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Abnormal optic disc and retinal vessels in children with surgically treated hydrocephalus

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Abstract
Aims: To investigate the morphology of the optic disc and retinal vessels in children with surgically treated hydrocephalus.
Methods: A prospective, population-based study was performed in 69 children (median age 9.6 years) with early surgically treated hydrocephalus. All children were examined by ophthalmoscopy. Additionally, optic disc and retinal vessel morphology was evaluated in 55 children by digital image analysis of ocular fundus photographs.
Results: Optic atrophy was found in 10 of 69 children (14%). In comparison with a reference group, the median optic disc area was significantly smaller ($p=0.013$) in the children with hydrocephalus. There was no corresponding difference in cup area, thus the rim area was significantly smaller in the hydrocephalic children ($p=0.002$). Children with hydrocephalus had an abnormal retinal vascular pattern, with significantly straighter retinal arteries and fewer central vessel branching points compared to controls ($p<0.001$ and $p<0.001$, respectively).
Conclusion: Hydrocephalus is associated with subnormal optic disc and rim areas and an abnormal vascular pattern, indicating a pre/perinatal disturbance of the development of these structures. A promising finding is that the frequency of optic atrophy in the present study was lower than previously reported, most likely reflecting improved perinatal care and better regulation of the intracranial pressure.

Key Words: hydrocephalus, digital image analysis, optic nerve morphology, retinal vessels.

Introduction

Hydrocephalus is a disorder in which reduced outflow or absorption of cerebrospinal fluid causes increased intraventricular and intracranial pressure with distension of the ventricles. Hydrocephalus may develop prenatally, perinatally or postnatally. The definition of infantile hydrocephalus, as used in this study, is hydrocephalus present at birth or developing within the first year of life. Surgical treatment with ventriculoperitoneal shunting or ventriculostomy may restore the pressure to normal levels[1,2].

Both anterior and posterior visual pathways may be affected in children with hydrocephalus.

Papilloedema is very rare in infants and young children and despite the high intracranial pressure, papilloedema is also absent in a majority of infants with hydrocephalus. [3] This is probably due to the fact that open sutures permit the head to enlarge in response to the increased pressure. However, large or rapid elevations in intracranial pressure may exceed this response, causing papilloedema.[4]

Optic atrophy (OA) is a well-known complication of raised intracranial pressure. In children OA may or may not have been preceded by papilloedema. A number of different mechanisms for OA in children with hydrocephalus have been described, including optic nerve ischaemia, optic nerve or chiasmal traction, chiasmal compression and trans-synaptic neuronal degeneration. [5] Optic nerve hypoplasia (ONH) is typically described as a small optic nerve head, pale in colour and sometimes surrounded by a double ring. [6,7] The growth of the normal optic disc and nerve is only partly completed at birth and growth continues until adulthood.[8, 9]

During the last few decades there have only been a few studies performed on children with hydrocephalus regarding ocular and fundus appearance. These studies have described optic disc oedema and/or atrophy (17% and 29%), detected using ophthalmoscopy. [3,10]

To our knowledge, no population-based morphometric study has been performed on the ocular fundus of children with surgically treated hydrocephalus. In the present study, therefore, we set out to describe optic disc and retinal vessel morphology, using both ophthalmoscopy and digital image analysis of fundus photographs in children with hydrocephalus.

Materials and Methods

The inclusion criteria for the study were a head circumference >2 standard deviation scores (SDS) greater than body length SDS and enlarged ventricles present at birth, or developing during the first year of life, requiring surgical treatment.[11] The inclusion criterion that the hydrocephalus should have necessitated neurosurgical treatment was used to delineate a homogenous group. There are a few children with transient hydrocephalus constituting less than ten percent of all. One subgroup is the very preterm infants with post haemorrhagic enlargement of the ventricles that may resolve within a few weeks when the blood is reabsorbed, some children with time limited disturbance of the CSF circulation after an infection and a group with "external" hydrocephalus during the first year of life due to a maturity dependent imbalance between CSF production and reabsorbtion.

Between 1989 and 1993, 103 children born in a well-defined area in south-western Sweden (the counties of Västra Götaland, Halland and Värmland) met the inclusion criteria. Six children died shortly after surgery and five children who had been surgically treated outside the region were excluded from this ophthalmologic follow-up study. Of the remaining 92 children, 15 did not agree to participate and two were excluded as they had moved out of the region. Six children did not want to take part of the ocular fundus examination. Hence, 69 children were available for the study, 32 girls and 37 boys, 7.2–12.8 years of age (median age 9.6 years), with a median GA at birth of 39 weeks (range 27-42 weeks) and a median birth weight SDS of +0.5 (range -4 – +4) (see Table 1). All children underwent an eye examination, including ocular fundus photography; 84% had some kind of visual deficit, such as subnormal visual acuity, strabismus, impaired stereo vision, refractive errors and/or visuo-perceptual problems. Nine children (13%) were visually impaired according to the definition of the World Health Organization (WHO 1997), and 64% had significant refractive errors.[12] Only correctly focused photographs with the optic disc centred were accepted for analysis; 55 of the children (27 girls and 28 boys) fulfilled this criterion. Of the remaining 14 children, all agreed to ophthalmoscopy.

Table 1 *Aetiology, gestational age, birth weight, and associated diagnoses in children with hydrocephalus (n=69) in relation to a comparison group of 140 healthy children.*

Aetiology	**Gestational age** (weeks) Md(range)	**Birth weight** SDS Md (range)	**Associated diagnoses** Cerebral paresis	Epilepsy	IQ<70
Hydrocephalus with myelomeningocele (n=26)	39 (33-42)	+0.5(-2.5– +4)	0/26	2/26 (8%)	4/21 (19%)
Hydrocephalus without myelomeningocele (n=43)	38(27-41)	+0.5 (-4 – +4)	12/43 (28%)	15/43 (35%)	17/40 (43%)
Reference (n=140)	40(35-42)	+0.2 (-4 –+5.5)	0	0	0

Reference group

A total of 99 healthy Swedish children (56 boys and 43 girls) born at term, with an age range of 3-19 years (mean age 10.1 years) constituted a reference group for the evaluation of ocular fundus morphology by the digital image analysing system.[13] No association between studied variables and sex and age could be found in these children. The visual acuities of the reference group ranged from 0.0 (logMAR) to 0.1 (logMAR) (median 0.0 logMAR).

The study was approved by the Committee for Ethics at the Medical Faculty, Göteborg University.

Digital image analysis of fundus photographs

The ocular fundus photographs were obtained, by film photography, through dilated

pupils and analysed quantitatively, using a specifically designed computer-assisted digital mapping system.[14]

The area of the optic disc was measured by marking the outlines with a cursor. The optic disc was defined by the inner border surrounding the nerve tissue; care was taken not to include the white peripapillary scleral ring. The cup was defined by its contour, and its definition was facilitated by the course of the vessels and by its pallor. The neuroretinal rim area was obtained by subtraction of the cup area from the disc area. The indices of tortuosity for arteries and veins were defined as the path length of the vessel divided by the linear distance from the vessel origin to a reference circle 3 mm from the centre of the optic disc. Vessels were also marked from their branching point to the reference circle, and within this area the total number of branching points (arteries and veins), that is, the number of retinal vessels, was calculated. The same method of digital analysis was used for both the hydrocephalic children and the reference group, and all measurements were performed by the same person.

Retrospective review of medical files

The aetiology of hydrocephalus varied. Hydrocephalus was associated with myelomeningocele (MMC) in 26 children, with intraventricular haemorrhage in 17 children, with malformations in 18 children, and with infections in four children. In four cases, the aetiology was unknown. Thirteen children were born preterm.

The time of the mother's last menstrual period was recorded, and GA was estimated by foetal ultrasonography, performed at week 17 of gestation (post-menstruation). The foetal ultrasonographic data were used to determine the GA at birth. The perinatal data and associated diagnoses are presented in Table 1.

Statistical methods

The ocular fundus variables for each child were calculated from the mean of the two eye measurements. Median and 95% confidence interval (CI) for the median were calculated for the areas of the optic disc, cup, and rim, the tortuosity of arteries and veins, and the number of vascular branching points. The Wilcoxon-Mann-Whitney test was used to compare the medians in the group of hydrocephalic children with the medians in the reference group.

Results

Optic nerve morphology

Optic disc variables for children with hydrocephalus and controls are shown in table 2.

Table 2. *Areas of the optic disc, cup, and neuroretinal rim of children with hydrocephalus (n=55) in relation to a reference group (n=99).*

Variables	**Hydrocephalus** Median (95% confidence interval)	**Controls** Median (95% confidence interval)	*p-value*
Optic disc area, mm^2	2.21 (1.31-3.20)	2.42 (1.44-3.46)	*0.01*
Cup area, mm^2	0.31 (0-0.96)	0.34 (0-0.84)	*ns*
Rim area, mm^2	1.79 (0.87-2.92)	2.07 (1.27-2.90)	*0.002*
tortuosity index for arteries	1.07 (1.02-1.13)	1.09 (1.03-1.17)	*<0.001*
Number of vascular branching points	23 (17-31)	28 (20-35)	*<0.001*

The children with hydrocephalus had a smaller median optic disc area than the reference group of healthy children (2.21 and 2.42 mm^2 respectively, p=0.01). No difference was found in the median cup area (0.31 vs. 0.34 mm^2). Thus, the children with hydrocephalus had a significantly smaller median rim area than the reference group (1.79 and 2.07 mm^2 respectively, p=0.002). (Fig.1&2)
Nine children (16%) had an optic disc area below the 5th centile (Table 3).
Examination by indirect ophthalmoscopy showed OA in 10 out of 69 children (14%); six had fundus photographs of acceptable quality for digital analysis. Three of these had an optic disc and rim area below the 5th centile for controls, two had large optic cups in normal sized discs, and one child had a normal disc appearance on the photographs.

Table 3 *Optic disc area, GA, aetiology of hydrocephalus, VA, strabismus, and associated conditions in hydrocephalic children with optic disc areas below the 5th centile for controls.*

Patient	gestational age, weeks	aetiology	optic disc area, mm^2	binocular visual acuity logMAR	strabismus	cerebral palsy	epilepsy	Full scale IQ
F	37+0	IVH	1.37	0.4	no	no	no	124
F	41+3	IVH	1.65	0.5	yes	yes	yes	90
F	40+0	Malformation	1.78	0.2	yes	yes	no	92
F	38+0	Myelomeningocele	1.77	0.0	yes	no	no	90
F	35+0	IVH	1.59	1.0	yes	no	no	68
F	36+5	Myelomeningocele	1.66	0.05	yes	no	no	107
F	40+0	Myelomeningocele	1.70	0.3	yes	missing	missing	missing
F	39+0	Malformation	1.78	0.3	yes	no	yes	61
F	35+6	Malformation	1.79	0.1	yes	no	yes	64

IVH = intraventricular haemorrhage, F=female, missing=missing information

Optic nerve morphology and clinical findings
Visual acuity among the 55 children ranged from ability to fixate a penlight to -0.1 logMAR (median 0.1). Refraction ranged from –1 to +6 dioptres (spherical equivalent). Strabismus was noted in 39 of 54 children (72%).
Five of the ten children with optic atrophy had a VA of ≤0.3(logMAR).
Among the children with VA≥0.5(logMAR), two out of three children had optic discs and neuroretinal rim areas smaller than the 5th centile for controls.
Strabismus was noted in seven out of nine children with optic atrophy.
Strabismus was present in 39 of the 54 children who also had an ocular fundus evaluation; 9 of these 39 (23%) had a rim area below the 5th centile (p=0.003).

Retinal vessel morphology
Of the 55 children who had fundus photographs taken, 51 children's retinal vessel morphology could be analysed. Children with hydrocephalus had an abnormal retinal vascular pattern, with significantly straighter retinal arteries and fewer central vessel branching points compared to controls ($p<0.001$ and $p<0.001$, respectively).
A reduced number of vascular branching points below the 5th centile for controls, was found in seven of 51 children (14%) with hydrocephalus (p=0.037). (Fig.1&3)
The two groups did not differ significantly in vein tortuosity.
There was no significant relationship between retinal vessel morphology and either visual acuity or strabismus.

Aetiology and gestational age
In comparison to those born at term, children born preterm were found to have smaller rim area as well as increased tortuosity of the central retinal vessels (p=0.015 and p=0.004, respectively). There was no other correlation between aetiology and ocular fundus variables.

Discussion
Independently of aetiology, children with hydrocephalus were found to have subtle abnormal optic nerve morphology in comparison with controls, illustrated by smaller optic disc and rim areas, as well as an abnormal retinal vascular pattern with less tortuous arteries and a reduced number of central vascular branching points.
Children with hydrocephalus born preterm had a significantly smaller rim area compared to those born at term. These findings are well in accordance with the results of Hellström et al., who found a small rim area in non-hydrocephalic children born at a GA of less than 29 weeks.[15] Also when excluding the children born preterm the group of children with hydrocephalus had smaller rim areas compared to controls.

Histologically, ONH is characterised by a reduction in both the number of axons and the optic nerve diameter. Optic atrophy is characterised by a similar histopathology, except that the diameter of the optic nerve may be diminished in some cases but preserved in others.[4,7] It is possible that ONH could be regarded as a non-progressive optic atrophy acquired at any time before full development of the visual system.[7] Hoyt and Good (1992) suggested that, depending on timing of the cerebral insult, the same type of lesion could result in either ONH or optic atrophy, while others have considered an association between a small optic disc and an early lesion.[16,17,18]
Jacobson et al. studied children with white matter damage and reported a small optic

disc area, only seen in children with brain damage (periventricular haemorrhage/periventricular leukomalacia) estimated as having occurred before 28 gestational weeks. 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.[19] In the present study, we found three children with significant cupping in normal sized discs. Two of these children were born at term, and one was born after 36 gestational weeks. All of them had strabismus, and VA was 0.4, 0.65, and 1.0, respectively. The aetiology of the hydrocephalus in this group was intraventricular haemorrhage in one case and malformations in the other two. McLoone et al. examined 104 children born before 34 weeks gestation and/or with birth weight less than 1500g with the RetCam, a cranial ultrasound and magnetic resonance imaging system; 24 of the 104 children had periventricular white matter damage (PVWM). They also found significantly smaller optic discs in babies with PVWM than in those without PVWM. They found a trend towards reduced optic disc area, optic cup area, and optic disc diameter with increasing severity of intraventricular haemorrhage; however, the only subgroup to differ significantly in optic disc area and optic cup area from the control group of premature children was the subgroup of children with IVH 4. The authors were unable to demonstrate a statistically significant association between disc morphology and timing of the cerebral insult.[20] However, they only included children born at less than 34 weeks of gestation and/or with birth weight of less than 1500 g, and used preterm children without signs of brain lesion as controls.

In the present study, we found no correlation between the aetiology of hydrocephalus (i.e. intraventricular haemorrhage or other cause) and ocular fundus variables.
The varying optic disc morphology has been suggested to be caused by factors such as secondary degeneration of ganglion cells and their fibres (retrograde, transsynaptic, or non-transsynaptic), defective trophic mechanisms, or deficient myelinisation.[16,17,21,22]
The smaller disc areas may reflect a reduced number of optic nerve axons; experimental and clinical studies have indicated that the size of the disc, especially in small discs, is related to the number of axons.[23,24,25] However, experimental studies on protein deprived rats have shown not only a reduced optic nerve diameter but also reduced diameters of the axons present.[26] One could speculate that the reduced optic disc and rim areas in children with hydrocephalus are therefore of a prenatal origin. We found no difference in optic disc area between the group of children born with hydrocephalus and those developing the condition during the first year of life.
Strabismus, which is a non-specific response to neurological insult, was found to be associated with smaller rim areas. More children with brain lesions, than healthy children, have strabismus. [27]

Abnormal vascular morphology was found in the group of children with hydrocephalus, with decreased tortuosity of the retinal arteries and a decreased number of central branching points. One can speculate that the straighter arteries and fewer branching points reflect the reduced nutritional demands of fewer neural elements.
When studying the subgroup of children with hydrocephalus being born preterm, they had fewer vascular branching points but instead an increased tortuosity of the retinal arteries. These findings are in accordance with previous results among preterm children, who have an increased tortuosity.[15] It has been suggested that impaired fetal

development may cause abnormalities on endothelial function. [28]
Six out of ten children classified as OA, at ophthalmoscopy, had their fundus photographs evaluated and 50% of these children did not show general atrophy, but a large optic cupping and a normal disc. This reflects the difficulty examining children, differentiating an optic atrophy from a large cupping in a fundus with a pale appearing optic disc.

Conclusion

Hydrocephalus has previously been associated with a high frequency of optic atrophy. In contrast, our results showed a relatively low frequency, which may reflect the improved medical care now given to children with hydrocephalus. In these children, the effect of hydrocephalus on the neural tissue results in a small optic disc and optic rim area, and also an abnormal vascular pattern, with a decreased tortuosity of the retinal vessels and fewer vascular branching points. These abnormal findings indicate a pre/perinatal influence on development of neural and vascular tissues in children with hydrocephalus.

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Fig 1. Fundus photography of a girl with hydrocephalus showing an example of a small optic disc area, a small neuroretinal rim area and a decreased number of retinal vascular branching points

Fig 2. *Areas of the optic disc, cup, and neuroretinal rim of children with hydrocephalus in relation to a reference group. The yellow area depicts the 5th to the 95th centile range, and the dotted line indicates the median for the control group.*

Fig 3. *Arterial tortuosity index and number of branching points in children with hydrocephalus in relation to a reference group. The yellow area depicts the 5th to the 95th centile range, and the dotted line indicates the median for the control group.*