

EXTENDED REPORT

Optic disc morphology may reveal timing of insult in children with periventricular leucomalacia and/or periventricular haemorrhage

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Aims: To evaluate the relation between optic disc morphology and timing of periventricular white matter damage, defined as either periventricular leucomalacia (PVL) or periventricular haemorrhage (PVH), as estimated by neuroradiology.

Methods: 35 children with periventricular white matter damage who had had neuroradiology performed and ocular fundus photographs taken had their photographs analysed by digital image analysis and compared with a control group of 100 healthy full term children. Timing of brain lesion was estimated by analysis of the brain lesion pattern on neuroradiological examinations (magnetic resonance imaging or computed tomography).

Results: Four of 35 children had a small optic disc area; these four children had a brain lesion estimated to have occurred before 28 weeks of gestation. Nine of 11 children with a large cup area had a PVL/PVH estimated to have occurred after 28 weeks of gestation. The children with PVL/PVH had a significantly larger cup area (median 0.75 mm²) than the control group (median 0.33 mm²) ($p=0.001$) and a significantly smaller neuroretinal rim area (median 1.58 mm²) than the controls (median 2.07 mm²) ($p=0.001$).

Conclusion: In a child with PVL/PVH and abnormal optic disc morphology, the possibilities of timing of the lesion should be considered.

Optic disc anomalies in children have been described by several authors in association with brain lesions.^{1–3} The number of children with brain lesions and number of surviving children born preterm are constantly increasing. In epidemiological studies where a thorough investigation of the aetiology to the visual impairment has been performed, it has been shown that children with cerebral dysfunction represent a major proportion of visually impaired children.^{4–6}

Lesions to the mature brain in a full term infant, for example, cortical lesions caused by asphyxia, result in specific functional deficits⁷ and morphological appearances.⁸ However our knowledge about the effects of lesions of the immature visual system, for example, periventricular leucomalacia (PVL) or periventricular haemorrhage (PVH), on function as well as on morphological ocular appearance, is limited. It should be noted that children with cerebral visual dysfunction may have acquired their brain lesions at different stages of maturity.^{6–9} It is, to our knowledge, not shown how the development (morphological and functional) of the injured immature visual system proceeds and how this development is affected by the timing of the lesion. In order to increase our knowledge in this field, we investigated the possible relation between optic disc morphology and estimated timing of brain lesion.

PATIENTS AND METHODS

Patients

Forty five children with neuroradiologically verified periventricular white matter damage following periventricular haemorrhagic infarction (PVH)¹⁰ or periventricular leucomalacia (PVL)¹¹ had fundus photographs of satisfactory quality taken at the Department of Pediatric Ophthalmology, Huddinge University Hospital or at the Department of Pediatric Ophthalmology, The Queen Silvia Children's

Hospital, Göteborg between 1994 and 2000. Children who underwent treatment for retinopathy of prematurity¹² ($n=3$) and/or had shunt treated hydrocephalus ($n=7$) were excluded from the study. Thus, 35 children (14 girls and 21 boys) with a median age of 7 years (range 4–11 years) were included in the study. Fifteen of the children were part of previously reported studies of ocular fundus morphology in preterm children and in children with PVL/PVH.^{3, 13} Visual acuity ranged from 20/200 to 20/20. Refraction in the group ranged from +4 to –1 dioptres.

The time of the mother's last menstrual period was recorded, and gestational age was estimated by fetal ultrasonography, performed at week 17 of gestation (post-menstruation). The fetal ultrasonographic data were used to determine the gestational age at birth. In no case was there more than 1 week's discrepancy between the two methods. The median gestational age at birth was 30 weeks (range 25–39 weeks). Birth weights (BW) were registered in 30/35 children; the median BW was 1450 g (range 710–3250 g). Median BW standard deviation score (SDS) was –1.4 (range –4.4 to 2.7); 10 of the 30 children were born small for gestational age (SGA)—that is, <–2 SDS.

One hundred healthy individuals born at term, constituted a reference group for evaluation of ocular fundus morphology. Detailed data for these children and adolescents are presented elsewhere.¹⁴

The study was approved by the committee for ethics at the medical faculty, Göteborg University. Informed consent was obtained from the parents after the nature of the procedures had been fully explained.

Digital image analysis and ophthalmological examination

An ophthalmological examination was performed in all children, including assessment of visual acuity, refraction in

cycloplegia, ophthalmoscopy, and fundus photography. Intraocular pressure was measured in five children with PVL/PVH, all of whom had large cupping of the optic discs.

All fundus photographs were evaluated by quantitative analysis of optic disc variables utilising a computer assisted digital mapping system.¹⁵ Only well focused photographs with the optic disc centred were accepted.

The optic disc and cup areas were measured by marking their outlines with a cursor. Care was taken to trace the outlines of the optic disc excluding the white peripapillary ring. The cup was defined by its contour, and the demarcation was facilitated by the course of the vessels and its pallor. The cup was easy to delineate in the majority of the children with PVL, as it was deep and had sharp boundaries. When the cup appeared shallow and had sloping walls and indistinct margins, it was more difficult to delineate and evaluation of multiple photographs, from slightly different angles, had to be performed.

In order to minimise magnification errors, the optic disc and cup areas were corrected for the refraction values.¹⁶

The fundus photographs were evaluated without knowledge of the neonatal data, the ophthalmological examina-

tions, or the neuroradiology estimation of the timing of the brain lesion.

Cerebral imaging

Cerebral computed tomography (CT) or magnetic resonance imaging (MRI) had been performed in all children in the study group. The technical quality of the images was considered good or excellent; most children had several examinations performed. The MRI examination or the latest CT was used for this study. No subject was younger than 4 years when imaged; hence the latest imaging procedure documented a permanent end stage of the brain lesion. The images were interpreted without knowledge of the optic disc variables.

Fifteen children had been examined with MRI and 20 with CT. The localisation and extent of brain tissue loss was estimated by established CT and MRI criteria of PVL.¹⁷⁻¹⁹

Periventricular white matter damage includes brain lesions following PVL and PVH, the latter in the literature said to have an obligatory association with intraventricular haemorrhage (IVH). It is well recognised that IVH/PVH is more common in the most immature neonates while PVL is more

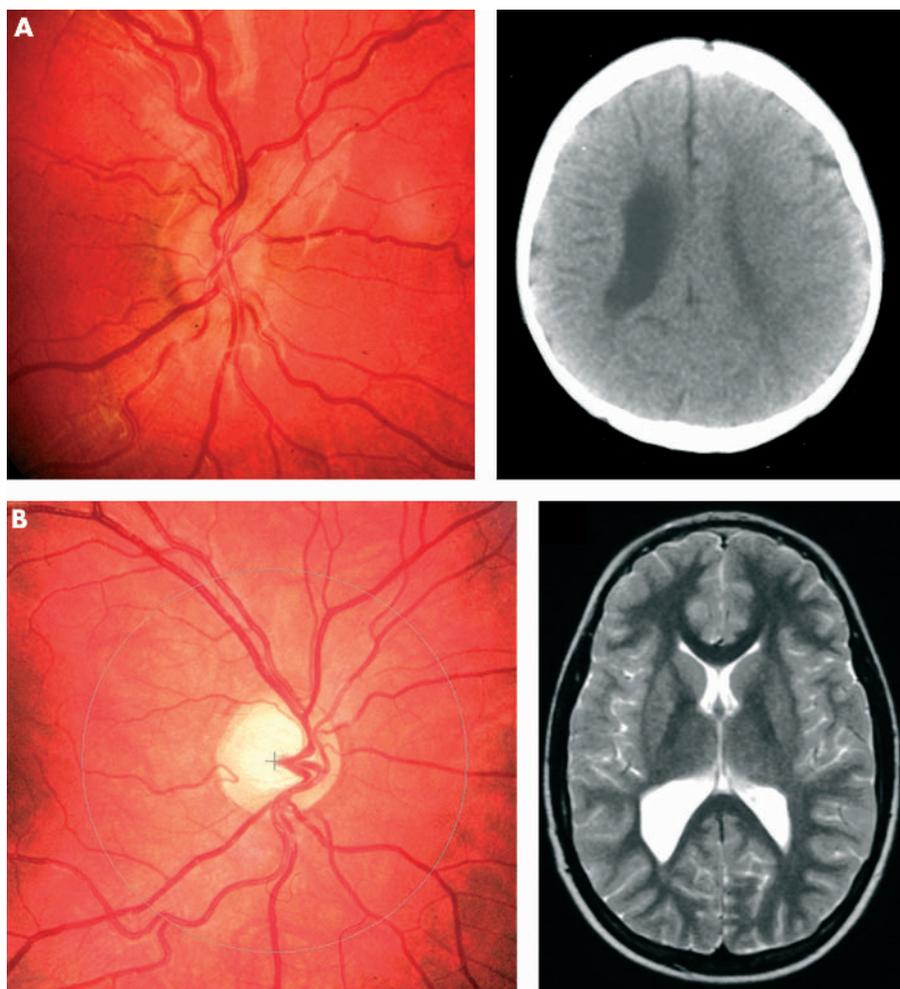


Figure 1 (A) Fundus photograph and CT of a 5 year old girl with gestational age at birth of 34 weeks, esotropia, and visual acuity 20/100. The optic disc has a small area. The CT scan shows extensive loss of periventricular white matter including almost all white matter in the right cerebral hemisphere. This image represents the end stage following a periventricular haemorrhagic infarction, indicating an early lesion. (B) Fundus photograph and MRI of a 10 year old boy with gestational age 31 weeks at birth and perinatal asphyxia. He is orthophoric, with visual acuity right eye 20/20, 20/30 left eye, and small bilateral defects in the inferior fields, normal intraocular pressure. The optic disc has a large cup in a normal sized optic disc. The T2 weighted MR scan demonstrates focal dilatation of the occipital horns, more pronounced in the right cerebral hemisphere, reflecting loss of peritrigonal white matter. White matter is preserved anteriorly as well as in centrum semiovale (not shown), indicating a late lesion.

frequent among those neonates less immature. The conditions necessary for both these lesions to occur are however not thought to be present much later than the 34th week of gestation (see Fig 1).²⁰

PVH is a primarily unilateral lesion with an aetiology closely related to a pre-existing IVH. It is also a lesion associated with often significant and widespread periventricular brain damage, while the presence of IVH shows poor correlation with permanent brain damage and subsequent handicap. The location of the periventricular white matter damage due to PVH is closely related to the foramen of Monro, in the anterior aspect of the periventricular white matter.^{21 22}

Periventricular leucomalacia (PVL) is an ischaemic lesion occurring in the periventricular watershed region. If present, PVL lesions are always found in the peritrigonal white matter.^{17 23} The lesions may extend beyond this location and in extensive cases may affect almost all white matter. However, most cases of mild to moderate PVL remain limited to the peritrigonal white matter.

When reviewing the end stage neuroradiology of a child showing periventricular white matter loss, it is not possible to determine if the primary lesion was associated with haemorrhage as in PVH or ischaemia as in PVL. However, PVH is located anteriorly and PVL posteriorly. By assessing the primary location of periventricular white matter, one may conclude that PVH is the most likely primary lesion when white matter loss is located anteriorly, while PVL is more probably the more posterior the lesions are located.

As discussed above, PVH is more common in the more immature neonate, around 24–26 weeks of gestation, while PVL occurs later with a peak around 33 weeks.²⁰ Based on these observations, it is possible to express an opinion about the likely timing of a lesion resulting in periventricular white matter loss by assessing the primary location, anterior or posterior.

In this study we initially attempted to assign each lesion to a narrow window of one or two gestational weeks. Having done this we found that two clusters formed, one early and one late, while almost no lesions were thought to have occurred in or around the 28th gestational week. Thus we divided the lesions in two groups, those thought to have occurred before and those after the 28th gestational week.

Statistical methods

The mean of the measurements of the two eyes was calculated for optic disc and cup area, in each individual. If both left and right fundus photographs were of optimal quality in a patient, the photograph from only one eye was used. The hypothesis of no difference in median values between children with white matter damage and controls were analysed by means of the Wilcoxon-Mann-Whitney U test.

RESULTS

The individual optic disc variables and the estimated age at insult are shown in Figure 2.

Four of the children had an optic disc area smaller than the 2.5% reference interval for the controls; all these children had an estimated brain lesion occurring before 28 weeks of gestational age (Figs 2 and 3). The median visual acuity in these children was 20/100, range 20/200 to 20/40.

Eleven of the children had a cup area larger than the 97.5% reference interval for the controls. Nine of these children had an estimated brain lesion occurring after 28 weeks of gestational age (Figs 2 and 3). The median visual acuity in these children was 20/40, range 20/200–20/20.

No difference was found in optic disc area between the two groups (median 2.24 mm² in children with PVH/PVL versus

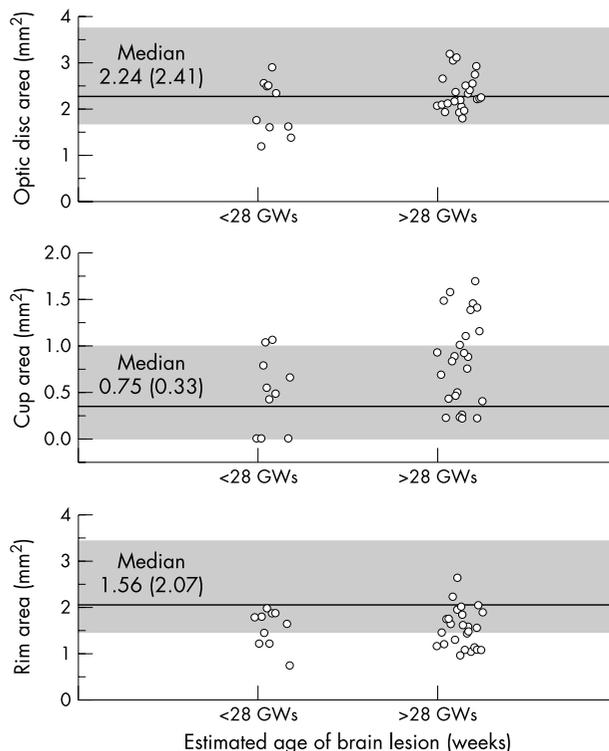


Figure 2 Individual optic disc variables depicted as open circles, in relation to timing of brain lesion as estimated by neuroimaging, before 28 gestational weeks (GW) or equal to and after 28 weeks of gestation. The 95th reference interval for healthy children is depicted as a shaded area.

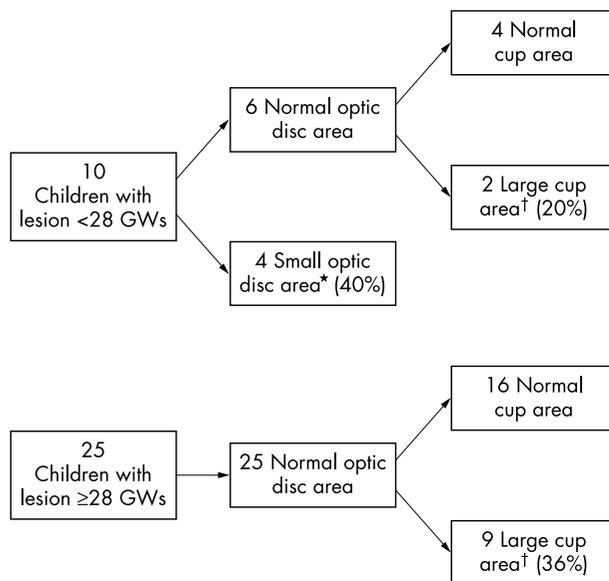


Figure 3 Schematic illustration of number of children and their optic disc morphology in relation to estimated timing of brain lesion. *Below the 2.5th centile of the reference group. †Above the 97.5th centile of the reference group.

median 2.41 mm² in the controls). The children with PVH/PVL had a significantly larger cup area (median 0.75 mm²) than the control group (median 0.33 mm²) (p = 0.001), resulting in a significantly smaller rim area (median 1.58 mm²) than the controls (median 2.07 mm²) (p = 0.001).

There was no significant association between optic disc morphology and birth weight calculated as standard deviation scores (SDS).

DISCUSSION

A small optic disc area was only seen in children with white matter damage (PVH/PVL) estimated to have occurred before 28 gestational weeks. However, a large cupping of the optic disc was more commonly seen among the children with a brain lesion estimated to have occurred after 28 gestational weeks.

One must remember that timing of PVL/PVH may be unrelated to gestational age at birth. Thus, cases of prenatal origin of PVL/PVH as well as postnatal origin of PVL/PVH have been reported. However, common to both groups is that the lesion has occurred between 24–34 weeks of gestation.^{24–25}

As earlier demonstrated, a lesion occurring in the mature visual system may result in various forms of optic disc atrophy.^{8–26} However, an insult to the immature visual system occurring during a period of synaptogenesis, apoptosis, and reorganisation may affect these processes, resulting in different morphological appearances.²⁷

The mechanisms that result in the varying optic disc morphology have been suggested to be caused by, for example, failure of differentiation of retinal ganglion cells,²⁸ secondary degeneration of ganglion cells and their fibres (retrograde, transsynaptic, or non-transsynaptic),²⁹ defective trophic mechanisms, or deficient myelinisation.³⁰

In the present study the primary lesion was located retrogenically and caused by a prenatal or perinatal lesion. It has been shown both in experimental and clinical studies that a lesion in this region of the visual system may cause transsynaptic degeneration.^{31–33} The extension of the transsynaptic degeneration is dependent on the developmental status at the time of insult and on the extension of the primary lesion.^{34–36}

In the mature eye, the optic disc and nerve are surrounded by the relatively firm supporting tissues of the sclera, pia mater, dura mater, and the lamina cribrosa, and the nervous tissue fills the space surrounded by the supportive structures. A pathological study demonstrates that a supporting tissue, lamina cribrosa, of the optic nerve has an adult appearance first at month 8 of gestation.³⁷ It may be speculated that a lesion that causes a reduction of the total number of retinal ganglion cells before the supportive tissues are fully developed may result in a small disc, as the supportive structures may still be able to adapt to the subnormal size of the nervous tissue of the optic disc/nerve. Correspondingly, a “later” lesion might result in a normal sized disc with a large cup, as the supportive elements have reached their full size, creating a normal sized disc, while the degeneration of nervous tissue creates a loss of substance identified as a large cup.

The finding of two children in whom neuroradiology showed evidence of an early lesion, while optic disc morphology revealed large cupping (indicating a late lesion), may appear to contradict our method of timing of the injuries. However, this may rather suggest that these children were subject to more than one episode of brain damage.

It is well known that adverse events during prenatal life might result in abnormal development of the visual system, for example, diabetes,³⁸ infections,³⁹ and various teratogens.⁴⁰

In the present study, the four children with small optic discs (small neuroretinal rim area) all had subnormal visual acuity. However, among the children with normal sized optic discs and large cups, also resulting in a small neuroretinal rim area, some children had normal visual acuity. This finding indicates that it is not the amount of axonal loss, but the type of axons damaged that is responsible for the visual

outcome. Thus, the axonal vulnerability may vary with type of axon and developmental stage.

The possibility of timing a cerebral insult should be considered in a child with cerebral visual impairment⁴¹ and abnormal optic disc appearance. Further studies are needed to demonstrate if knowledge of the timing adds information about the pattern of visual deficits as well as prognosis of visual outcome.

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