The Clinical and Morphologic Spectrum of Optic Nerve Hypoplasia

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Purpose: The purpose of this study was to characterize the clinical and morphologic spectrum of all children referred for optic nerve hypoplasia to a tertiary referral hospital in Sweden during a 9-year period. ***Subjects and Methods:*** A retrospective review was undertaken of the charts of 117 children (age range, 0.25-16 years), treated at the Children's Hospital, Göteberg between 1988 and 1996, after the diagnosis of optic nerve hypoplasia. Ocular fundus morphologic condition was evaluated by digital image analysis of fundus photographs in 50 children, and neuroimaging was performed in 57 children. ***Results:*** Of the 117 children with optic nerve hypoplasia, 66 (56%) were boys and 51 (44%) were girls. Preterm birth occurred in 24 (20%), and 14 (12%) were born small for gestational age. Additional diagnoses, such as fetal alcohol syndrome, septo-optic dysplasia, perinatal adverse events, and neuropsychiatric disorders, were made in 88%; 7% had unilateral optic nerve hypoplasia. Most of the children had small optic disc, cup, and neuroretinal rim areas, as well as retinal vascular abnormalities; 75% were visually impaired, and a high incidence of nystagmus and strabismus was found among these children. ***Conclusion:*** This study indicates that optic nerve hypoplasia has a wide clinical and morphologic spectrum and is associated with a broad range of disorders of the central nervous system. It is suggested that differences in *the etiology and timing of the lesion* as well as *associated lesions* may explain this spectrum of optic nerve hypoplasia in children. (J AAPOS 29;3:212-20)

Optic nerve hypoplasia is one of the more common congenital anomalies causing visual impairment in the Western world.[1] It is histologically characterized by a subnormal number of optic nerve axons and is an unprogressive, nonspecific manifestation of damage at any site of the visual pathways, sustained anytime before its full development.[2-6] It may cause a wide range of visual disabilities, and several recent reports have demonstrated a high frequency of associated central nervous system (CNS) abnormalities in children with optic nerve hypoplasia, indicating the complexity of this diagnosis.[7-9]

Because histologic studies are impossible to perform in vivo, indirect signs of a reduced number of optic nerve axons are used to confirm the diagnosis. These indirect signs may be functional (impaired visual acuity or visual fields) and/or morphologic (pallor of the optic disc, double-ring sign, small size of the optic disc, or a small neuroretinal rim area). It should be pointed out that the optic nerve morphology in hypoplasia may vary considerably and that a small optic disc size is not a prerequisite for the diagnosis, as suggested by Frisén and Holmegaard.[2] Because optic nerve reference values for children have not been available and standardized techniques suitable for routine determination of the optic nerve morphology have been lacking, the differentiation between normal and abnormal morphology has been difficult. Consequently, there are no standardized studies on optic nerve morphology in a group of children selected on the basis of optic nerve hypoplasia.

The aim of this study was to characterize the clinical and morphologic (by objective measurements) spectrum of optic nerve hypoplasia in a large unselected group of children with a clinical diagnosis of optic nerve hypoplasia. They were referred to a tertiary children's hospital during a 9-year period in a universal health care system with good record retrieval mechanism.

SUBJECTS

Study Group

Between 1988 and 1996, 117 children (median age, 7 years; range, 0.25-16 years) were examined at the Department of Pediatric Ophthalmology, Children's Hospital, Göteberg (a

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tertiary referral hospital that serves a population of 1.5 million) and received the diagnosis optic nerve hypoplasia. A retrospective chart review was performed, with information regarding gestational age (GA) at birth, birth weight, maternal intake of alcohol and drugs, diagnosis (ophthalmologic and others), visual acuity, and refraction being extracted from the medical files. The clinical diagnosis of optic nerve hypoplasia was made initially by 1 of 4 pediatric ophthalmologists. After the patients' files were thoroughly checked by one of the authors (A. H.), the ophthalmologist who originally diagnosed optic nerve hypoplasia had a chance to review the file and, if available, the fundus photographs to confirm the diagnosis. The clinical diagnosis of optic nerve hypoplasia was based on indirect signs of a subnormal number of axons (ie, functional [impaired visual acuity or visual fields]) and/or morphologic conditions (pallor of the optic disc, double-ring sign, abnormal vascular pattern, small size of the optic disc, or a small neuroretinal rim area).

Reference Group

One hundred healthy full-term individuals (56 boys and 44 girls), with an age range of 2.6 to 19.6 years, constituted a reference group for evaluation of ocular fundus morphology. Detailed data for these children and adolescents are presented elsewhere.[10]

The study was approved by the Committee for Ethics at the Medical Faculty, Göteborg University. Informed consent was obtained from the parents and, if old enough, from the children themselves.

METHODS

All children had an eye examination, including assessment of motility, visual acuity, ophthalmoscopy, cycloplegic refraction, and fundus photography in cycloplegia. Visual acuity was tested using methods suitable for the age and capacity of the children: "hundreds and thousands" for the youngest children; the HVOT-test, usually for children aged 3 to 5 years; and Snellen's E chart and letter chart for older school children.[11]

Fifty (43%) of the 117 children with optic nerve hypoplasia had fundus photographs of satisfactory quality that were analyzed quantitatively, using a computer-assisted digital mapping system.[12] The optic disc area was measured by marking the outlines with a cursor. The computer automatically calculated the projected area. The inner border surrounding the nerve tissue defined the optic disc; care was taken not to include the white peripapillary scleral ring. The cup was defined by contour, and its definition was facilitated by the course of the vessels and its pallor. The cup was easy to delineate when it appeared deep and had steep 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 views had to be performed. The neuroretinal rim area was obtained by subtraction of the cup area from the disc area. The index of tortuosity for

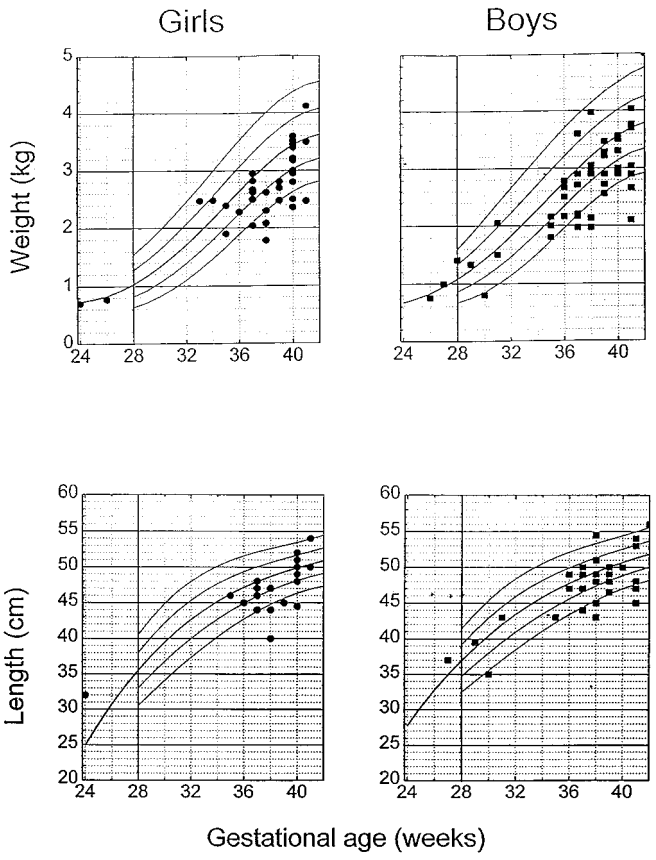


FIG 1. Birth weight and height in relation to GA in children with optic nerve hypoplasia, compared with Swedish reference values.[15] *Circles* indicate girls, and *squares* indicate boys. *Lines* indicate mean ± 1 and 2 SD for boys and girls, respectively.[15]

arteries and veins was 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 center of the optic disc. Vessels were also marked from their branching point to the reference circle, and the total number of branching points—arteries and veins—(ie, retinal vessels) within this area was calculated. The optic disc and cup areas were corrected for the refraction values to minimize magnification errors.[13]

The digitized fundus images were evaluated without knowledge of the retrospective chart reviews. Fundus photographs of both eyes were used in 28 children. In 22 children, the photograph of only 1 eye was used (due to insufficient quality of the fundus photograph from the other eye).

STATISTICAL METHODS

The mean value of the 2 eye measurements for each individual was calculated for each fundus variable. Median values and 95% CI of the median were calculated for each fundus variable. The distributions of the measurements of the fundus variables were compared with the 5th and 95th centiles and the median of the reference values.[10] The

TABLE 1. Additional diagnoses of 117 children with ONH

		Children with		
	N	Fundus photographs	Performed CT or MRI	Pathologic neuroimaging
FAS	25	16	5	4
SOD	6	3	6	6
PVL	12	8	9	9
Tetraplegia	7	1	3	3
Spastic diplegia	3	1	3	2
Hemiparesis	3	1	2	2
Microcephalus	2	1	1	1
Hydrocephalus	2		2	2
Encephalopathy	2	1	1	1
Perinatal asphyxia	3	1	3	1
Mental retardation	7	2	6	3
Delayed psychomotor development	3	1		
Autism	5		3	1
DAMP	2	1		
Hyperactivity	2			
Epilepsy	1		1	
Muscular hypertonia	1	1	1	1
Muscle eye and brain disease	1	1	1	1
Goldenhar syndrome	1			
Reynolds syndrome	1			
Congenital varicella	1		1	
Congenital toxoplasmosis	1		1	1
Congenital cytomegalovirus	2		1	1
Craniopharyngioma	1	1		
Intrauterine growth retardation	2		1	1
GH insufficiency	2	2	1	1
Postnatal shortness	2			
Noonan syndrome	1			
Atrium septum defect	1	1	1	
None	15	7	4	
Total	117	50	57	41

DAMP, Dysfunction in Attention, Motor-control and Perception; *ONH*, optic nerve hypoplasia.

probability of the observed number of individuals outside the 5th or 95th centile limits of the reference interval was calculated for each fundus variable.[14] The relationship between optic disc area and tortuosity for arteries and veins was evaluated by means of the Spearman rank order correlation coefficient. The Bonferroni-Holm sequential adjustment for multiple tests was performed to obtain an overall significance level of at least 5%.[15]

RESULTS

Clinical Spectrum—General

Sixty-six (56%) of the 117 children with optic nerve hypoplasia were boys. The median postmenstrual GA at birth was 38 weeks (range, 24-43 weeks). Twenty-four (20%) children were born preterm, and 14 (12%) were born small for gestational age (SGA) (ie, less than –2 SD in birth length and/or birth weight compared with Swedish reference values (Figure 1).[16]

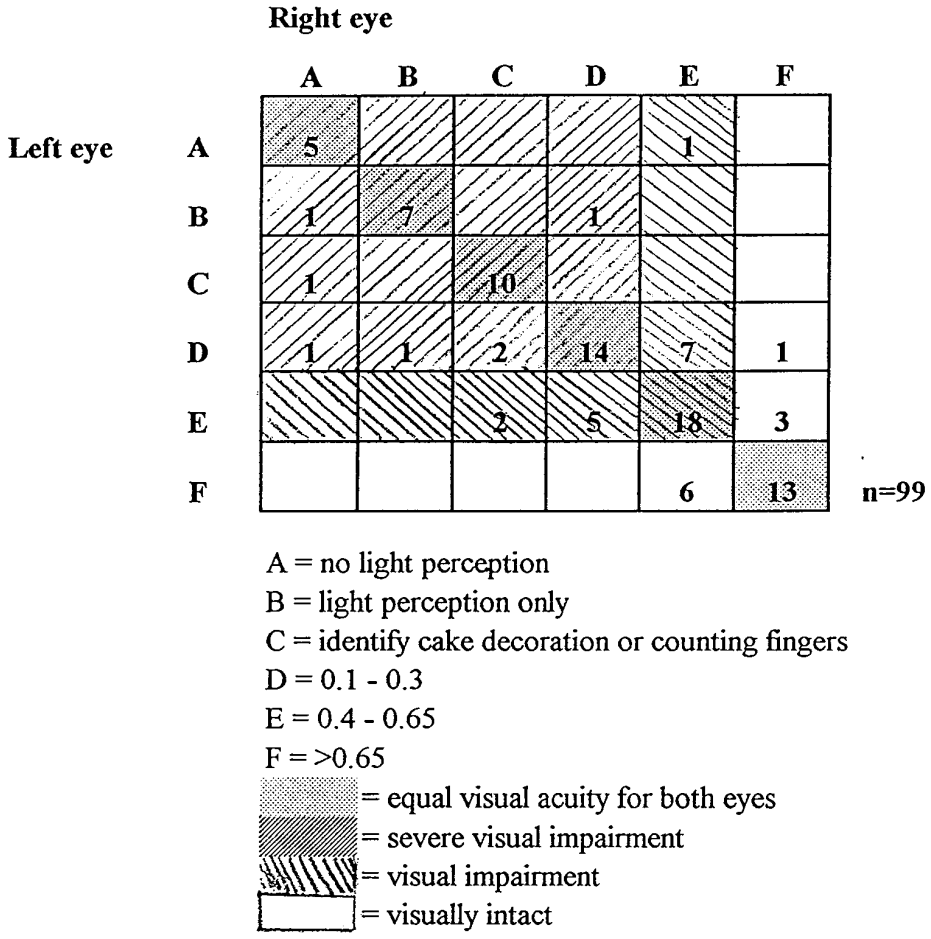
An additional diagnosis was made in 88% of the children (Table 1). Neuroimaging was performed in 57 patients and contributed to the diagnosis in 46 of these children. Magnetic resonance imaging (MRI) was performed in 29 patients, and computed tomography (CT) was performed in 28 patients. The most frequent diagnoses among the 117 children were intrauterine or perinatal hemispheric injuries (23%), fetal alcohol syndrome (FAS) (21%), neuropsychiatric disorders (16%), and septo-optic dysplasia (SOD) or growth hormone (GH) insufficiency (10%).

Clinical Spectrum—Ophthalmologic

Eight (7%) children had unilateral optic nerve hypoplasia. The results of the visual acuity tests were available for 99 children. Forty-three (43%) of these were severely visually impaired (visual acuity for both eyes <0.3), 33 (33%) had reduced vision (visual acuity <0.65), and 23 (23%) were visually intact (visual acuity >0.65) (Table 2). Six of the 13 children with normal vision had FAS and had demonstrated a delayed visual maturation.

Nystagmus was seen in 22 (18%) children, and in 11 of these, the visual acuity was less than 0.3. Strabismus

TABLE 2. Visual acuity in 99 patients with ONH



ONH, optic nerve hypoplasia.

occurred in 27 (23%) of the children. Hyperopia greater than 2 D was seen in 19 (16%) of the children, and 18 (15%) children had myopia less than -1 D.

Morphologic Spectrum

The median optic disc area (2.04 mm^2; 95% CI, 1.69-2.23 mm^2) was significantly smaller (P <.0001) among the children with optic nerve hypoplasia compared with the median optic disc area of the reference group (2.67 mm^2).[10] Twenty-seven (54%) of the children with optic nerve hypoplasia did not have a demonstrable cup, which is a 4.5 times higher proportion than in the reference group (12%).

The median index of tortuosity for arteries (1.10, 95% CI, 1.08-1.11) among the children with optic nerve hypoplasia was the same as in the reference group. The children with optic nerve hypoplasia had a significantly larger dispersion of the arterial tortuosity than the reference group; 14 children (29%) had tortuosity values outside the 90th reference interval (P = .001). The median index of tortuosity for veins (1.09, 95% CI, 1.08-1.10) was significantly larger (P = .01) among the children with optic nerve hypoplasia compared with the median for the reference group (1.07). Eleven (22%) children had venous tortuosity above the 95th centile (P = .0001).

The median number of vascular branching points (17; 95% CI, 15.5-18.5) was significantly lower (P <.0001) among the children with optic nerve hypoplasia compared with the median for the reference group (23). Twenty-seven (54%) children had a lower number of branching points than the fifth centile of the reference group (P <.0001).

The individual fundus values (optic disc area, cup area and rim area, tortuosity index for arteries and veins, and number of vascular branching points) and medians in relation to age and to the reference centiles of healthy children are given in Figures 2 and 3.

There was no correlation between the size of the optic disc and the vessel characteristics.

Morphologic Spectrum Versus Clinical Spectrum

Of the 7 children with normal visual acuity that had fundus photographs analyzed, 5 had FAS (subnormal optic disc size in combination with increased tortuosity of *both* retinal arteries and veins), 1 had craniopharyngioma with

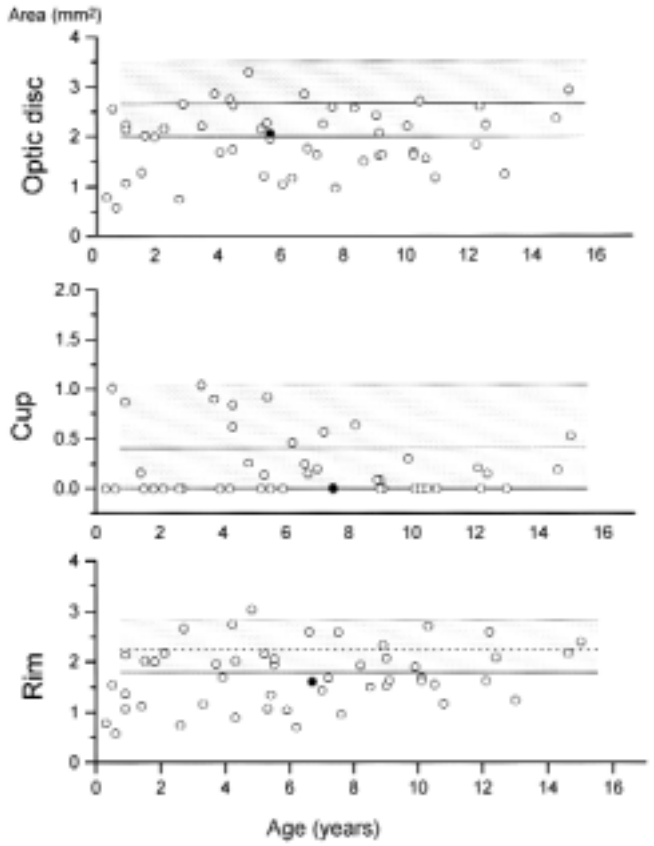


FIG 2. Individual values of optic disc, cup, and neuroretinal rim areas and group median (*solid circle*). The shaded area depicts 5th to 95th centile range, and *centerline* indicates median for healthy reference group.[11]

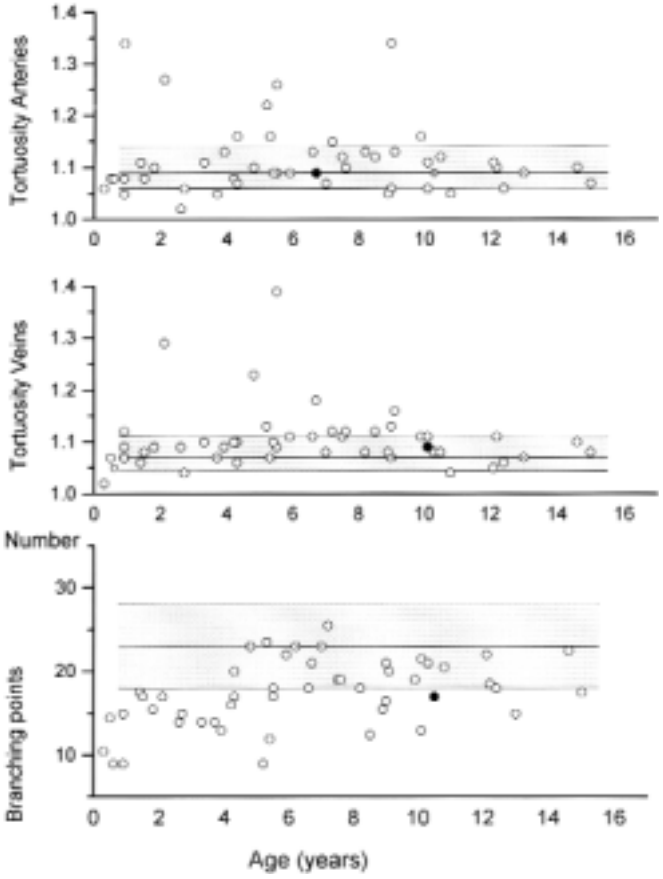


FIG 3. Individual values of index of tortuosity for arteries and veins and number of branching points and group median (*solid circle*). *Shaded area* depicts 5th to 95th centile range, and *centerline* indicates median for healthy reference group.[11]

subnormal optic disc and rim area, and 1 had periventricular leukomalacia (PVL) with normal disc area, large optic cup, and small neuroretinal rim area. Of the 5 children with an optic disc area above the median, 3 had a visual acuity below 0.3 on their best eye. Of the 24 children with an optic disc area below the fifth centile, 16 children had a visual acuity below 0.3 and only 2 of these 24 children had a visual acuity over 0.6.

DISCUSSION

Individuals with optic nerve hypoplasia have a markedly wide clinical and morphologic spectrum, ranging from apparently healthy children with normal visual acuity to children with disabilities who have severe visual impairment. Knowledge of this spectrum is of great importance for facilitating detection and optimizing treatment.

Clinical Spectrum

Sex Distribution. There seems to be a slight predominance of boys with optic nerve hypoplasia, varying in proportion from 56% to 75%.[17-20] This preponderance of boys was also found in this study (56%). Although some studies have reported an equal frequency of boys and girls, to our knowledge there are no studies where a predominance of girls has been reported in optic nerve hypoplasia.[9,21] On the other hand, optic disc anomalies, such as morning glory, are more predominant in girls.[22]

GA/SGA. Optic nerve hypoplasia has been reported to be associated with both postmaturity and prematurity.[23,24] In this study, 20% of the children with optic nerve hypoplasia were born preterm. It might be speculated that the improved prenatal and perinatal care, resulting in the increased survival rate of preterm children, might have changed the panorama of optic nerve hypoplasia.[25] Of the 117 children studied, 12% were born SGA, compared with the expected incidence of 2.5% in a healthy population. The increased frequency of children born SGA might reflect prenatal adverse events to the fetus.

Additional Diagnoses. A wide spectrum of *CNS anomalies* has been reported in association with optic nerve hypoplasia. The proportion of patients with such anomalies ranges from 39% to 81%.[9,20,26-29] The optic nerve may thus be regarded as a marker of abnormal brain development, as the visual pathways traverse the brain from its

anterior to its posterior parts. Any maldevelopment or early insult along the visual pathways may result in optic nerve hypoplasia. Naturally, the frequency of associated lesions depends on the selection and diagnostic methods used for confirming the diagnosis.

SOD is a congenital midline brain abnormality that includes absence of the septum pellucidum in addition to optic nerve hypoplasia.[30] Optic nerve hypoplasia has also been described in association with a wide range of pituitary hormone insufficiencies, although GH is the earliest, and therefore the most common, pituitary hormone to be affected.[31] It should also be noted that optic nerve hypoplasia has been described in isolated GH insufficiency, without agenesis of the septum pellucidum.[32] The reported proportion of SOD and GH insufficiency in association with optic nerve hypoplasia ranges between 13% and 53%.[9,19,27,28] SOD is diagnosed clinically by neuroimaging (preferably MRI), which might explain the higher proportion (40% to 50%) of this diagnosis noted in the reports where neuroimaging has been an inclusion criterion.[9,27] In this study, only 10% of the children with optic nerve hypoplasia had SOD or GH insufficiency. This could possibly be due to the inclusion in the study of all children with optic nerve hypoplasia and not only those being investigated by neuroimaging, who presumably might have more severe optic nerve hypoplasia. It should be pointed out that pituitary hormone insufficiency is one of the more important optic nerve hypoplasia–related diagnosis to recognize because untreated, it may lead to hypoglycemia, growth retardation, and even sudden death.[33]

It was not suggested until recently that a prenatal or perinatal insult affecting the periventricular white matter (ie, *PVL*) could be associated with optic nerve hypoplasia.[9,25] CNS abnormalities suggestive of intrauterine or perinatal hemispheric injuries were reported by Brodsky and Glasier[9] in the same proportion (25%) as found in this study (23%). The relatively high proportion of intrauterine or perinatal hemispheric injuries as a cause of optic nerve hypoplasia might be due to the increase in preterm births seen and the increased knowledge and interest in the association between PVL and optic nerve hypoplasia.[9,25]

There was a surprisingly high proportion of children with *FAS* (21%) among the patients with optic nerve hypoplasia, possibly because of the research interest and awareness of this diagnosis at our institution. Optic nerve hypoplasia has been reported in 48% of children with FAS.[34] It is also possible that the proportion of children with FAS has been underestimated in other reports, because it might be masked by other diagnoses, such as microencephaly, cerebral atrophy, mental retardation, and behavioral problems.[35]

In early reports, *bilateral and unilateral optic nerve hypoplasia* was reported with equal frequencies; in later reports bilateral optic nerve hypoplasia far exceeds the unilateral optic nerve hypoplasia.[18] It was also stated that unilateral optic nerve hypoplasia was less commonly associated with other CNS lesions.[26,29] With increasing knowledge and increasing use of sensitive diagnostic methods, it has been demonstrated that unilateral optic nerve hypoplasia is associated with other CNS anomalies in 6% and 25% of patients, depending on the selection criteria.[10,28] These are lower figures than reported among children with bilateral optic nerve hypoplasia. In this study 3 of 8 children with unilateral optic nerve hypoplasia had an additional diagnosis, which is slightly more than earlier reported.

TABLE 3. Prenatal exposure of alcohol/drugs/narcotics as apparent from the medical files in 117 children ONH

	No.
Alcohol	25
Hashish	1
Terfluzine	1
Benzodiazepine (oxazepam)	2
Tricyclic antidepressant (clomipramine)	2
Total	31

ONH, optic nerve hypoplasia.

Visual Impairment. There have been varying reports in the literature regarding visual function among children with optic nerve hypoplasia, ranging from normal vision to a high frequency of children who can only perceive light or have no light perception.[20,23,27,36,37] In this study, more than 75% were visually impaired, although the entire visual spectrum was represented.

It should be noted that 10 of 43 children with severe visual impairment were younger than 3 years and that visual testing in this age group is unreliable. In addition, it has been shown that children with optic nerve hypoplasia may have delayed visual maturation.[38] Other factors that might influence the results of the visual tests are the mental capacity and the cooperation of the child. Cognitive disorders, often associated with the diagnoses seen among the children with optic nerve hypoplasia, might also hamper the visual test results.

Refraction. There are varying reports in the literature regarding refraction abnormalities among children with optic nerve hypoplasia, and a high proportion of myopia (23% over 4 D) has been reported.[39] In this study we found the same proportions of myopia and hyperopia (15% to 16%).

Morphologic Spectrum

As clearly demonstrated, there is a wide variability in optic disc and retinal vessel morphology among children with optic nerve hypoplasia (Figures 2 and 3). Most children with optic nerve hypoplasia had *a small optic disc area.* As a consequence of the small optic disc area, there were *a reduced frequency and size of the optic disc cups*, as has been demonstrated previously.[40] *A normal optic disc area* was noted in some patients with perinatal insults who had *large cups.* This has also been described by Jacobson et al[25] as a variant of optic nerve hypoplasia in children with PVL.

A large proportion of the children with optic nerve hypoplasia had increased *vascular tortuosity of arteries and veins.* This has previously been demonstrated in children with optic nerve hypoplasia in association with FAS and SOD, as well as in prematurity.[41-43] Other conditions associated with abnormal tortuosity of the retinal arteries are aortic coarctation and several genetic syndromes.[44,45] Marked tortuosity of the retinal vessels seems to be a nonspecific reaction of the retinal vessels, being induced at different ages by a variety of stimuli. This study supports an association between optic disc anomalies and an abnormal retinal vascular pattern, independent of FAS and preterm birth.[46] The clinical implications of marked vascular tortuosity are not known, but it may be a useful marker of prenatal and perinatal adverse events, not only affecting the vascular system but also the optic nerve and the CNS.

A low number of *vascular branching points* were seen among children with optic nerve hypoplasia (ie, they had fewer retinal vessels than expected). The underlying mechanisms and the importance of these findings are not known. It might be speculated that lack of vascular growth factors or a reduced retinal oxygen demand in underdeveloped retinal nervous tissue in children with severe optic nerve hypoplasia may be the cause.

Pathogenetic Mechanisms and Etiology

The cause of optic nerve hypoplasia is probably multifactorial. Differentiation of the retinal ganglion cells begins at 6 weeks of embryonic life, and it has been suggested that a failure of this differentiation is the cause of optic nerve hypoplasia. Consequently, the lesion would be induced before the seventh week of gestation.[18,47] However, a recent report demonstrates an important role for the homeobox gene in the development of SOD, which indicates that optic nerve hypoplasia might develop even earlier than previously thought.[48] In addition, the frequent association between optic nerve hypoplasia and other CNS anomalies suggests that another explanatory factor for optic nerve hypoplasia may be a secondary degeneration of ganglion cells and their fibers.[4,7,9,49] Depending on the anatomic location of the insult, this degeneration could be transsynaptic retrograde, as suggested in PVL, or simply retrograde, as suggested in, for example, craniopharyngioma.[24,49] In addition, various teratologic agents (eg, alcohol) may cause antegrade optic nerve hypoplasia. The prenatal exposure of known teratogens is shown in Table 3. Because these data were revealed from interviews and file records, the impact of the etiologic cause might be underestimated. The pathogenetic mechanisms that have been suggested for the teratogenecity of alcohol include interference with apoptosis, defective trophic mechanisms, deficient myelinization, and excessive cell death at the rim of the anterior neural plate.[26,50] The children with FAS demonstrated a specific morphologic appearance with subnormal optic disc size in combination with increased tortuosity of both retinal arteries and veins.

To our knowledge, the use of antidepressive drugs (eg, clomipramine) has not been previously associated with optic nerve hypoplasia. However, there are some reports that indicate a relationship between prenatal exposure of clomipramine and toxic effects in infants.[51] Other causative prenatal and perinatal factors that have been discussed in association with optic nerve hypoplasia are a young maternal age, maternal diabetes, maternal anticonvulsant therapy, and premature or postmature birth.[18,19,36, 52,53] Optic nerve hypoplasia has also been associated with other ocular abnormalities (eg, aniridia and albinism) as well as with suprasellar congenital tumors and many other CNS abnormalities.[9,27,49,54,55] Consequently, it seems reasonable to assume that the adverse effects on the embryo and fetus of a teratogen are multifactorial and influenced by factors such as timing of the exposure, dose, and genetic predisposition.

Timing

In this study, it was shown that optic nerve hypoplasia might have a considerable morphologic variability in conditions occurring at different times during prenatal and perinatal life. 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 lesion that causes a reduction of the total number of retinal ganglion cells before the supportive tissues are fully developed (first to second trimester) may result in a small disc because the supportive structures may still be able to adapt to the subnormal size of the nervous tissue of the optic disc/nerve. Correspondingly, a "late" lesion (third trimester) might result in a normal-sized disc with a large cup because the supportive elements have reached their full size, creating a normal-sized disc, whereas the degeneration of nervous tissue creates a loss of substance identified as a large cup.[25] As demonstrated by Hoyt et al,[56] patients with congenital hemianopsia had obvious segmental atrophy of the optic disc, but also a reduced horizontal diameter, suggesting that the optic nerves were also hypoplastic. Margo et al[57] reported optic atrophy with normal-sized nerves in 2 similar patients. On the basis of these data, Hoyt and Good[7] suggested that the same type of lesion could result in either optic nerve hypoplasia or optic atrophy, depending on the timing of the lesion. It may also be speculated that a primary prenatal adverse event causing optic nerve hypoplasia might result in a higher vulnerability for a perinatal secondary insult. It seems possible that the *timing of the lesion* might be an explanatory factor for the varying appearance of the optic disc noted in children with a clinical diagnosis of optic nerve hypoplasia.

Diagnostic Criteria

Optic nerve hypoplasia implies a subnormal number of optic nerve axons, and consequently, a subnormal volume

of neural tissue in the optic nerve. The neural tissue volume can only be indirectly estimated by analyzing the retinal nerve fiber layer or by morphologic measurements of the optic nerve size. In children, however, there are, at present, no practical means of determining the retinal nerve fiber layer, leaving optic nerve measurements as the method of choice. However, optic disc size alone may not be a reliable criterion of optic nerve hypoplasia because of the large interindividual normal variation in optic disc size. Frisén and Quigley[58] demonstrated in humans a relationship between the estimated number of optic nerve axons and the visual acuity. This finding was supported in this study, where a small optic disc was correlated with low visual acuity. It therefore seems reasonable to take into account both morphologic and functional criteria in the diagnosis of optic nerve hypoplasia. The finding of reduced vision in a patient with a small optic disc thus supports the diagnosis of optic nerve hypoplasia. In cases with reduced vision but normal to subnormal disc size, other *morphologic* signs (ie, reduced rim area, pallor of the disc, double ring, and abnormal vessel) may be used as additional diagnostic aids.

Considerations of the Subjects

This study was a retrospective chart review. All children who were treated at the department of pediatric ophthalmology after the diagnosis of optic nerve hypoplasia between 1988 and 1996 were included. Because the department is located at the children's hospital, many children with pediatric disorders were referred for an ophthalmologic examination, which might have contributed to the relatively large frequency (88%) of additional diagnoses among children with optic nerve hypoplasia.

CONCLUSION

This study indicates that optic nerve hypoplasia has a wide clinical and morphologic spectrum and is associated with a broad range of CNS disorders. It is suggested that optic nerve hypoplasia may be caused by a number of etiologic factors and that differences in *etiology and timing of the adverse events* as well as various *associated lesions* might be explanatory factors for this wide spectrum. The variation in manifestations may also reflect variations in the severity of optic nerve hypoplasia and differences in diagnostic criteria. The seriousness of the disorder, the large number of associated lesions, and the broad morphologic variability clearly emphasize the need for strict diagnostic criteria in optic nerve hypoplasia.

References

1. Blohmé J, Tornqvist K. Visual impairment in Swedish children. Acta Ophthalmol 1997;75:681-7.
2. Frisén L, Holmegaard L. Spectrum of optic nerve hypoplasia. Br J Ophthalmol 1978;62:7-15.
3. Whinery RD, Blodi FC. Hypoplasia of the optic nerve: a clinical and histopathologic correlation. Trans Am Acad Ophthalmol Otolaryngol 1963;67:733-8.
4. Mosier MA, Liberman MF, Green WR, Knox DL. Hypoplasia of the optic nerve. Arch Ophthalmol 1978;96:1437-42.
5. Hotchkiss ML, Green WR. Optic nerve aplasia and hypoplasia. J Pediatr Ophthalmol Strabismus 1979;16:225-40.
6. Novakovic P, Taylor DSI, Hoyt WF. Localising patterns of optic nerve hypoplasia-retinal to occipital lobe. Br J Ophthalmol 1988; 72:176-82.
7. Hoyt CS, Good WV. Do we really understand the difference between optic nerve hypoplasia and atrophy? Eye 1992;6:201-4.
8. Zeki SM, Hollman AS, Dutton GN. Neuroradiological features of patients with optic nerve hypoplasia. J Pediatr Ophthalmol Strabismus 1992;29:107-12.
9. Brodsky MC, Glasier CM. Optic nerve hypoplasia-clinical significance of associated central nervous system abnormalities on magnetic resonance imaging. Arch Ophthalmol 1993;111:66-74.
10. Hellström A, Svensson E. Optic disc size and retinal vessel characteristics in healthy children. Acta Ophthalmol 1998;78:260-7.
11. Lindstedt E. Appraisal of visual behavior: the use of a checking list. In: Kooijman AC, et al, editors. Low vision: research and new developments in rehabilitation. Amsterdam: IOS Press; 1994. p. 15-9.
12. Strömland K, Hellström A, Gustavsson T. Morphometry of the optic nerve and retinal vessels by computer-assisted image analysis. Graefes Arch Clin Exp Ophthalmol 1995;233:150-3.
13. Bengtsson B. The variation and covariation of cup and disc diameters. Acta Ophthalmol 1976;54:804-18.
14. Altman DG. Practical statistics for medical research. 1st ed. London; Chapman & Hall; 1994. p. 186.
15. Holm S. A simple sequentially rejective multiple test procedure. Scand J Statist 1979;6:65-70.
16. Niklasson A, Ericson A, Fryer JG, Karlberg J, Lawrence C, Karlberg P. An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977-1981). Acta Paediatr Scand 1991;80:756-62.
17. Edwards WC, Layden WE. Optic nerve hypoplasia. Am J Ophthalmol 1970;70:950-9.
18. Walton DS, Robb RM. Optic nerve hypoplasia: a report of 20 cases. Arch Ophthalmol 1970;84:572-8.
19. Acers TE. Optic nerve hypoplasia: septoopticpituitary dysplasia syndrome. Trans Am Ophthalmol Soc 1981;79:425-57.
20. Siatkowski MR, Sanchez JC, Andrade R, Alvarez A. The clinical, neuroradiographic, and endocrinological profile of patients with bilateral optic nerve hypoplasia. Ophthalmology 1997;104:493-6.
21. Zeki SM, Dutton GN. Optic nerve hypoplasia in children. Br J Ophthalmol 1990;74:300-4.
22. Pollock S. The morning glory disc anomaly: contractile movement, classification, and embryogenesis. Doc Ophthalmol 1987;65:439-60.
23. Jan JE, Robinson GC, Kinnis C, MacLeod PJM. Blindness due to opticnerve atrophy and hypoplasia in children: an epidemiological study. Dev Med Child Neurol 1977;19:353-63.
24. Burke JP, O'Keefe M, Bowell R. Optic nerve hypoplasia, encephalopathy, and neurodevelopmental handicap. Br J Ophthalmol 1991;75:236-9.
25. Jacobson L, Hellström A, Flodmark O. Large cups in normal sized optic discs—a variant of optic nerve hypoplasia in children with periventricular leukomalaci. Arch Ophthalmol 1997;115:1263-9.
26. Lambert SR, Hoyt CS, Narahara MH. Optic nerve hypoplasia. Surv Ophthalmol 1987;32:19.
27. Zeki SM, Hollman AS, Dutton GN. Neuroradiological features of patients with optic nerve hypoplasia. J Pediatr Ophthalmol Strabismus 1992;29:107-12.
28. Cibis GW, Fitzgerald M. Optic nerve hypoplasia in association with brain anomalies and abnormal electroretinogram. Doc Ophthalmol 1994;86:11-22.
29. Skarf B, Hoyt CS. Optic nerve hypoplasia in children. Arch Ophthalmol 1984;102:62-7.
30. de Morsier G. Etudes sur les dysraphies cranio-encéphaliques, III: agenesie du septum lucidum avec malformation du tractus optique:

la dysplasie septo-optique. Schweiz. Arch Neurol Neurochir Psychiatr 1956;77:267-92.
31. Hoyt WF, Kaplan SL, Grumback MM, Glaser JS. Septo-optic dysplasia and pituitary dwarfism. Lancet 1970;2:893-4.
32. Costin G, Murphree AL. Hypothalamic-pituitary function in children with optic nerve hypoplasia. Am J Dis Child 1985;139:249-54.
33. Brodsky MC, Conte FA, Taylor D, Hoyt CS, Mrak RE. Sudden death in septo-optic dysplasia. Arch Ophthalmol 1997;115:66-70.
34. Strömland K. Ocular abnormalities in the fetal alcohol syndrome. Acta Ophthalmol Suppl 1985;63 Suppl 171:1-49.
35. Clarren SK, Alvord EC, Sumi MS, Streissguth AP. Brain malformations related to prenatal exposure to ethanol. J Pediatr 1978;92:64-7.
36. Peterson RA, Walton DS. Optic nerve hypoplasia with good visual acuity and visual field defects: a study of children of diabetic mothers. Arch Ophthalmol 1977;95:254-8.
37. Bjork A, Laurell CG, Laurell U. Bilateral optic nerve hypoplasia with normal visual acuity. Am J Ophthalmol 1978;86:524-9.
38. Strömland K, Hellström A. Fetal alcohol syndrome—an ophthalmological and socioeducational prospective study. Pediatrics 1996;97:845-50.
39. Weiss AH, Ross EA. Axial myopia in eyes with optic nerve hypoplasia. Graefes Arch Clin Exp Ophthalmol 1992;230:372-7.
40. Jonas JB, Gusek GC, Naumann GOH. Optic disc, cup and neuroretinal rim size, configuration and correlations in normal eyes. Invest Ophthalmol Vis Sci 1988;29:1151-8.
41. Hellström A, Chen YH, Strömland K. Fundus morphology assessed by digital image analyses in children with fetal alcohol syndrome. J Pediatr Ophthalmol and Strabismus 1997;1:17-23.
42. Hellström A, Wiklund L-M, Svensson E, Albertsson-Wikland K, Strömland K. Optic nerve hypoplasia with isolated tortuosity of the retinal veins—a marker of endocrinopathy. Arch Opthalmol. In press 1999.
43. Hellström A, Hård A-L, Chen YH, Niklasson A, Albertsson-Wikland K. Ocular fundus morphology in preterm children-influence of gestational age, birth size, perinatal morbidity and postnatal growth. Invfest Ophthalmol Vis Sci 1997;38:1184-92.
44. Johns KJ, Johns JA, Feman SS. Retinal vascular abnormalities in patients with coarctation of the aorta. Arch Ophthalmol 1991;109:1266-8.
45. Goldberg MF, Pollack IP, Green WR. Familial retinal arteriolar tortuosity with retinal hemorrhage. Am J Ophthalmol 1972;73:183-91.
46. Brodsky MC. Congenital optic disc anomalies. Surv Ophthalmol 1994;39:89-112.
47. Billson FA. The clinical significance of optic nerve hypoplasia. Trans Ophthalmol Soc NZ 1973;25:179-80.
48. Dattani MT, Martinez-Barbera JP, Thomas PQ, Brickman JM, Gupta R, Martensson IL, et al. Mutations in the homeobox gene HESX1/Hesx1 associated with septo-optic dysplasia in human and mouse. Nat Genet 1998;19:125-33.
49. Taylor DSI. Congenital tumors of the anterior visual system with dysplasia of the optic discs. Br J Ophthalmol 1992;66:455-63.
50. Phillips DE, Krueger SK, Rydquist JE. Short and long-term effects of combined pre- and postnatal ethanol exposure (three trimester equivalency on the development of myelin and axons in rat optic nerve. Int J Dev Neurosci 1991;9:631-47.
51. Schimmell MS, Katz EZ, Shaag Y, Pastuszak A, Koren G. Toxic neonatal effects following maternal clomipramine therapy. J Toxicol Clin Toxicol 1991;29:479-84.
52. Margalith D, Jan JE, McCormick AQ, Tze WJ, Lapointe J. Clinical spectrum of congenital optic nerve hypoplasia: Review of 51 patients. Dev Med Child Neurol 1984;26:311-22.
53. Hoyt CS, Billson FA. Maternal anticonvulsants and optic nerve hypoplasia. Br J Ophthalmol 1978;62:3-6.
54. Layman PR, Anderson DR, Flynn JT. Frequent occurrence of hypoplastic optic disks in patients with aniridia. Am J Ophthalmol 1974;77:513-6.
55. Spedick MJ, Beauchamp GR. Retinal vascular and optic nerve abnormalities in albinism. J Pediatr Ophthalmol Strabismus 1986;23: 58-63.
56. Hoyt WF, Rois-Montenegro EN, Behrens MM, Eckelhoff RJ. Homonymous hemioptic hypoplasia. Br J Ophthalmol 1972;56: 537-45.
57. Margo CE, Hamed LM, McCarthy J. Congenital optic tract syndrome. Arch Ophthalmol 1991;109:1120-2.
58. Frisén L, Quigley HA. Visual acuity in optic atrophy: a quantitative clinicopathological analysis. Graefes Arch Clin Exp Ophthalmol 1984;222:71-4.

An Eye on the Arts – The Arts on the Eye

Were my Master to grant me but a single glance through these sightless eyes, I would without question choose to see first a child, then a dog.

—Helen Keller (an epigram from *The symbol of the dog in the human psyche* by Eleanora M)