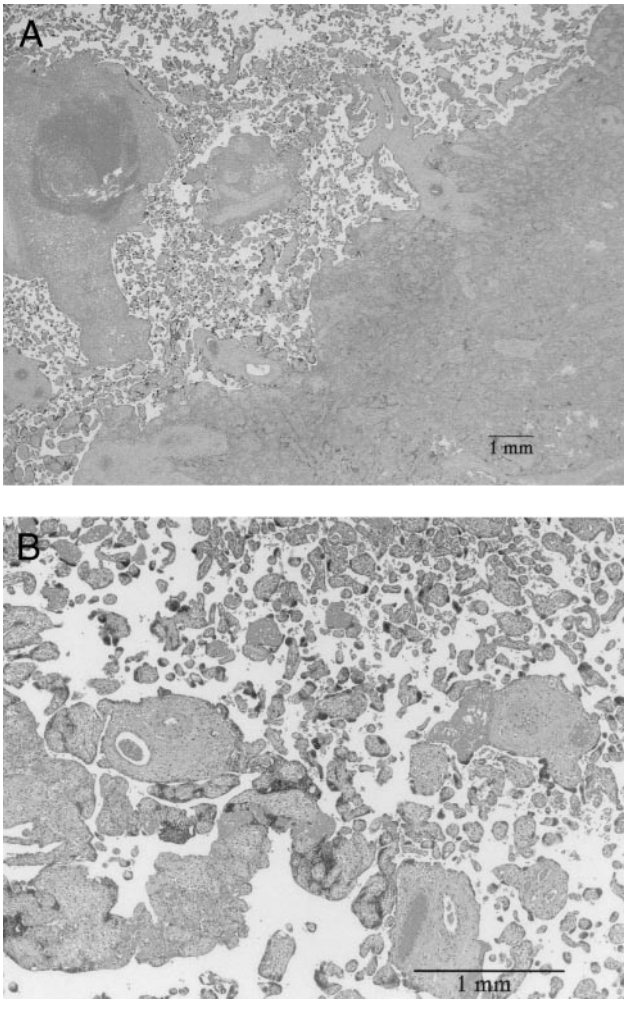

Fig 1. Photomicrographs of placental tissue, stained with hematoxylin and eosin, from a case of GLDC accompanied by ischemic changes in villi. A, Extensive infarction and thrombosis with perivillous fibrin deposition. B, Ischemic change in villi including increased syncytiotrophoblastic knots, shrinkage of villi, and accelerated intervillous fibrin deposition.

placentation in cases with prenatal and intrapartum insults, only a few studies have reported placental features in relation to PVL[8,9] or neurologic impairments including cerebral palsy.[41] In this study, we focused on PVL in premature infants. This was because the pathogenesis of white matter injury is suggested to differ between mature and premature infants,[3,6,7] and the onset of brain injury is probably difficult to estimate in cases with neurologic impairment not limited to PVL. To clarify prenatal and perinatal associations with PVL, we classified PVL cases into 4 groups according to the onset of injury assumed from both ultrasonographic findings and clinical courses. The methods we applied to the diagnosis of PVL and the estimation of the onset of brain injury, despite several minor problems concerning accuracy, were based on previous reports,[3,20–26,10] which are widely accepted. Infants with the complication of IVH were also included in our study: the prevalence of total IVH (grade≥II) was significantly higher in PVL cases than in controls. This, together with the significantly longer duration of mechanical ventilation, might reflect the more serious neonatal courses of most PVL cases. However, after adjustment for these confounders in logistic regression analyses, the significant relations between placental findings and PVL remained.

The important placental findings include lesions relating to disturbance of placental circulation, which consists of maternal blood flow and fetal blood flow to or through the placenta. Lesions, such as massive retroplacental hematoma, extensive infarction, and marked fibrin deposition, grouped as GLDC are considered to be related to disturbed maternal circulation in the placenta.[29] Uteroplacental hypoperfusion not only leads to fetal hypoxia but also diminishes the nutritional supply to the fetus and impairs removal of metabolic products from the fetus.[42] In the present study, gross examination revealed a significantly elevated frequency of GLDC in PVL cases, especially in the Antenatal and Peripartum brain injury groups. This result suggests that critical disturbance of uteroplacental circulation in some cases resulted in fetal hypoxia or malnutrition contributing to white matter injury. Moreover, it is indicated that acute disturbance had occurred subsequently to chronic disturbance in the cases of fresh GLDC coexisting with old lesions. The his-

topathologic examination also demonstrated a significantly increased percentage of ischemic changes in villi of PVL cases, especially in the Antenatal and Peripartum groups. The features which we noted as ischemic changes in this study, including excessive numbers of syncytiotrophoblastic knots, shrinkage of villi, and accelerated perivillous fibrin deposition, are generally presumed to result from impaired uteroplacental blood flow,[30–32] whereas Fox described an increase in syncytial knots as suggesting reduced fetal villous perfusion.[29] At any rate, these villous changes indicate that the fetuses had been suffering from hypoxic or ischemic stress in the uterus. Our results suggest that serious disturbance of placental circulation contributed to the genesis of PVL in a significant proportion of cases with prenatal and peripartum brain injury.

Some investigators have reported chorioamnionitis or intrauterine infection to be a risk factor for PVL or cerebral palsy.[8–12] Others have suggested funisitis[8,43] or vasculitis in the chorionic plate and umbilical cord[9] (ie, fetal inflammation) to be more important risk factors. In our study, the prevalences of chorioamnionitis and umbilical cord inflammation in PVL cases were only slightly higher than those of controls, and the differences were not significant. The possibility remains of the inflammation in PVL cases being more severe: we found marked infiltration of neutrophils into the umbilical cord as well as the chorionic plate in most cases of chorioamnionitis with PVL, although quantification was difficult in the microscopic study.

However, the fact that 38% of control cases with chorioamnionitis (some of which also had severe inflammation including funisitis) did not develop PVL indicates that intrauterine infection alone is not sufficient to cause white matter injury whereas circulatory disturbance may be capable of causing PVL by itself. We speculate that the development of PVL in cases with intrauterine infection requires other additive factors, including fetal specificity for the inflammatory response, the species of pathogen as well as the severity and duration of infection, or subsequent perinatal events such as abruptio placentae.

Multiple pregnancy, particularly with a monochorionic placenta, has also been shown to increase the risk of neurologic damage.[34–36] In the present study, the proportions of the M-D form were similar in twin placentas with and without PVL (data not shown). It was noteworthy, however, that all 4 M-D placentas in the Antenatal + Peripartum subgroup were TTTS, and all 4 D-D placentas in this subgroup also had GLDC and/or ischemic changes in their villi; placental hypoperfusion was suggested even in D-D placentas. With all the possible mechanisms, multiple pregnancies may have the potential to disturb placental circulation resulting in fetal brain injury irrespective of chorionicity.

We found no differences in the percentages of umbilical cord abnormalities between PVL cases and controls, contrary to some earlier reports.[37,38] Furthermore, we found no differences in the frequencies of villous edema, chorionic vessel thrombi, and chorangiosis (data not shown), whereas other authors have described relationships between these findings and neurologic impairment.[31,32,41]

Interestingly, some cases in the Postnatal and Unknown groups also had obvious ischemic changes in villi. It is possible that not only postnatal events but also prenatal stress contributed to the development of PVL in these cases. The period of brain injury was judged from clinical information in this study, but it is not unreasonable to speculate as to the onset of injury from placental findings in some cases. It is also noteworthy that all cases in the Antenatal + Peripartum subgroup had ≥1 finding of GLDC, M-D twin placentas with TTTS, or chorioamnionitis with severe inflammation. This study demonstrated that placental examination facilitates the detection of certain crucial changes during the antenatal and intrapartum periods in PVL cases. The gross lesions with disturbance of uteroplacental circulation and the histologic ischemic changes in villi correlated with PVL in our study. It would be worthwhile to identify key obstetric episodes or clinical signs that may cause or be associated with the placental findings that were documented herein. Additional studies are needed to investigate the relationship between these placental abnormalities and obstetric features such as maternal complications, cardiotocographic features, and ultrasonographic findings.

CONCLUSION

Our results suggest that disturbed placental circulation contributed to PVL development in the majority of cases with prenatal and peripartum brain injury. In cases with chorioamnionitis, additional factors seemed to participate in the genesis of PVL. Evaluation of the placenta is essential for a better understanding of the cause of PVL. Recognition of obstetrical features relevant to such placental abnormalities requires additional comprehensive investigations.

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Great geniuses have the shortest biographies.

—Ralph Waldo Emerson (1803–1882)

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