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Original Article

Two-year neurological outcome of very-low-birth-weight children with prenatal absent or reversed end-diastolic flow velocity in the umbilical artery

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Abstract

Objective: The aim of this study was to investigate the 2-year neurological outcome of very-low-birth-weight (VLBW) children who had abnormal umbilical blood flow velocity prenatally.
Materials and Methods: We performed a prospective collection of infants prenatally diagnosed with abnormal umbilical blood flow velocity at a tertiary referral center from January 1, 2001 to September 30, 2005. VLBW children with prenatal absent or reversed end-diastolic flow velocity (AREDV) in the umbilical artery were investigated and compared with two similar demographic control groups of VLBW children without AREDV: one group with fetal growth restriction and the other without it. A follow-up study at 2 years of age for Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) of the Bayley Scales among the three groups was analyzed.
Results: Twenty-four VLBW children were identified to have AREDV prenatally, of whom four died during the neonatal period. After 2 years, five children were lost to follow-up and 15 were rescued, of whom 11 had absent end-diastolic velocity and four reversed end-diastolic velocity. We compared the remaining 15 children with the two control groups [28 children in the matched control group with intrauterine fetal growth restriction (IUGR), and 38 children in the matched control group without IUGR], and no significant differences were found in MDI ($p = 0.938$) and PDI ($p = 0.496$) scores at 2 years of age. However, we also surveyed the children with a gestational age of ≤29 weeks and found a significant difference in MDI scores ($p = 0.048$), but not in PDI scores ($p = 0.219$), among the three groups.
Conclusion: VLBW children delivered earlier than 29 gestational weeks with abnormal umbilical blood flow velocity prenatally have greater mental developmental delay at 2 years of age.

Keywords: absent or reversed end-diastolic velocity; intrauterine growth restriction; Mental Developmental Index; Psychomotor Developmental Index; very low birth weight

Introduction

Doppler velocity measurement is applied extensively in prenatal diagnosis, and blood flow velocity waveforms of numerous vessels were detected to predict the fetal condition, especially the umbilical artery [1−7]. Abnormal umbilical artery flow with absent or reversed end-diastolic flow velocity (AREDV) during pregnancy is a strong indication of placental insufficiency. The increased placental vascular resistance is reflected as a decreased diastolic phase of the umbilical artery waveform [2,4,8,9]. Moreover, end-diastolic flow of the umbilical artery vanishes and ultimately reverses in a progressively worsened condition, and AREDV is present in the Doppler waveform finally. When AREDV occurs prenatally, close follow-up or expeditious delivery should be considered.

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Perinatal mortality and morbidity (such as intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, respiratory distress syndrome, and necrotizing enterocolitis) of fetuses with AREDV in the umbilical artery have been discussed well, especially in the growth-restricted fetuses [1,3,8,10,11], but the long−term neurodevelopmental outcome is controversial [12−14]. Furthermore, very low birth weight (VLBW, <1500 g) is an independent predictor for long-term neurodevelopmental sequelae [15,16].

We carried out a prospective study to investigate the 2-year neurodevelopmental outcome of VLBW infants with and without AREDV prenatally. Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) scores of VLBW children with AREDV who were at least 2 years old were surveyed and compared with those of two matched control groups of VLBW children without AREDV delivered during the same period: one group with intrauterine fetal growth restriction (IUGR) and the other group without it. The objective of our study was to evaluate whether antenatal abnormal umbilical artery flow velocity is an independent predictor and can predict the neurodevelopmental sequelae of VLBW children in the future.

Materials and methods

A prospective cohort study was performed to investigate the 2-year neurodevelopmental outcome of VLBW children prenatally diagnosed with abnormal umbilical blood flow velocity at a tertiary referral center from January 1, 2001 to September 30, 2005. VLBW newborns with AREDV were compared with two similar demographic control groups of VLBW newborns without AREDV. Control Group 1 consisted of VLBW neonates with IUGR and Control Group 2 consisted of VLBW neonates without IUGR, both born during the same period and were matched after birth according to their gestational age. IUGR was diagnosed when the estimated fetal weight was $<10^{th}$ percentile by ultrasound examination, and this was confirmed after birth. All cases of chromosomal or congenital anomalies, preterm premature rupture of membranes, and chorioamnionitis were excluded. Exclusion criteria such as chromosomal and congenital anomalies were determined by karyotyping through the amniocentesis or cordocentesis, and ultrasound evaluation prenatally. Doppler waveforms were obtained with a pulsed wave Doppler ultrasound system (Toshiba SSA-340A, Toshiba SSA-370A, Aloka 2000, or Voluson 730 Pro) after identification of the free-floating portion of umbilical arteries by color flow imaging. The angle between the Doppler beam and the flow was maintained at less than 60° for all measurements. After the initial observation of AREDV, pregnant women were admitted and they underwent continuous cardiotocography monitoring in the high-risk pregnancy antepartum surveillance unit. Fetal biophysical profile was assessed every day and sequential umbilical blood flow velocity was measured every 12 hours until delivery. Indications for termination of pregnancy were progressive worsening maternal conditions, oligohydramnios (an amniotic fluid index of less than 5), ominous fetal heart beat tracings in cardiotocography (such as absent baseline variability and any of the following: recurrent late deceleration, recurrent variable deceleration, or bradycardia) without improvement after medical treatment [17], and a biophysical score of below 4.

Neurodevelopment in children was evaluated with the MDI and PDI scores of the Bayley Scales of Infant Development, second edition [18]. Developmental delay was defined as abnormal neurodevelopment identified by clinical psychologists and as an MDI or a PDI score of <70 (2 standard deviations below the mean score of 100). Examinations were performed at discharge from hospital and at 3 months, 6 months, 12 months, 18 months, and 24 months of corrected age. A follow-up study at 2 years of age for MDI and PDI among the three groups was analyzed.

Statistical analysis

Descriptive statistics for continuous variables such as maternal age, delivery age, parity, and birth weight were calculated and reported as mean ± standard deviation. Categorical variables were described using frequency distributions and reported as *n* (%). The analysis of variance test was used to detect differences in the means of continuous variables. The *p* values were based on Chi-square test or Fisher's exact test for categorical variables. Correlations between birth weight and MDI and between birth weight and PDI in the three groups were determined using Pearson's correlation coefficients and scatter plots. We also constructed a receiver-operating characteristic (ROC) curve and sought an optimum cutoff point of predicting the delivery age (weeks) for AREDV group. The optimum cutoff point was defined as the closest point on the ROC curve to the point (0, 1), that is, a false positive rate of zero and sensitivity of 100%. The area under curve and 95% confidence interval were calculated. Due to confounders, the independent and joint effects of two variables (three groups and birth weight) on MDI and PDI were investigated by simple and multiple linear regression analyses. Statistical analysis was performed using SPSS, version 18.0 (SPSS Inc, Chicago, IL, USA). Tests were two tailed, with a significance level of 0.05.

Results

Twenty-four VLBW newborns were identified with prenatal AREDV in the umbilical artery at Mackay Memorial Hospital from January 1, 2001 to September 30, 2005. Four expired during the neonatal period; of the remaining 20 neonates, 16 had absent end-diastolic velocity and four reversed end-diastolic velocity. After 2 years, of the 20 cases, five children were lost to follow-up, 11 had absent end-diastolic velocity, and 4 had reversed end-diastolic velocity. Clinical characteristics of these 15 cases with AREDV are summarized in Table 1. The average age of pregnant women was 31.7 ± 3.6 years (range 26−37 years) and the mean gestational age at delivery was 31.3 ± 2.2 weeks (range 26−35 weeks). The average birth weight was 1030 ± 215 g (range

Table 1
Clinical characteristics of 15 cases with AREDV.

No.	Maternal age (y)	Delivery age (wk)	Parity	Sex	Delivery method	Birth weight (g)	Apgar score (1 min)	Apgar score (5 min)	AREDV	IUGR	Preeclampsia	Oligohydramnios	MDI	PDI
1	37	30	1	M	C/S	926	5	7	A	+	+		110	100
2	29	26	1	M	C/S	690	3	7	A	+	+		78	92
3	31	29	1	F	C/S	538	8	9	R	+			50	50
4	38	31	2	F	C/S	1114	6	7	R	+			82	103
5	31	32	1	F	C/S	1094	7	10	A	+		+	110	110
6	32	29	2	M	C/S	748	3	7	R	+	+		68	65
7	32	33	1	F	C/S	1316	6	8	A	+	+	+	78	84
8	26	33	1	M	C/S	980	4	9	R	+	+	+	88	80
9	27	27	3	M	C/S	688	7	8	A	+	+		50	57
10	36	31	3	M	C/S	1390	8	9	A		+		72	69
11	36	35	1	M	C/S	1424	9	9	A	+	+	+	80	77
12	29	35	1	F	C/S	1178	7	9	A	+			96	80
13	31	32	2	M	C/S	1224	7	8	A	+	+	+	92	106
14	31	31	1	F	C/S	1046	5	7	A	+			76	77
15	29	35	1	F	C/S	1098	9	10	A	+		+	98	77

A = absent end–diastolic flow velocity; C/S = cesarean section; F = female; M = male; MDI = Mental Developmental Index; PDI, Psychomotor Developmental Index; R = reversed end-diastolic flow velocity.

538–1424 g), and 14 cases (93.3 %) were found to have IUGR. Nine of the 15 children were found to have the complications of preeclampsia (60%), which was defined as blood pressure ≥140/90 mmHg after 20 weeks of gestation combined with proteinuria ≥1+ dipstick (30 mg/dL), and six were found to have oligohydramnios (40%). Fetal heart beat tracings in cardiotocography revealed absent variability in eight cases, late deceleration in three, severe variable deceleration in seven, and bradycardia in one. All the 15 neonates were delivered via cesarean section and sent to neonatal intensive care unit for further management. Table 2 reveals the perinatal characteristics and 2-year neurological outcome of the three groups. A comparison between 15 children with prenatal AREDV and the two control groups (28 children in the matched control group with IUGR and 38 in the matched control group without IUGR) showed that cesarean section rate and preeclampsia were significantly higher in the AREDV group and the control group with IUGR than in the control group without IUGR ($p < 0.001$). In addition, the incidence of oligohydramnios was significantly higher in the AREDV group than in the two control groups ($p = 0.014$). At 24 months, the mean MDI score of the 15 children with AREDV was 81.9 ± 13.7 (range 50–110) and the mean PDI score was 81.8 ± 13.9 (range 50–110). The results of MDI and PDI scores were not statistically significant among the three groups. Fig. 1 shows scatter plots to demonstrate the relationships between birth weight and MDI and between birth weight and PDI among the three groups. Slopes of the AREDV group were higher than those of two control groups even though the correlations (Pearson's correlation analysis) were not statistically significant. Thus, we constructed an ROC curve to cite the optimum cutoff point of predicting the neurological outcome related to delivery age in the AREDV group and found it to be 29 gestational weeks (Fig. 2). Table 3 lists perinatal characteristics and 2-year neurological outcome of the three groups with a delivery age of ≤29 weeks. Comparing the four children with prenatal AREDV with the two control groups (12 children in the matched control group with IUGR and 31 in the matched control group without IUGR), the incidences of cesarean section rate and preeclampsia were found to be significantly higher in the AREDV group and the control group with IUGR than in the control group without IUGR ($p = 0.003$ for cesarean section rate and $p < 0.001$ for preeclampsia), but the incidence of oligohydramnios was not significantly different among the three groups ($p = 0.57$). In addition, we found that cases with a 5-minute Apgar score of ≤7 were increased significantly in the control group with IUGR, but not in the AREDV group or the control group without IUGR ($p = 0.01$). Developmental delay (MDI or PDI score of <70) was noted in the AREDV group,

Table 2
Perinatal characteristics and 2-year neurological outcome.

	AREDV ($n = 15$)	Matched control group with IUGR ($n = 28$)	Matched control group without IUGR ($n = 38$)	p
Maternal age (y)	31.7 ± 3.6	30.0 ± 4.7	30.1 ± 5.3	NS
Delivery age (wk)	31.3 ± 2.2	30.6 ± 2.4	27.1 ± 2.3	<0.001
Parity	1.47	1.36	1.5	NS
Male sex	8 (53.3)	19 (67.9)	23 (60.5)	NS
Cesarean section	15 (100.0)	25 (89.3)	20 (52.6)	<0.001
Birth weight (g)	1030 ± 215	1127 ± 211	1041 ± 259	NS
5-min Apgar score ≤7	5 (33.3)	14 (50.0)	12 (31.6)	NS
Preeclampsia	9 (60.0)	20 (71.4)	3 (7.9)	<0.001
Oligohydramnios	6 (40.0)	3 (10.7)	3 (7.9)	0.014
MDI	81.9 ± 13.7	83.6 ± 14.2	82.9 ± 15.6	NS
PDI	81.8 ± 13.9	84.4 ± 15.4	79.3 ± 17.7	NS

Data are presented as mean ± standard deviation, or n (%).
AREDV = absent or reversed end-diastolic flow velocity; IUGR = intrauterine fetal growth restriction; MDI = Mental Developmental Index; NS = not statistically significant ($p > 0.05$); PDI = Psychomotor Developmental Index.

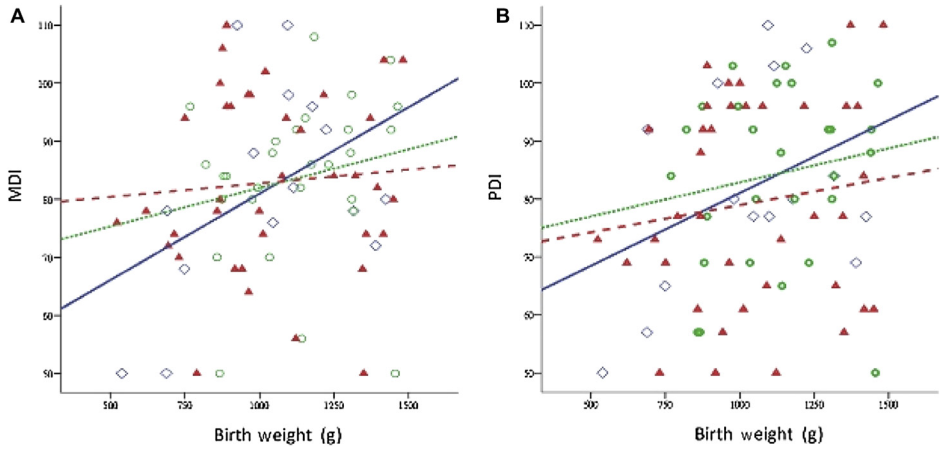

Fig. 1. Relationships between (A) birth weight and MDI, and (B) birth weight and PDI in the three groups: (▲) AREDV group, (○) matched control group with IUGR, and (◇) matched control group without IUGR. AREDV = absent or reversed end-diastolic flow velocity; IUGR = intrauterine fetal growth restriction; MDI = Mental Developmental Index; PDI = Psychomotor Developmental Index.

but not in the two control groups. For the four children with prenatal AREDV, delivered at ≤29 weeks, the mean MDI score was 61.5 ± 13.9 and the mean PDI score 66.0 ± 18.4. We also found a significant difference in MDI ($p = 0.048$), but not in PDI ($p = 0.219$) scores, among the three groups.

Discussion

In animal models, increased placental impedance has been found to generate abnormally small brain weight and present delayed development [19–21]. One human study used magnetic resonance imaging to measure the brain tissue volume in premature IUGR infants with placental insufficiency (presented by abnormal Doppler measurements), and found a significant decrement in intracranial volume and cerebral cortical gray matter [22]. Although abnormal umbilical artery flow with AREDV during pregnancy is a substantial evidence of placental insufficiency, the relationship between umbilical artery Doppler velocimetry and long-term neurodevelopmental outcome of children remains controversial. Several studies have revealed an association between AREDV in the umbilical artery and adverse neurological sequelae [10,12,23–25], but the others have reached the opposite conclusion [13,26,27]. Some authors suggested that when the effects of gestational age and IUGR are taken into consideration, AREDV in the umbilical artery appears to be a poor

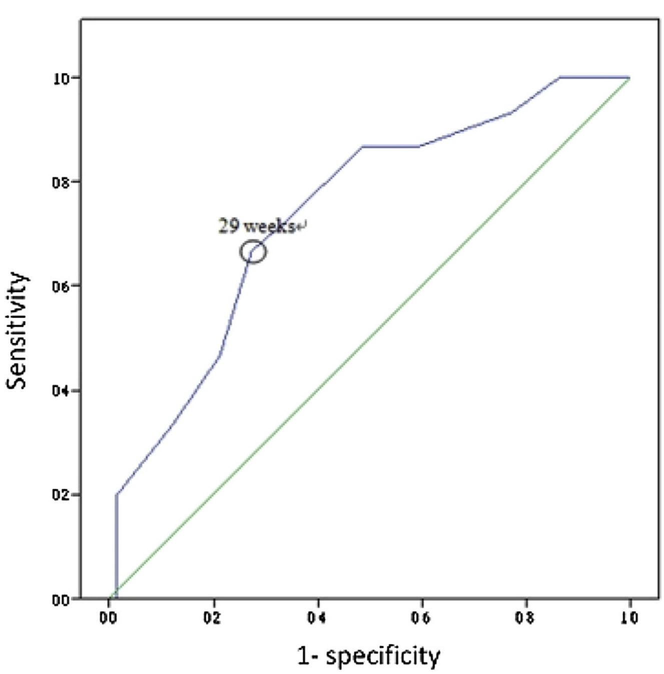

Fig. 2. ROC curve for predicting the optimum cutoff point of neurological outcome related to delivery age (weeks) in the AREDV group. The optimum cutoff point (open circle) was defined as the closest point on the ROC curve to the point $(X, Y) = (0, 1)$, where $X = 1 - $ specificity and $Y = $ sensitivity. AREDV = absent or reversed end-diastolic flow velocity; ROC = receiver-operating characteristics.

Table 3
Perinatal characteristics and 2-year neurological outcome (delivery age ≤29 weeks).

	AREDV ($n = 4$)	Matched control group with IUGR ($n = 12$)	Matched control group without IUGR ($n = 31$)	p
Maternal age (y)	29.8 ± 2.2	29.4 ± 4.7	29.5 ± 5.2	NS
Delivery age (wk)	27.8 ± 1.5	28.3 ± 0.9	26.3 ± 1.7	0.001
Parity	1.8 ± 1.0	1.5 ± 0.5	1.5 ± 0.7	NS
Male sex	3 (75.0)	7 (58.3)	21 (67.7)	NS
Cesarean section	4 (100.0)	11 (91.7)	14 (45.2)	0.003
Birth weight (g)	666.0 ± 89.8	946.3 ± 131.2	963.6 ± 218.6	0.021
5-min Apgar score ≤7	2 (50.0)	10 (83.3)	11 (35.5)	0.010
Preeclampsia	3 (75.0)	7 (58.3)	1 (3.2)	<0.001
Oligohydramnios	0 (0.0)	1 (8.3)	1 (3.2)	NS
MDI	61.5 ± 13.9	80.8 ± 12.5	81.2 ± 15.8	0.048
PDI	66.0 ± 18.4	82.7 ± 16.4	76.9 ± 16.4	NS

Data are presented as mean ± standard deviation, or number (%).
AREDV = absent or reversed end-diastolic flow velocity; IUGR = intrauterine fetal growth restriction; MDI = Mental Developmental Index; NS = not statistically significant ($p > 0.05$); PDI = Psychomotor Developmental Index.

predictor [14,28]. Our study surveyed 15 children with prenatal AREDV in the umbilical artery between 26 gestational weeks and 35 gestational weeks and found no significance in the MDI and PDI scores among the three groups. This result is compatible with previous studies of Wilson et al [26] and Kirsten et al [13]. Wilson et al [26] carried out a study of 40 children with abnormal umbilical artery flow velocity waveforms and followed their neurological development with Denver development screening test at 5 years of age; they found no association between abnormal waveform and neurodevelopment. Kirsten et al [13] followed 193 surviving infants with Amiel–Tison neurological assessments at 6-monthly intervals until 4 years of age, and found no difference in the developmental quotients and motor outcome between the infants with absent end-diastolic velocities and the control groups. Our study also revealed some associations between AREDV, IUGR, preeclampsia, and oligohydramnios. The incidences of preeclampsia were significantly higher in the AREDV group and the control group with IUGR than in the control group without IUGR ($p < 0.001$). This finding is consistent with the finding of previous studies that preeclampsia predisposes to an increase in vascular resistance and thus diminishes uteroplacental perfusion, which also results in IUGR [29–31]. Furthermore, we found that the incidence of oligohydramnios is significantly higher in the AREDV group than in the two control groups ($p = 0.014$). One reason for this result is that oligohydramnios is related to uteroplacental insufficiency as well as to AREDV in the umbilical artery.

In addition, we depicted an ROC curve and found that the optimum cutoff point of predicting the neurological outcome related to delivery age in the AREDV group was 29 gestational weeks. The incidences of cesarean section rate and preeclampsia were still significantly higher in the AREDV group and the control group with IUGR than in the control group without IUGR, but the incidence of oligohydramnios was not significantly different among the three groups ($p = 0.57$). One explanation is that decreased amniotic fluid is an ominous sign of chronic hypoxemia and usually happens during the later trimester. The number of neonates with a 5-minute Apgar score of ≤ 7 were increased significantly in the control group with IUGR, but not in the AREDV group or the control group without IUGR ($p = 0.01$). This is opposite to the result of one previous study that an increase in the incidence of low Apgar score is related to progressively worsening umbilical velocimetry [11]. Our important finding is that developmental delay (an MDI or a PDI score of <70) was noted in the AREDV group, but not in the two control groups. We also found a significant difference in MDI ($p = 0.048$) but not in PDI ($p = 0.219$) scores, among the three groups. We concluded that the children born earlier than 29 gestational weeks with prenatal AREDV in the umbilical artery have obviously lower levels of cognitive, language, and social skill developments at 2 years of age. When AREDV in the umbilical artery occurs prior to 29 gestational weeks, prudent prenatal counseling to the parents about the poor prognosis of fetal mental development is necessary.

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