Relation of Retinopathy of Prematurity to Brain Volumes at Term Equivalent Age and Developmental Outcome at 2 Years of Corrected Age in Very Preterm Infants

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Keywords

Brain volume · Developmental outcome · Magnetic resonance imaging · Mental developmental index · Psychomotor developmental index · Preterm birth · Retinopathy of prematurity

Abstract

Background: Retinopathy of prematurity (ROP) is a major complication of preterm birth and has been associated with later visual and nonvisual impairments. **Objectives:** To evaluate relationships between any stage of ROP, brain volumes, and developmental outcomes. **Methods:** This study included 52 very preterm infants (gestational age [mean ± SD]: 26.4 ± 1.9 weeks). Total brain, gray matter, unmyelinated white matter (UWMV), and cerebellar volumes were estimated in 51 out of 52 infants by magnetic resonance imaging at term-equivalent age. Bayley Scales of Infant Development were used to assess developmental outcomes in 49 out of 52 in-

fants at a mean corrected age of 24.6 months. **Results:** Nineteen out of 52 infants developed any stage of ROP. Infants with ROP had a lower median (IQR) UWMV (173 [156–181] vs. 204 [186–216] mL, $p < 0.001$) and cerebellar volume (18.3 [16.5–20] vs. 22.3 [20.3–24.7] mL, $p < 0.001$) than infants without ROP. They also had a lower median (IQR) mental developmental index (72 [56–83] vs. 100 [88–104], $p < 0.001$) and a lower psychomotor developmental index (80 [60–85] vs. 92 [81–103], $p = 0.002$). Brain volumes and developmental outcomes did not differ among infants with different stages of ROP. **Conclusion:** Any stage of ROP in preterm infants was associated with a reduced brain volume and an impaired developmental outcome. These results suggest that common pathways may lead to impaired neural and neurovascular development in the brain and retina and that all stages of ROP may be considered in future studies on ROP and development.

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Introduction

With the increasing survival of extremely preterm infants, a proportionately greater number of infants are affected by major complications of prematurity, where neurodevelopmental disability and visual problems are among the most common [1, 2]. Preterm birth coincides with a critical period of brain development but also with that of vascular development [3].

The retina is incompletely developed at preterm birth. Retinopathy of prematurity (ROP) is considered to be a consequence of a primary arrest of retinal vascularization and a neurovascular disease involving both vascular and neural components [4, 5]. Postnatal head growth retardation can be regarded as a proxy of brain growth and coincides with suppression of retinal vascular growth and with low levels of IGF-1, an important vascular and neural growth factor [6]. These events can be further related to the development of severe ROP and low brain volumes at term-equivalent age [6, 7].

Preterm infants who develop severe ROP appear to be at an increased risk for visual [2] and nonvisual neurodevelopmental comorbidities and delayed white matter maturation as estimated by magnetic resonance imaging (MRI) at an early postnatal age and at term-equivalent age [8–11]. These findings suggest the presence of common mechanisms in the development of these complications [6].

Although ROP is defined according to different stages, the disease is a continuous process of impaired vascular and neuronal retinal development. Therefore, our aim in this study was to evaluate the relationship between the presence of any stage of ROP, brain growth, and later developmental outcomes at 2 years of corrected age.

Materials and Methods

Study Population

The original prospective study included 64 very preterm infants born in the neonatal intensive care unit (Lund, Sweden) between January 2005 and May 2007, where IGF-1 concentrations from birth until term age in relation to growth, MRI-estimated brain volume, and developmental outcome were evaluated [7, 12, 13]. Fifty-two infants completed the study until term age, 51 out of 52 underwent MRI at term age, and 49 out of 52 received a follow-up examination at 2 years of corrected age. Inclusion criteria were: gestational age <31 weeks, absence of major congenital anomalies, and written informed parental consent. Of the 64 recruited infants, 9 did not survive until term age and the parents of 3 infants chose to leave the study.

This study was approved by the regional ethical review board of Lund, Sweden, and adhered to the tenets of the Declaration of Helsinki. All pregnancies were dated by ultrasound at 17–18 weeks of gestation.

Clinical Data

The weight standard deviation score at birth was calculated from a Scandinavian intrauterine growth curve based on fetal weights estimated by ultrasound [14]. Cumulative doses (mg/kg) of administered hydrocortisone and betamethasone were registered until postmenstrual age (PMA) 35 weeks. Total steroid exposure was estimated by converting the betamethasone dosage into hydrocortisone equivalents (1:40). Bronchopulmonary dysplasia was defined as a requirement for supplemental oxygen at PMA 36 weeks. Septicemia was defined as the presence of a positive blood culture and concomitant increased levels of C-reactive protein.

Nutritional Regime and Calculation of Intake

The nutritional strategy used for the infants has been described previously [7] and was based on individualized enteral nutrition using maternal or donor breast milk (fortified if required) and additional parenteral nutrition, initiated as soon as possible after birth. Maternal and donor breast milk were analyzed weekly for protein and energy contents, and enteral and parenteral daily intakes of protein (g/kg/day) and energy (kcal/kg/day) were prospectively calculated from birth until at least PMA 35 weeks.

Cerebral Ultrasound

Cerebral ultrasounds were performed on days 1, 3, and 7, at 3 and 6 weeks of age, and at term. Severe intracranial hemorrhage was defined as the presence of IVH grade III or parenchymal hemorrhage. White matter damage was defined as the presence of periventricular echodensities or cysts that persisted for >7 days. Severe brain damage was defined as severe intracranial hemorrhage and/or white matter damage.

ROP Examination

ROP screening followed the Swedish national protocol and began at 5–6 weeks of age, but not before PMA 31 weeks. The infants underwent retinal examinations through dilated pupils biweekly to once weekly depending on ROP severity until either the retina was fully vascularized or the condition was considered stable. ROP was classified according to the International Classification of Retinopathy of Prematurity [15], and treatment followed the recommendations of the Early Treatment for Retinopathy of Prematurity Cooperative Group [16].

Magnetic Resonance Imaging

MRI was performed on a 3-T Siemens Magnetom Allegra head scanner (Siemens AG Medical Solutions, Erlangen, Germany) in 51 out of 52 infants at term age (mean $\pm$ SD: 40.1 $\pm$ 0.6 gestational weeks). The protocol for image acquisition and image processing has previously been described in detail [7]. We calculated the total brain volume (TBV), gray matter volume (GMV), and unmyelinated white matter volume (UWMV) in 46 infants and the cerebellar volume in 51 infants.

Assessment at 2 Years of Corrected Age

A psychologist assessed developmental outcomes in 49 out of 52 infants at a mean ($\pm$ SD) corrected age of 24.6 ($\pm$ 0.8) months by means of the Bayley Scales of Infant Development (BSID-II) with 2 different index scales, i.e., the MDI and the PDI, as previously described [13].

Table 1. Clinical characteristics according to the presence of retinopathy of prematurity

	No ROP (<i>n</i> = 33)	ROP (<i>n</i> = 19)	<i>p</i> value
Gestational age, weeks	27.4 (24.3 to 30.6)	25.0 (23.0 to 27.1)	<0.001
Birth weight, g	970 (592 to 1,716)	634 (348 to 854)	<0.001
SDS weight at birth	-0.7 (-4.4 to 0.8)	-1.8 (-4.7 to 0.6)	0.1
Apgar score <7 at 5 min	11 (33)	10 (53)	0.172
Male/female ratio	15/18 (45%/55%)	10/9 (53%/47%)	0.62
Severe brain damage ^a	2 (6)	3 (16)	0.342
Septicemia	7 (21)	12 (63)	0.002
Total steroid intake ^b , mg/kg	0 (0 to 112)	34 (0 to 105)	<0.001
Bronchopulmonary dysplasia	22 (67)	16 (84)	0.206
Energy intake ^c , kcal/kg/day	120 (104 to 140)	121 (93 to 134)	0.653
Protein intake ^c , g/kg/day	3.2 (2.6 to 3.7)	3.0 (2.6 to 3.6)	0.082

Values are presented as medians (range) or numbers (%). The total number of patients was 52. SDS, standard deviation score. ^a Intraventricular hemorrhage grade III, parenchymal hemorrhage, and/or white matter damage as defined by a cerebral ultrasound. ^b Calculated hydrocortisone equivalents from birth until postmenstrual age 35 weeks. ^c From birth until postmenstrual age 35 weeks.

Statistical Analysis

Statistical analysis was performed with SPSS 23 for Microsoft Windows (IBM, Armonk, NY, USA). $p < 0.05$ was considered statistically significant. Univariate analyses of differences between groups were assessed with the Mann-Whitney U test or the χ^2 test as appropriate. Correlations between continuous variables were evaluated with the Spearman rank correlation coefficient.

Adjustment for other variables was performed with multiple linear regression analysis. In all models GA, birth weight (BW), and gender were included as independent variables. Additionally, all variables exhibiting significant univariate associations with the respective outcome variables (Table 2) were entered into the multivariate model as independent variables. Thus, independent variables entered into the analysis for cerebellar volume and UWMV, respectively, were: GA (days), BW, gender, septicemia, and total steroid intake (hydrocortisone equivalents in mg/kg) from birth until PMA 35 weeks. The independent variables entered into the analysis for MDI were: GA, BW, gender, Apgar score <7 at 5 min, and total steroid intake from birth until PMA 35 weeks. The independent variables entered into the analysis for PDI were: GA (days), BW, gender, and severe brain damage.

Results

Clinical Characteristics and Development of ROP

Table 1 presents the clinical characteristics of infants with and without ROP. Infants with any ROP ($n = 19$) had a lower GA, a lower BW, a higher frequency of septicemia, and a higher total steroid intake compared to infants without ROP.

Clinical Characteristics in Relation to Cerebellar Volume, UWMV, MDI, and PDI

Table 2 presents relationships between clinical characteristics and cerebellar volume, UWMV, MDI, and PDI, respectively. GA correlated with cerebellar volume ($r_s = 0.56$, $p < 0.001$), UWMV ($r_s = 0.71$, $p < 0.001$), and both MDI ($r_s = 0.46$, $p = 0.001$) and PDI ($r_s = 0.34$, $p = 0.015$). BW correlated with cerebellar volume ($r_s = 0.71$, $p < 0.001$), UWMV ($r_s = 0.82$, $p < 0.001$), and MDI ($r_s = 0.41$, $p = 0.004$). Apgar score <7 at 5 min was associated with a lower MDI ($p = 0.047$), and severe brain damage was associated with a lower PDI ($p = 0.025$). Any septicemia was associated with cerebellar volume ($p = 0.022$) and UWMV ($p = 0.021$). A higher total steroid intake correlated with a lower cerebellar volume ($r_s = -0.45$, $p = 0.001$), UWMV ($r_s = -0.50$, $p < 0.001$), and MDI ($r_s = -0.39$, $p = 0.006$).

Stages of ROP in Relation to Brain Volume and Neurodevelopmental Outcome

Out of 52 infants, 33 had no ROP, 9 had ROP stage 1 or 2, and 10 had ROP stage 3 (9 of these 10 infants received laser treatment). None of the infants had ROP >stage 3.

Infants with ROP stage 1 or 2 had a lower mean TBV, GMV, UWMV, cerebellar volume, MDI, and PDI compared to infants without ROP ($p = 0.001$, $p = 0.007$, $p < 0.001$, $p < 0.001$, $p = 0.008$, and $p = 0.024$, respectively). Infants with treated ROP had lower TBV, UWMV, cerebellar volume, and MDI ($p = 0.03$, $p = 0.002$, $p = 0.005$, and $p = 0.002$), whereas no significant difference could be shown for GMV or PDI, as compared to infants without ROP.

Table 2. Relationships between clinical characteristics and cerebellar volume and unmyelinated white matter volume at a postmenstrual age of 40 weeks and MDI and PDI at 2 years of corrected age

	Cerebellar volume <i>p</i> value	Unmyelinated white matter volume <i>p</i> value	MDI <i>p</i> value	PDI <i>p</i> value
Gestational age (days)	<0.001	<0.001	0.001	0.015
Birth weight (g)	<0.001	<0.001	0.004	0.191
Apgar score <7 at 5 min	0.992	0.78	0.047	0.344
Male/female ratio	0.178	0.379	0.312	0.13
Severe brain damage ^a	0.298	0.9	0.111	0.025
Septicemia	0.022	0.021	0.199	0.294
Total steroid intake ^b (mg/kg)	0.001	<0.001	0.006	0.079
Bronchopulmonary dysplasia	0.063	0.076	0.362	0.656
Energy intake ^c (kcal/kg/day)	0.72	0.723	0.961	0.787
Protein intake ^c (g/kg/day)	0.138	0.907	0.496	0.957
Maternal educational level ^d	–	–	0.099	0.352
Paternal educational level ^d	–	–	0.131	0.223

The total number of patients was 52. MDI, Mental Developmental Index; PDI, Psychomotor Developmental Index. ^a Intraventricular hemorrhage grade III, periventricular hemorrhagic infarction, and/or white matter disease as defined by a cerebral ultrasound. ^b Calculated hydrocortisone equivalents from birth until postmenstrual age 35 weeks. ^c From birth until postmenstrual age 35 weeks. ^d University degree vs. no university degree.

Table 3. Brain volumes at a postmenstrual age of 40 weeks and Mental Developmental Index and Psychomotor Developmental Index at 2 years of corrected age in infants with any ROP or no ROP

	Any ROP ^a	No ROP ^b	<i>p</i> value
Total brain volume, mL	371 (329–390)	416 (377–445)	<0.001
Gray matter volume, mL	193 (161–201)	204 (186–231)	0.054
Unmyelinated white matter volume, mL	173 (156–181)	204 (186–216)	<0.001
Cerebellar volume, mL	18.3 (16.5–20)	22.3 (20.3–24.7)	<0.001
Mental Developmental Index	72 (56–83)	100 (88–104)	<0.001
Psychomotor Developmental Index	80 (60–85)	92 (81–103)	0.002

Values are presented as medians (IQR). ROP, retinopathy of prematurity. ^a *n* = 19. ^b *n* = 32.

The mean values of brain volumes and developmental outcomes did not differ between infants with ROP (stages 1–3) and those with treated ROP.

Any ROP in Relation to Brain Volumes and Developmental Outcome

Table 3 presents the median (IQR) values of brain volumes (TBV, GMV, UWMV, and cerebellar volume) and developmental outcomes (MDI and PDI) in infants with and without ROP. In univariate analysis infants with any ROP had significantly lower TBV, UWMV, cerebellar volumes, MDI, and PDI than infants without ROP.

Multiple linear regression analysis was performed in order to further evaluate the relationship between any ROP and brain volumes at term-equivalent age and neurodevelopmental outcome at 2 years of age. After adjustment for GA the relationships between any ROP and TBV and GMV, respectively, did not remain significant and were not further evaluated in multivariate models. Figure 1a–c shows the relationships between any ROP and cerebellar volume, UWMV, MDI, and PDI, respectively.

Table 4 presents the contribution of any ROP to cerebellar volume, UWMV, MDI, and PDI following multivariate regression analysis. The relationships between any ROP and cerebellar and UWMV, respectively, re-

Fig. 1. Median and IQR of cerebellar volume (a), unmyelinated white matter volume (b), and Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) (c) in relation to the presence or absence of retinopathy of prematurity (ROP). ** $p \leq 0.01$; *** $p \leq 0.001$.

Table 4. Contribution of any ROP to cerebellar volume and to UWMV at a postmenstrual age of 40 weeks and to MDI and PDI at 2 years of corrected age in a linear regression model

Outcome variable	<i>p</i> value	Any ROP (yes/no)	
		R^2	adjusted R^2
Cerebellar volume ^a	0.029	0.50	0.43
UWMV ^a	0.030	0.58	0.52
MDI ^b	0.007	0.38	0.29
PDI ^c	0.03	0.42	0.35

ROP, retinopathy of prematurity; UWMV, unmyelinated white matter volume; MDI, Mental Developmental Index; PDI, Psychomotor Developmental Index. ^a Included independent variables: any ROP (yes/no), gestational age (days), birth weight (g), gender, septicemia (yes/no), and total steroid intake (calculated hydrocortisone equivalents in mg/kg) from birth to a postmenstrual age of 35 weeks. ^b Included independent variables: any ROP (yes/no), gestational age (days), birth weight (g), gender, Apgar score <7 at 5 min, and total steroid intake (calculated hydrocortisone equivalents in mg/kg) from birth to a postmenstrual age of 35 weeks. ^c Included independent variables: any ROP (yes/no), gestational age (days), birth weight (g), gender, and severe brain damage (IVH grade III, and/or parenchymal hemorrhage, and/or WMD).

mained significant after adjustment for GA, BW, gender, septicemia, and total steroid intake. The relationship between any ROP and MDI remained significant after adjustment for GA, BW, gender, Apgar score <7 at 5 min,

and total steroid intake. The relationship between any ROP and PDI remained significant after adjustment for GA, BW, gender, and severe brain damage.

Discussion

Our main findings were that the presence of any stage of ROP was associated with a lower cerebellar volume and UWMV at term-equivalent age and with impaired cognitive and motor development at 2 years of corrected age. Thus, infants with less severe ROP (stage 1 or 2) exhibited a degree of brain volume reduction and neurodevelopmental impairment similar to that of infants with more severe ROP (stage 3).

Several studies have shown an association between ROP and impaired later developmental outcomes [2, 9–11]. The majority of studies compare severe ROP to no ROP and do not include less severe stages of ROP. A recent case-control study comparing severe ROP with no or stage 1 ROP found severe ROP to be associated with reduced cerebellar and brainstem volumes at term and with neurodevelopmental deficits at 15 months and 2 years of age [17]. One study considered different stages of ROP and found the severity of neonatal ROP to be a marker for functional disability at 5.5 years of age. They found high rates of disability in VLBW infants who develop severe ROP and subsequently have unfavorable visual outcomes [18].

Several features of retinal and brain development have links to common pathways that in turn may be affected by insults associated with very preterm birth. This is supported by similar risk factors being associated with ROP, lower brain volumes, and impaired neurodevelopment, which suggests common antecedent events that affect migration and proliferation in both the retina and the brain. The signaling and mitogenic protein and transcription factor sonic hedgehog is a key factor in both cerebellar and retinal proliferation during early development [19, 20].

In this study, ROP was primarily associated with a lower cerebellar volume and UWMV. These respective brain regions and the retina may present a common vulnerability due to depletion of the same trophic factors. IGF-1 is an anabolic hormone that is critical to both vascular and neural development. Low IGF-1 levels in preterm infants have been associated with ROP [21], decreased brain volumes, and impaired neurodevelopmental outcomes at 2 years of corrected age [7, 13].

The relationship between ROP and poor white matter development as determined by diffusion tensor imaging and tractography has been evaluated in one study where severe ROP predicted a white matter maturational delay in the optic radiations but also in other regions of posterior white matter. The delayed white matter maturation was present independently of other signs of brain injury [11]. The retinal nerve fiber layer as estimated by spectral-domain optical coherence tomography at term-equivalent age is thinner in very preterm infants and has been shown to correlate with white matter injury at term-equivalent age and later impaired neurodevelopment [22].

The presence of supratentorial brain injury has previously been associated with impaired cerebellar growth [23]. The presence of severe brain damage, as defined by cerebral ultrasound, was not related to any ROP or to the estimated cerebellar volume in the current study although the small number of infants with severe brain damage could have obscured such an association.

In addition to a lower cerebellar volume and UWMV, infants with any ROP had significantly lower MDI and PDI scores at 2 years of corrected age. Stage 1 ROP is sometimes difficult to diagnose and subtle forms may be missed at examination. However, similar findings were reported in another study, in which the stage of ROP *per se* did not determine the subsequent presence of neurodevelopmental impairment [9]. Several studies have also documented the importance of cerebellar volume, particularly with respect to cognitive function in preterm infants at 2 years of age [13, 24, 25].

The accumulated dose of steroid intake displayed a significant association with any ROP, lower cerebellar and UWMV, and lower MDI. Postnatal corticosteroid exposure in preterm infants has previously been related to an increased risk of ROP, an altered optic radiation structure, and impaired cerebellar growth [26–28]. The neonatal cerebellum has the highest number of glucocorticoid receptors [29]. In mice, glucocorticoids inhibit proliferation of cerebellar granular neuron precursors [30].

In conclusion, we found that the development of any stage of ROP in very preterm infants was associated with reduced brain volumes and impaired developmental outcomes at 2 years of corrected age. Though based on a small cohort of infants, our results suggest that any type of ROP, not just severe, should be considered in future studies on ROP and developmental outcomes. These findings also raise the possibility of common pathways essential for the development of the retina and brain. Therefore, strategies aimed at preventing any stage of ROP may also have neuroprotective effects on the developing brain.

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Disclosure Statement

Insulin-like growth factor 1 is covered by the patent owned by or licensed to Premacure AB, Uppsala, Sweden. A.H., D.L., and I.H.P. own shares in the company with a financial interest in Premacure AB. A.H., D.L., L.E.H.S., and I.H.P. work as consultants for Shire Pharmaceuticals (Lexington, MA, USA).

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