

Birth Weight Deviation and Early Postnatal Growth Are Related to Optic Nerve Morphology at School Age in Children Born Preterm

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ABSTRACT: The aim of this study was to evaluate the influence of early and later postnatal growth variables on optic disc morphology in children ($n = 53$) born at gestational age <32 wk. On fundus photographs taken at a median age of 5.4 y, the optic discs were evaluated using digital image analysis and compared with those of a control group ($n = 203$). The results were analyzed in relation to gestational age, birth weight (BW) SD score (SDS), IGF-1 weight at postmenstrual age 32 wk (SDS), and weight, length, and head circumference (SDS) at follow-up. The preterm children's optic disc and neuronal rim areas were smaller than in the control group. Low BW (SDS) and weight at wk 32 (SDS) were associated with larger area of the optic cup and reduced neuronal rim area. Preterm children with known brain lesions ($n = 6$) had significantly larger cups than preterm children without known brain lesions. The association found between both low BW and poor early growth and later reduced neuronal tissue of the optic nerve indicate that early weight gain is important for neural development in preterm children. (*Pediatr Res* 67: 325–329, 2010)

The prematurely born infant is prone to neuronal and vascular tissue insults when born into extrauterine life during a sensitive period of maturation of the CNS, when synaptogenesis, apoptosis, myelination, reorganization, and vasculogenesis/angiogenesis take place.

Preterm birth carries a high risk for peri- or postnatal brain lesions, and brain damage is a common cause of visual impairment in children in developed countries (1). White matter damage (WMD) occurs in 30 to 50% of children born before 30-wk gestational age (GA) (2,3) or with a birth weight (BW) <1500 g (4). Periventricular leucomalacia (PVL) is frequent in children born preterm and may cause visual impairment (5) and/or cerebral palsy (6). Intraventricular hemorrhage (IVH) has been reported to occur in 61% of infants born before 34-wk GA (7). It may be associated with variable degrees of ischemia and WMD and can cause hydrocephalus that may further impair vision.

Preterm birth as well as poor intrauterine¹ growth in full-term babies has been shown to be associated with subnormal disc and neuronal rim areas of the optic nerve and with an abnormal retinal vessel pattern (8–12). McLoone et al. (7) reported, in a group of preterm infants with IVH, a trend

toward smaller optic disc, neuronal rim, and cup area with increasing severity of IVH, but only children with IVH grade IV were reported to have a significantly increased incidence of optic nerve hypoplasia. They found no association between the optic disc morphology and timing of brain injury. Large cups in normal-sized optic discs have been reported in preterm children with PVL born at GA <37 wk (12). In another study, children with PVL had a significantly smaller disc area if the damage was estimated to have occurred before 28 postmenstrual weeks and a larger cup of the optic disc and a smaller neuronal rim area if the cerebral WMD was estimated to have occurred later than 28 postmenstrual weeks (13). Children operated on for hydrocephalus have been reported to have smaller optic disc and neuronal rim areas than controls (14).

IGF-1 is essential for normal vascularization of the retina (15), and low levels of postnatal serum levels of IGF-1 are associated with development of retinopathy of prematurity (ROP) (16) and head growth deficits (17). IGF-1 is a growth factor important for the development of the CNS, promoting proliferation, maturation, and differentiation of neural stem cells and neuronal and oligodendrocyte precursors (18).

The aim of this study was to compare optic disc morphology in preterm infants with that of a control group and to evaluate the influence of GA, BW and postnatal growth variables on the ocular fundus morphology.

MATERIAL AND METHODS

Study group. The subjects were part of a larger cohort of children born between December 1999 and April 2002 with a GA of <32 wk, who were previously examined with regard to postnatal serum levels of IGF-1 in relation to ROP. Of the initial study group ($n = 70$), which is described in detail elsewhere (16), 66 were examined regarding ophthalmologic outcome at school age. For inclusion in the ocular fundus analysis, fundus photographs taken at the time of the eye examination had to be of satisfactory quality with the optic nerve head well centered (within half a disc size off center). Fifty-three children (24 boys and 29 girls) had fundus photographs, which allowed evaluation of the optic nerve head and were included in the study. All children were examined with ophthalmoscopy. Median corrected age at examination was 5.4 y (range 4.8–6.1). The median GA at birth was 27.1 wk (range 23.4–31.1), and the median BW was 970 g (range 530–2015). Nine infants (17.0%) were born small for gestational age (SGA) [BW SD score (SDS) <-2] (range -5.0 to -2.3) and at 32 wk, 34 (64%) infants had weight SDS <-2 . ROP had been found in 34 infants and nine developed ROP stage 3, of whom four children were treated with laser ablation. Six children had

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Abbreviations: BW, birth weight; GA, gestational age; IVH, intraventricular hemorrhage; PVL, periventricular leucomalacia; ROP, retinopathy of prematurity; SGA, small for gestational age; WMD, white matter damage

Table 1. Characteristics at base line

Characteristics	n = 53
Neonatal	
GA weeks, mean (SD)	27.6 (2.08)
median (range)	27.1 (23.4 to 31.1)
BW g, mean (SD)	1063 (343)
BWSDS, median (range)	-0.9 (-5.0 to 2.2)
SGA (<-2 SDS), n (%)	9 (17.0)
Weight wk 32 (SDS), median (range)	-2.4 (-5.2 to -1.0)
Weight wk 32 <-2 SDS, n (%)	34 (64.2)
Male sex, n (%)	24 (45.2)
Singletons, n (%)	37 (69.8)
Other morbidity	
ROP stage <3, n (%)	25 (47.2)
ROP stage 3 total, n (%)	9 (17.0)
ROP treated, n (%)	4 (7.5)
BPD n (%)	10 (18.9)
NEC n (%)	2 (3.8)
Brain lesion*, n (%)	6 (11.3)

BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; CP cerebral palsy.

* Definition of brain lesion: IVH \geq grade III, hydrocephalus, WMD/PVL, and/or CP.

known brain lesions *i.e.* IVH \geq grade III and/or hydrocephalus, WMD including PVL, and/or cerebral palsy. Characteristics at baseline are presented in Table 1. Visual acuity of the best eye ranged from 0.05 [log minimum angle of resolution (logMAR) 1.3] to 1.25 (logMAR -0.1) (median 0.8, logMAR 0.1). Spherical equivalent of refraction ranged from +8.6 to -2.8 diopter. Four children were >4 diopter hyperopic.

The 13 children (seven boys and six girls) who lacked fundus photographs of sufficient quality had significantly lower serum IGF-1 levels and a lower weight at 32 wk (SDS) than the children included in the fundus evaluation ($p = 0.021$ and 0.0086 , respectively). There were no significant differences in GA and BW (SDS) between the included children and those who lacked useful photographs. Visual acuity of the best eye among the children without fundus photographs was significantly lower (median 0.4, logMAR 0.4, range: light perception to $0.9 \approx \log\text{MAR } 0.1$) than in those with fundus photographs (median 0.8, logMAR 0.1, range: 0.05–1.25, logMAR 1.3 to -0.1), $p < 0.001$. Their head circumference (SDS; $n = 10$) was smaller (median -0.6, range -3.1 to 0.3) than in the study group (median 0.3, range -1.2 to 2.0), $p < 0.001$. As judged from ophthalmoscopy and evaluation of the suboptimal photographs, only three of the 13 children had a fundus considered normal. In the remaining 10 children, large cupping of the disc was found in three, tortuous vessels in four, macular hypoplasia in three, and temporal dragging of retinal vessels after laser ablation in one child. One girl had drusen in the optic nerve diagnosed using ultrasound. Four of the children without digital optic disc analysis had brain lesions, three of them had WMD/PVL, one boy with hydrocephalus had undergone neurosurgical shunt treatment, and two had cerebral palsy. In addition, one girl had Rett syndrome, one had Barter syndrome, and one boy had Prader-Willi syndrome. After laser ablation, one girl developed cataracts and underwent cataract extraction, and later secondary implantation of intraocular lenses. One girl had corneal clouding of unknown etiology.

Control group. The control group consisted of two groups of children, altogether 203 (94 boys and 109 girls), previously presented in other studies (19,20). Median GA was 40 wk (range 28–43). Three children were born prematurely (GA 27.6, 35.0, and 36.3 wk, respectively). Six children were born SGA (-2.0 to -3.3 SDS). The control children were aged 3 to 19 y. The age discrepancy between the groups was accepted because ocular fundus variables in the ages 3 to 19 y have been found not to be age dependent (19). Visual acuity of the children ranged between 0.63 and 1.25 (logMAR 0.2 to -0.1; median 1.0 logMAR 0.0).

Digital image analysis of fundus photographs. The ocular fundus photographs were taken through dilated pupils and analyzed quantitatively, using a specially designed computer-assisted digital mapping system developed to focus on morphologic factors of importance for pre- and perinatal adverse events (19,21). The mean value of the two eye measurements was calculated for each studied fundus structure (22). If the fundus photograph of only one eye was of sufficient quality, that eye was used ($n = 44$).

The optic disc, cup, and peripapillary crescent areas are defined by marking their outlines with a cursor (A.H.), Figure 1. The projected area is

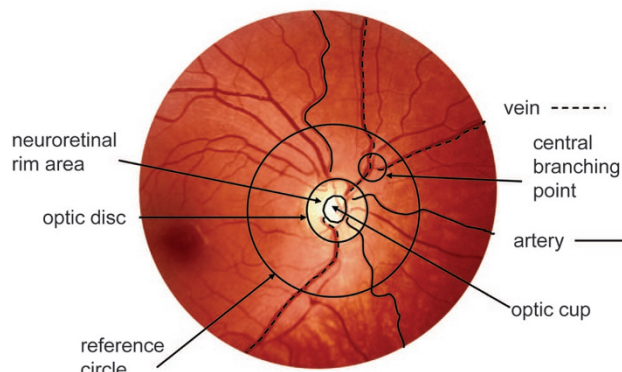


Figure 1. Drawing of the ocular fundus illustrating limits for optic disc area, cup area, and neuroretinal rim area.

automatically calculated by a computer. The optic disc is defined by the inner border surrounding the nerve tissue; care is taken not to include the white peripapillary scleral ring. The cup is defined by its contour, and its demarcation is facilitated by the course of the vessels and the pallor of the cup. The cup is easy to delineate when it appears deep and has steep boundaries. When the cup appears shallow and has sloping walls and indistinct margins, it is more difficult to delineate, and evaluation of multiple photographs from slightly different views has to be performed. The neuroretinal rim area is obtained by subtraction of the cup area from the disc area.

Ophthalmologic examination. All children had an ophthalmologic examination, including visual acuity, refraction, orthoptic status, and indirect ophthalmoscopy.

Peri- and postnatal growth variables including IGF-1 levels. SDSs for BW and weight at wk 32 were calculated for all children. To adjust for gender and differences in GA, a reference was used for calculation of SDS (23). In the neonatal period, venous blood samples (0.5 mL) had been taken weekly, and they were analyzed using a procedure described in the original article (16). The mean values of serum IGF-1 samples obtained during postmenstrual age from 30 to 33.9 wk were used for analysis. At the examination at school age, head circumference (24), weight, and length (25) were measured and were expressed as SDSs.

Statistical methods. Descriptive statistics are given as mean, SD, median, and range. For comparison between two groups Fisher's nonparametric permutation test was used for continuous and ordered variables (26). Correlation was estimated with Pearson correlation coefficient and analyzed with Pitman's nonparametric permutation test (27). All tests were two sided and conducted at 5% significance level.

Ethics. The Ethics Committee at the Sahlgrenska Academy at Gothenburg University approved of the study. Written consent was received from the children's parents.

RESULTS

Optic disc morphology in preterm children versus control group. The children born preterm ($n = 53$) demonstrated smaller areas of the optic disc and neuronal rim and larger cup area than the control group ($n = 203$), $p < 0.001$, $p < 0.001$, and $p = 0.027$, respectively, Table 2 and Figure 2.

Optic disc morphology in preterm children in relation to BW and postnatal growth variables. Low BW (SDS) and weight at wk 32 (SDS) were associated with larger area of the optic cup ($r = -0.37$, $p = 0.0083$ and $r = -0.38$, $p = 0.0064$, respectively) as well as with a smaller neuronal rim area of the optic nerve head ($r = 0.35$, $p = 0.010$ and $r = 0.31$, $p = 0.023$), as exemplified in Figure 3. There was no correlation between sex, GA, ROP, IGF-1 or length, weight, and head circumference SDS at follow-up and the optic disc structures at school age.

Optic disc morphology in children with severe ROP and without severe ROP. Preterm children with ROP grade 3

Table 2. Ocular fundus variables in children born very preterm and the control group

Ocular fundus variable	Preterm group (n = 53)	Control group (n = 203)	Preterm group versus control group (<i>p</i> value*)
Optic disc area, mm ²			
Mean (SD)	2.2 (0.3)	2.4 (0.4)	<0.001
Median (range)	2.2 (1.3–2.7)	2.3 (1.6–5.3)	
Cup area, mm ²			
Mean (SD)	0.4 (0.3)	0.3 (0.2)	0.0027
Median (range)	0.4 (0–1.4)	0.3 (0–1.6)	
Rim area, mm ²			
Mean (SD)	1.7 (0.4)	2.1 (0.4)	<0.001
Median (range)	1.7 (1.1–2.4)	2.1 (1.3–3.9)	

* Fisher's nonparametric permutation test.

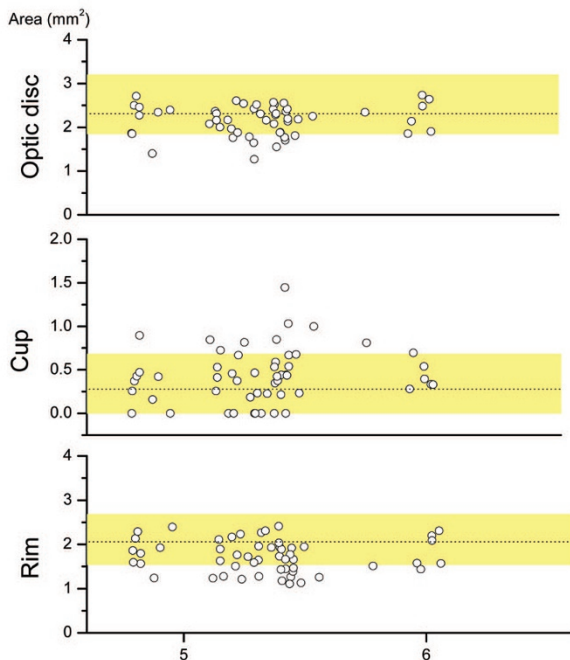


Figure 2. Area of optic disc, cup, and rim in preterm children in relation to a reference of control children. The yellow field depicts the range between the fifth and the 95th centile, and the dotted center line indicates the median of the control group.

without and with plus disease ($n = 9$) did not differ significantly from the children without severe ROP regarding the optic disc variables.

Optic disc morphology in children with and without known brain lesions. Preterm children with known brain lesions ($n = 6$) had a significantly larger cupping of the disc (mean 0.7, SD 0.2, median 0.7, range 0.5–1.0) than the preterm children without known brain lesions ($n = 47$) (mean 0.4, SD 0.3, median 0.4, range 0–1.4), $p = 0.046$. Among the children without photographs that could be analyzed, there were four children with known brain lesions, and in three of them, a large cup of the optic nerve head was noted at ophthalmoscopy according to a study protocol. However, no estimation of the optic disc size had been made.



Figure 3. Fundus photograph of a boy born at gestational age 30 wk with poor BW (BW SDS, -1.7) and perinatal weight gain (wk 32 weight SDS, -3.1), and with WMD. The optic cup is large (1.0 mm²) and the neural rim is small (1.3 mm²) in comparison with the median for cup (0.3 mm²) and rim areas (2.1 mm²) for the reference group.

DISCUSSION

In this study, we found that both low SDS for BW and weight at wk 32 were associated with increased cupping and decreased neural tissue area in the optic nerve head. This finding has to our knowledge, not been reported before. In addition, we found a negative effect of preterm birth on neural tissue as exemplified by a smaller optic disc and neuronal rim area among the preterm children in comparison with the control group. This is in accordance with a previous study of optic disc variables in preterm children with the same mean GA (27 wk) (9). In another study of preterm children with a mean GA of 29 wk, no differences in optic disc variables were observed in comparison with a control group (8). Optic nerve hypoplasia is characterized by a small diameter of the optic nerve head with a reduced number of retinal ganglion cell axons, due to irreversible damage at some time before full development of the optic nerve (28). Growth of the optic disc continues after birth at term, but at a much reduced rate and the insult resulting in optic nerve hypoplasia mostly takes place early in pregnancy, but may occur later or even postnatally (9,12,13,28). In a Swedish study of optic nerve hypoplasia epidemiology, children who were born preterm and/or SGA had increased risk for optic nerve hypoplasia (29). Our finding of a reduced rim area in the optic nerve head may reflect a low number of axons or a low axonal volume. We do not know whether this finding is representative for other neural tissue changes in the brain of the children born preterm. High frequency of neurologic morbidity has been reported for children with a BW <1500 g, ~10% have cerebral palsy, and ~50% have cognitive or behavioral deficits (4,30,31). In our study group, 90% of the preterm children had a BW <1500 g.

Poor early growth was common as reflected in an increase in frequency of weight SDS < -2 from 17% at birth to 64% at 32 wk.

The importance of early growth in preterm infants with BW < 1000 g was also reported in a study where higher rate of growth and weight gain from birth to discharge was associated with lower incidence of cerebral palsy and subnormal mental development index as well as neurodevelopmental impairment (32).

In this study, we found no significant correlation between serum levels of IGF-1 during gestational wk 30 to 33 and ocular fundus morphology. Fundus photography demands cooperation, concentration, and fixation, and it is not surprising that a majority of the 13 children who lacked fundus photographs were more disabled and had significantly lower serum IGF-1 levels than the children with fundus photographs. Four of these 13 children had known brain lesions and three of them had large optic cups at ophthalmoscopy. If we had received photographs of sufficient quality from all the children, the results might have been different. Thus, we cannot exclude an influence of IGF-1 in early optic nerve development.

IGF-1 is an important somatic growth factor, which promotes brain development, angiogenesis in the brain, and protection of neural tissue damage (33,34). Injury to periventricular white matter (35) and corpus callosum (36) has been linked to injury to oligodendrocyte precursors, which are important for myelination (31). Lin et al. (37) showed that IGF-1 protects oligodendrocyte progenitor cells in the neonatal rat brain.

It is known that IGF-1 serum levels fall rapidly after preterm birth (38). *In utero* the IGF-1 levels rise during the third trimester and children with poor BW and poor weight gain have lower levels of IGF-1 (39–41). IGF-1 is related to GA, BW, and nutrition. A recent study reported that a long duration of low levels of serum IGF-1 was associated not only with ROP and poor head circumference (17) but also with increased frequency of other morbidities in premature infants, such as IVH, necrotizing enterocolitis, and bronchopulmonary dysplasia (42). A strong correlation between postnatal IGF-1 levels and weight development (41,43) has earlier been shown. Our finding that poor postnatal weight development was associated with later optic nerve morphology may thus in part be explained by a reduced source of factors promoting neural growth in these infants.

In this study, no associations between the variables weight, length, or head circumference at school age and optic nerve morphology were noted.

In conclusion, as previously demonstrated, preterm birth is associated with changes in the neural tissue of the optic nerve head. The association found between both low weight at birth and poor early growth and later optic nerve morphology indicates that early weight gain is important for neural development in preterm children.

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