OPTIC NERVE HYPOPLASIA: Septo-Optic-Pituitary Dysplasia Syndrome*

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INTRODUCTION

FOR ALMOST A CENTURY (1864 to 1962) OPTIC NERVE HYPOPLASIA WAS DESCRIBED AS A rare and isolated ocular anomaly, characterized by a small, pale optic nerve and blindness.

Only during the last 20 years, and essentially in the last decade, has the association of optic nerve hypoplasia and congenital defects of certain anterior midline brain structures, notably the septum pellucidum and pituitary, been described. Also only during this later period has the wide disparity in the clinical expression of these related defects been emphasized and the entire spectrum of the septo-optic-pituitary dysplasia syndrome been fully recognized.

Heretofore, there has not been a single large series of patients with optic nerve hypoplasia quantitatively studied to establish an in vivo "anatomic profile" of the hypoplastic optic nerve, or to correlate the degree of dysplasia with visual function. Furthermore, the true incidence of associated midline brain defects has not been established in a large consecutive series of patients with optic nerve hypoplasia.

With the advent of ultrasonography and computed tomography, the size of the optic nerves can be determined and the presence of associated midline brain defects can be detected in a noninvasive and atraumatic manner. Visually evoked potential studies may also be useful in determining gross visual function in the infantile and preliterate patients.

The purpose of this investigation is to quantitatively study a large group of patients with optic nerve hypoplasia in order to more precisely determine the degree of dysplasia (hypoplasia) and its relationship with visual function, and to determine the frequency of coincidence of anterior midline brain defects and dysfunction. It is furthermore the purpose of this study to review possible teratogenic, intrauterine environmental and genetic factors that may have a pathogenic role in the development of these correlated congenital defects. A final purpose is to develop a co-

*Totally supported by an unrestricted grant from Research to Prevent Blindness, New York City.

hesive classification system for this spectrum of the septo-optic pituitary dysplasia syndrome.

REVIEW OF HISTORICAL BACKGROUND

For the sake of preserving chronologic documentation as well as established nomenclature, the syndrome of septo-optic-pituitary dysplasia will be treated as separate components. Furthermore, segmental or incomplete optic nerve hypoplasia will be treated as separate from diffuse or complete optic nerve hypoplasia in order to preserve its own unique historical background.

The earliest descriptions of optic nerve hypoplasia are attributed to Newman[1] (1864) and to Briere[2] (1877), but these two recorded descriptions are too incomplete to adequately distinguish between aplasia (absence) and hypoplasia (underdevelopment) of the optic nerves.

In 1884, Magnus[3] described a small pale optic nerve with presence of the retinal vessels in one eye of a small child. The child had no apparent useful vision in that eye. This case presentation is therefore the first to completely describe all the characteristics of optic nerve hypoplasia.

During the next 50 years isolated case reports appeared in the medical literature, recording an additional 15 cases of optic nerve hypoplasia.[4]

In 1941 Scheie and Adler[5] described complete aplasia (absence) and partial aplasia (hypoplasia) of the optic nerves. They described a 3-year-old male child with congenital blindness, fixed and unreactive pupils, wandering nystagmus, and small, pale optic discs with normal retinal vasculature. They proposed that the embryogenesis was a fetal developmental arrest of the primary mesoderm in aplasia, and of the ganglion cell layer in hypoplasia.

In 1941 Reeves[6] first reported the association of optic nerve hypoplasia and absence of the septum pellucidum in a 7-month-old infant with congenital blindness and otherwise normal development. The pupillary reflexes were absent and the optic nerves were small and pale, described as "aplastic." Pneumoencephalography demonstrated absence of the septum pellucidum.

In 1956 De Mosier[7] described the necropsy findings of a patient with hypoplasia of the optic nerves and agenesis of the septum pellucidum and defined this as "septo-optic dysplasia." Within six years he accumulated 36 cases of septum pellucidum agensis, nine of which demonstrated an associated optic nerve hypoplasia.[8]

In 1966 Helveston[9] reviewed the literature on optic nerve hypoplasia, which revealed a total of 22 cases, half of which were unilateral. He also described an additional unilateral case.

In 1970 two reports appeared in the literature describing 45 new cases of optic nerve hypoplasia, indicating that this condition was not so rare an anomaly as it previously had been considered. Edwards and Layden[10] described 25 patients with optic nerve hypoplasia, 14 bilateral and 11 unilateral. The male to female ratio was 19:6. Nystagmus was present in eight of the 14 bilateral cases, and esotropia was present in seven of the 10 unilateral cases. Seven of the 14 bilateral cases demonstrated clinical evidence of CNS disease, including cerebral palsy, seizure disorders, and mental retardation. Only one of the 11 unilateral cases had suggestive evidence of CNS disease. Radiographic studies of the optic foramina were performed in nine cases and considered to be unhelpful in the diagnosis. There were no familial occurrences and no elicited history of maternal exposure to drugs or known toxins.

In the same year Walton and Robb[11] described 20 cases of optic nerve hypoplasia, 12 of which were bilateral. Eleven of the 12 bilateral cases had an associated nystagmus and all eight of the unilateral cases had associated strabismus. The male to female ratio of occurrence was 12:8. Notably, 15 of the 20 patients were first-born children of otherwise healthy mothers. No associated neurologic or general physical defects were reported. The optic discs were described as small and pale and frequently demonstrated a "double ring" sign with the small disc surrounded by a pale halo bordered on either side by a rim of pigment.

Also in 1970, Hoyt et al[12] first described the association of pituitary dwarfism with septo-optic dysplasia and reported nine patients with these associated findings. Pneumoencephalography was performed on three of the children and absence of the septum pellucidum was demonstrated in all three.

Also in that same year, Kaplan and co-workers[13] described six patients with optic nerve hypoplasia, midline brain defects, and pituitary dwarfism. The findings included congenital diabetes insipidus in two; bilateral optic nerve hypoplasia in all six; pendular nystagmus in five; inconstant and irregular field defects in five; and documented growth hormone deficiency in six with multiple trophic hormone deficiencies in four. Pneumoencephalography was performed in four and demonstrated absence of the septum pellucidum in three. They ascribed the hypopituitarism to a diencephalic defect resulting in deficiency of hypothalmic-hypophysiotropic factors.

These studies were reconfirmed over the next several years,[14-17] more clearly defining the septo-optic pituitary dysplasia syndrome.

Wilson et al[18] recently suggested a primary hypothalamic defect as the cause of hypopituitarism, utilizing releasing hormone studies.

Clark and Meyer[19] emphasized the importance of recognizing neonatal hypoglycemia and seizures, in association with congenital blindness, as a characteristic presentation of septo-optic-pituitary dysplasia in infancy. They reviewed eight cases of this syndrome, and hypoglycemia was present in five.

The concept of segmental (partial or incomplete) optic nerve hypoplasia has been alluded to for a number of years, but especially since the report by Schwartz[20] in 1915. He described a patient with bilateral optic nerve hypoplasia, 20/40 vision, and binasal hemianopic field defects. He postulated an isolated failure in development of the uncrossed nerve fibers.

In 1923 Cords[21] described a patient with unilateral optic nerve hypoplasia with loss of the central field and preservation of the peripheral field, suggesting dysplasia of the maculopapillar fibers.

In 1930 Vellhagen[22] described a unilateral case with nasal field loss only.

In 1947 Missiroli[23] described three siblings with bilateral optic nerve hypoplasia and binasal visual field defects.

In 1972 Seely and Smith[24] reviewed 12 cases of optic nerve hypoplasia with documented visual field defects. Seven of these were bilateral, with binasal field defects in four, nasal in one, temporal in one, and generalized constriction in one. The five unilateral cases demonstrated nasal field defects in three, temporal in one, and central in one. In four cases of their own, three were bilateral, all three showing centrocecal defects. The unilateral case showed temporal field loss.

In 1972 Hoyt and colleagues[25] expanded the concept of segmental optic nerve hypoplasia with the description of three patients with "homonymous hemioptic hypoplasia" of the optic nerves. The three patients had spastic paralysis, epilepsy, hemiatrophy of the limbs, and homonymous hemianopsia. The optic nerves were described as slightly small with loss of the corresponding homonymous retinal nerve fiber pattern. They proposed that this represented congenital retrograde axonal degeneration leading to hemihypoplasia of the optic nerves, resulting from damage to the optic tract or radiation or both.

Frisén and Holmegaard[26] also reported a similar case with hemihypoplasia and widespread congenital neurologic defects. They too emphasized the disparate spectrum of optic nerve hypoplasia and described a wide range of both functional and anatomic defects.

In 1977 Petersen and Walton[27] speculated on the relationship of the "tilted disc syndrome" with segmental optic nerve hypoplasia. They described 17 children, all born of diabetic mothers, who exhibited segmental optic nerve hypoplasia with normal visual acuity and with visual

field defects corresponding to the hypoplastic area of the disc. Thirteen of the 17 were bilateral. Visual fields were obtained in eight children, all demonstrating inferior altitudinal or sector defects. The nerve heads were described as showing superior truncation or tilting.

The history of the "tilted disc syndrome" also dates back almost 100 years.

In 1882 Fuchs[28] described the inferior conus of the optic nerve and its frequent association with situs inversus of the disc.

In 1922 von Szily[29] noted that in association with the conus, the lower portion of the retina was less pigmented and that the refractive error in this same area was more myopic.

In 1936 Ziering[30] correlated distinctive upper and temporal field defects in these patients with the tilted disc, inferior conus, and ectasia of the fundus.

In 1946 Rucker[31] described six patients with the tilted disc-conus-ectasia of the "choroid" with bitemporal field defects. He emphasized that the field defects often extended somewhat into the upper nasal quadrants and thus were distinguishible from true bitemporal defects caused by chiasmal lesions.

In the 1960s several articles described the refractive nature of these visual field defects.[32-34] As the myopic correction corresponding to the area of the fundus ectasia was increased, the scotoma decreased in most cases. In the few patients who did not improve with increased myopic correction, an additional increase in target size essentially eliminated the field defect. It was therefore assumed that in some cases the functional capacity of the hypoplastic area was less than in the adjacent fundus.

In 1973 Graham and Wakefield[35] described 16 patients with tilt-conus-ectasia syndrome with bitemporal field defects. Visual acuity was generally good in all patients. They could not demonstrate the refractive relativity of the field defects in the majority of their patients. They postulated two causes for the field defects. In those few patients who demonstrated a "refractive" field defect, where increasing the myopic correction decreased the size of the field defect, the defect is one of localized ectasis. In the majority of their cases where the field defect did not improve with increased myopic correction, stretching of the photoreceptors may have been responsible. Furthermore, in cases where the variable myopia of the fundus is not observed, a localized hypoplasia of the retina or optic nerve may have been responsible.

In 1976 Young et al[36] described a similar series of patients and were able to obtain the eyes of one patient at autopsy. The patient had also demonstrated the tilt-conus-ectasia syndrome with upper altitudinal field

defects. The retina, choroid, and optic nerve histologically appeared normal, and no apparent cause for the upper altitudinal field defects could be demonstrated.

In 1978 Dorrell[37] studied 60 tilted discs demonstrating the crescent, depression of one side of the disc, and the oblique direction of the retinal vessels as they entered the eye. The direction of the tilt was nasally in 36 eyes (60%), downward in seven (12%), and inferotemporally in 17 (28%). With the aid of intense red-free light and both color and stereoscopic photographs, fewer nerve fibers appeared to enter the optic nerve head in the sector related to the crescent. He found that the visual field defects corresponded to the direction of the tilt and suggested this provided further evidence of diminished axons. He further suggested that contraction of the scleral canal over a segment of the optic disc circumference and the paucity of nerve fibers entering this segment of the nerve are features shared by the tilted discs and hypoplastic optic nerves.

The association of tilted optic nerves and craniofacial anomalies was recently described by Margolis and Siegel.[38] They described nine patients with the optic nerve tilt-conus-ectasia syndrome in association with hypertelorism, Crouzon's disease, and Apert's disease.

REVIEW OF EMBRYOLOGY

By the 2.6-mm stage of embryonic development, the optic pits are visible on each side of the anterior end of the neural canal. The optic pits grow rapidly and by the 4-mm stage form the hollow optic vesicles that are connected with the lumen of the neural canal by the optic stalks.

At the 4.5-mm stage the fetal fissure forms by invagination of the optic vesicles in a ventrolateral position. The outer wall, which is to become the retina, has by this time increased to several cell layers in thickness. At the 5.5-mm stage, through further invagination of the fetal fissure, these cells have nearly come in contact with the posterior layer of the optic vesicle, which is later to become the retinal pigment epithelial layer.

At this stage the fetal fissure extends from the ventrolateral portion of the margin of the optic cup into the optic stalk. The point where the fissure ends on the stalk marks the point of future entrance into the optic nerve of the central retinal vessels, which are in the process of developing from paraxial mesoderm, which in turn has already invaded this groove and filled the optic cup. They represent the hyaloid vascular system running through the upper part of the fetal fissure at the site of the future optic disc, and forward to the posterior surface of the lens. Progressive invagination of the cup and elongation of the stalk continue.

At the 10-mm stage the fetal fissure begins to fuse, first in the midzone and then extending proximally toward the posterior pole and distally to the margin of the cup. The proximal end does not close entirely, for the hyaloid vessels and their mesodermal sheaths have grown into the optic cup and have formed the primitive optic papilla.

At the 17-mm stage the retinal ganglion cells develop and send dendritic processes into the papilla, which already contains the hyaloid vessels. These dendrites then proceed through the papilla into the groove in the optic stalk and along the undersurface toward the brain, reaching the chiasm at the 18-mm stage.[39]

The anterior wall of the diencephalon forms the lamina reuniens between the 16- and 22-mm stages. It is from this area that later the septum pellucidum and other midline structures arise at approximately the 145-mm stage. Development of the septum pellucidum depends also on the normal expansion of the hemispheres and development of the corpus callosum.

The anterior lobe of the pituitary develops from pharyngeal ectoderm (Rathke's pouch) in the 4- to 6-mm stage. Between the 5- to 9-mm stages Rathke's pouch comes in contact with the floor of the diencephalon and loses its pharyngeal attachment during the 11- to 14-mm stage. The posterior lobe (neurohyphophysis) develops as an invagination in the floor of the diencephalon during the 8- to 11-mm stage and is identifiable as a distinct structure by the 14-mm stage. The anterior pituitary invests the infundibulum and posterior pituitary beginning at the 22-mm stage and is completed by the 170-mm stage.[40]

The embryogenesis of optic nerve hypoplasia is uncertain, and perhaps as multifarious as its clinical expression. Within the framework of currently accepted developmental stages, three major embryogenic theories have evolved.

When occurring as an isolated ocular defect, it appears that primary failure of the ganglion cells occurs between the 12- and 17-mm stages.[5]

When optic nerve hypoplasia occurs in association with CNS anomalies, two other embryogenic theories have been proposed.[41] First, normally developing ganglion cells that reach a malformed chiasm at the 18-mm stage cannot proceed across the midline into the opposite tracts, and thereafter undergo retrograde degeneration. The second hypothesis suggests that the hypoplasia results from stretching of the optic nerves during abnormal development of the cerebral hemispheres and ventricular system, with retrograde degeneration of the ganglion cells of the retina. It is further proposed that developmental arrest may occur even later in those cases in which mainly uncrossed fibers are affected, these

fibers normally growing along the optic nerve at a later time than the crossed fibers.

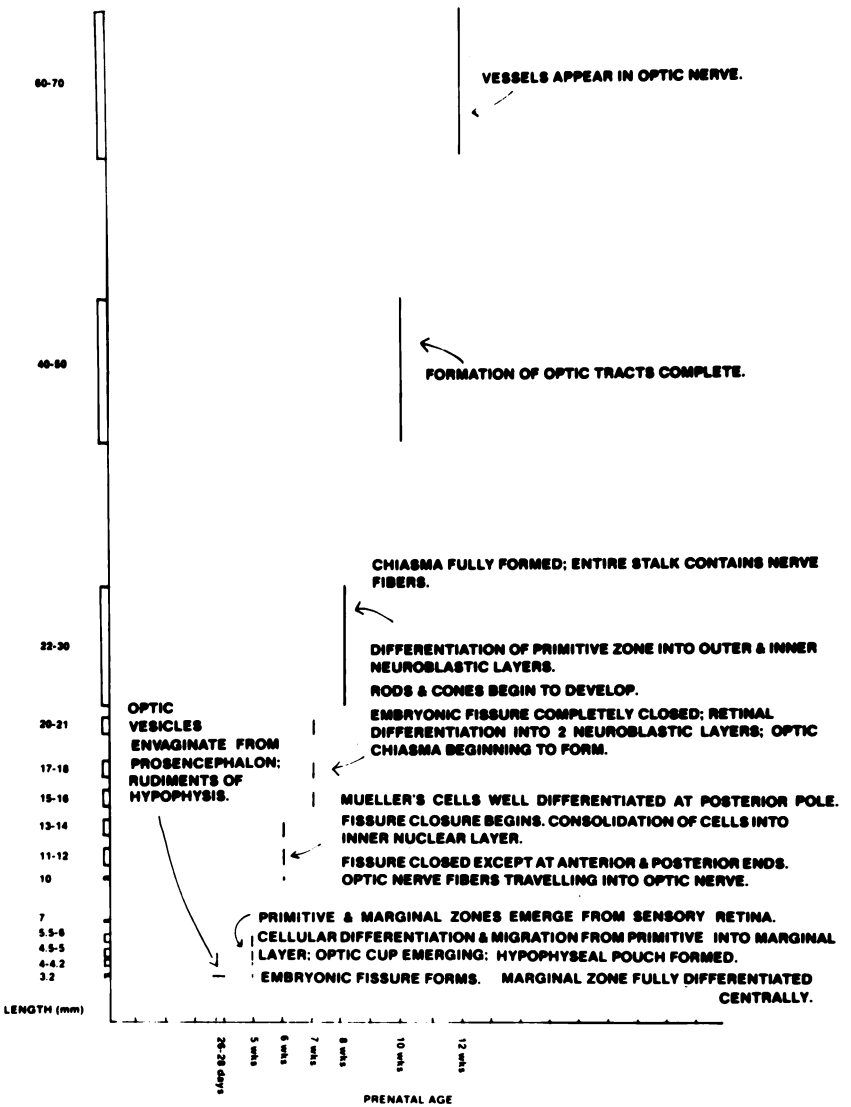
Hotchkiss and Green[42] postulated that optic nerve hypoplasia may result from an insult suffered by a normally developing system occurring any time between the sixth week and the fourth month of gestation. The manifestations of this insult would depend on the point in time at which the trauma was sustained and the structural importance of the damaged developing area to the maturing ocular structures. Associated CNS abnormalities described with optic nerve hypoplasia indicate there may also be a relatively wide period of tissue susceptibility during which significant disruption of the developing ocular system may occur (Fig 1).

REVIEW OF HISTOPATHOLOGY

In 1926 Szymanski[43] reported the occurrence of optic nerve hypoplasia in one eye of a cat. He described the essential histopathologic finding of absence of ganglion cells and nerve fiber layer with a small hypoplastic optic nerve.

In 1962 Hogan and Zimmerman[44] reviewed five cases of optic nerve hypoplasia on file in The Registry of Ophthalmic Pathology, Armed Forces Institute of Pathology. None of the five cases occurred as an isolated congenital anomaly. Associated defects included anencephaly (three cases), hydranencephaly with absence of the cerebral hemispheres (one case) and multiple ocular anomalies (one case). Consistent findings in all cases were marked paucity or absence of the ganglion cell layer of the retina, absence of the nerve fiber layer, and absence of axis cylinders in the optic nerve. The retinal vasculature was normal in all five cases.

In 1963 the first clinical-pathologic study of optic nerve hypoplasia was reported by Whinery and Blodi.[45] They described a 70-year-old woman with a blind right eye who had been followed for 37 years. The eye demonstrated a deep coloboma involving an anomalous nerve head, attenuated retinal vessels, pigmentary degeneration of the retina, and choroidal atrophy. The eye was blind and there was no direct pupillary response. The anterior chamber was noted to be shallow in 1958. In September 1960, the patient had the sudden onset of pain. The eye was injected and the intraocular pressure was 57 mm Hg. The pressure could not be reduced and the eye was enucleated two days later. Histologic examination demonstrated keratitis and iris necrosis with peripheral synechia. The peripheral retina was normal. In an abrupt transitional zone in the posterior one fourth of its extent, the retina lost its normal structure and there was absence of the "visual cell layer." Nasal to the disc was an



NORMAL OCULAR DEVELOPMENTAL MILESTONES

FIGURE 1

old chorioretinal scar. From there to the disc the retina was atrophic, hyalinized, and gliotic with only the outer nuclear area remaining. The same retinal changes were noted temporal to the disc. The entire posterior pole showed pigmentary degeneration of the retina and choroid. The ganglion cells were sparse throughout the retina. The physiologic cup of the optic nerve was replaced by a deep cavity filled with glial elements. No true cribriform plate could be identified and only a few nerve fibers crossed into the optic nerve. The nerve itself was disorganized and consisted mainly of glial elements. No true sheaths of the optic nerve were present and the orbital fat was in direct contact with the nerve.

In 1976 Young et al[36] presented a clinical-pathologic report of the optic nerve tilt-conus-ectasia syndrome. They describe a 60-year-old woman who was confined to a mental hospital and was examined prior to her death from generalized metastatic carcinoma. She had bilateral tilted discs with inferior crescents, ectasia of the lower fundus, and superior altitudinal visual field defects. The eyes were obtained at autopsy and serial vertical sections were prepared. The optic nerves showed forward displacement of the disc tissue superiorly, while inferiorly the retinal pigment epithelium and choroid were displaced away from the disc, forming a conus or crescent. The sclera appeared thinner below than above, suggesting an ectasia. On serial sections of each globe, the entire retina, retinal pigment epithelium, and choriocapillaris appeared normal. There were fewer larger choriodal vessels below than above. They could demonstrate no apparent cause for the visual field defects.

Mosier, et al[46] described the clinical-pathologic report of a 9-month-old infant with hydranencephaly and optic nerve hypoplasia. The infant showed amaurotic eye movements with nystagmus, and there was no pupillary reflex. Both optic nerves were small and pale with the "double ring" sign. The retinal vessels were normal. The baby died of meningoperitonitis. Histologically the retina demonstrated total absence of ganglion cells and nerve fiber layers with normal outer nuclear areas. The optic nerve demonstrated circumferential encroachment by the retina and choroid with intrusion of the retinal pigment epithelium over the lamina cribrosa.

In 1979 Hotchkiss and Green[42] presented the clinical and histopathologic features of 22 cases (35 eyes) with optic nerve hypoplasia. Autopsy data was correlated in 18 of the 22 cases, and in four intstances the eyes were surgically obtained. Seventeen of the 18 autopsy cases were stillborn and 12 of these were anencephalic. The configuration of the optic nerve head varied considerably. In some the retinal pigment epithelium extended over the edge of the nerve head with a prominent scleral-

laminar junction, forming the "double ring sign." In others there was normal termination of the retinal pigment epithelium at the disc margin. The nerve fiber content of the optic nerves also varied. In 77% of the eyes studied there was a variable number of glial elements only. The other 23% showed the presence, but reduced number, of nerve fibers in the optic nerve. Retinal ganglion cells were absent in 54% of the eyes and present in reduced number in 40%. One bilateral case showed a nearly normal complement of ganglion cells. In 66% of the eyes no nerve fiber layer could be detected and the remaining eyes showed a reduced number. The retinal vessels were considered to be normal in 80% of the eyes and less than full complement in 20%. A posterior choroidal coloboma was present in 17% of the eyes. Persistent remnants of the hyaloid vascular system were present in 37% of the eyes. The maternal history revealed an incidence of hydramnios in 33%, significant illness during pregnancy in 33%, and a history of drug exposure in 22%. The median maternal age was 25 years. Thirty-three percent of the mothers were primipara. Sixty-four percent of the 22 cases were female and 64% of the cases were bilateral.

REVIEW OF PATHOGENESIS

Little is known about specific factors responsible for the developmental defect in optic nerve hypoplasia. Two primary modes of transmission have been proposed for possible causative factors: (1) a genetic alteration and (2) alteration of the intrauterine environment by maternal metabolic or toxic stress.

Genetic factors have been implicated basically by three recurring observations in patients with optic nerve hypoplasia: familial occurrences, young maternal age, and an increased incidence of the first-born child being affected.

Alteration of the intrauterine environment by potential teratogenic factors has been suggested in an increased incidence of maternal drug ingestion, maternal diabetes, and fetal exposure to certain viruses.

GENETIC FACTORS

Familial Occurrences—In 1947 Missiroli[23] described three siblings (two sisters and one brother) with bilateral optic nerve hypoplasia and binasal field defects. Both parents were normal and noncosanguineous, and there was no relevant family history. No mechanism of transmission was postulated.

In 1961 Kytilä and Miettenin[47] reported two affected brothers with bilateral optic nerve hypoplasia in an otherwise normal and noncosanguiñeous family. No mechanism of transmission was postulated for this sibling occurrence.

In 1975 Hackenbruch et al,[48] described five members of a family, spanning four generations, with bilateral optic nerve hypoplasia. Three family members were examined and two were deceased. From family records, it was presumed that the two deceased members were affected. The three patients examined had defective vision, nystagmus, and small, pale optic nerves. The proposed mechanism of transmission was that of an autosomal dominant trait, but the same clinical expression could also have been inherited as an autosomal recessive trait.

Young Maternal Age—In 1978 Huseman,[49] described the coincidence of young maternal age and the septo-optic-pituitary dysplasia syndrome.

Elster and McAnarney[50] reviewed nine reported cases of septo-optic-pituitary dysplasia and found a mean maternal age of 18 years.

Lippe et al,[51] found that the mean maternal age in another series of 14 patients with septo-optic-pituitary dysplasia was 19.25 years, with a comparative population mean age of 24.7 years.

Van Dyk[52] pointed out the similarity of the young maternal age data in septo-optic-pituitary dysplasia with the data regarding spontaneous abortions in young mothers with the monosomy X (X O karyotype) chromosomal anomaly. He cited two patients of his own with optic nerve hypoplasia born to 16-year-old mothers.

Incidence of First-Born—In 1970 Walton and Robb[11] described 20 cases of optic nerve hypoplasia, 15 of which were first-born children. The growth and development pattern was essentially normal in all the patients.

In 1980 Krause-Brucker and Gardner[53] reported five children with septo-optic-pituitary dysplasia, all of whom were the first-born.

ALTERATION OF INTRAUTERINE ENVIRONMENT

Maternal Drug Ingestion—In 1966 McKinna[54] described four cases of optic nerve hypoplasia in children born of mothers who had ingested large amounts of quinine as an abortive agent during the first trimester of pregnancy. All four patients were blind and one was also deaf.

In 1978 Hoyt and Billson[55] described seven children with optic nerve hypoplasia born of epileptic mothers receiving the anticonvulsant pheny-

toin. Four of the children also had systemic anomalies including cleft palate, ventriculoseptal heart defects, microcephaly, and hypoplastic kidneys. Two of them also had siblings with systemic anomalies.

Diabetes—The association of optic nerve hypoplasia and maternal diabetes was reported by Petersen and Walton[27] in 1977. Out of a total of 93 patients with optic nerve hypoplasia, 17 were born of diabetic mothers. There were three sets of siblings totalling nine patients in this study group. Fifteen of the 17 cases were bilateral. Almost all had good vision and demonstrated the optic nerve tilt-conus-ectasia form of segmental optic nerve hypoplasia.

Viral Infections—In 1973 Bistner, et al[56] described the occurrence of optic nerve hypoplasia in newborn cattle infected with the bovine diarrhea-mucosal disease virus.

In 1976 Hittner, and colleagues[57] described four infants with cytomegalovirus infection and optic nerve anomalies: two with optic nerve hypoplasia, one with a partial coloboma, and one with microphthalmia and a total coloboma. All the anomalies were unilateral. Two of the mothers were diabetic, and one of these had previously given birth to a blind infant with congenital heart disease.

SUBJECTS AND METHODS

Sixty-two patients with the diagnosis of optic nerve hypoplasia were identified in the state community from the diagnostic files of this institution, the State School for the Blind, and the State Department of Visual Services. Fifty of these patients could be located and contacted, 45 of whom were willingly recalled for study.

The study protocol included complete ocular and general physical examination with anthropometric profile and maternal history; electrophysiologic testing including electroretino-oculography and visual evoked potential; and echographic measurements of the optic nerves and computed axial tomography of the optic nerves and brain, with special emphasis on the midline brain structures. Neuroendocrine evaluation was obtained when deemed appropriate from the general clinical evaluation and the anthropometric growth and development profile. The protocol was followed as completely as possible with few exceptions, and these exceptions usually were because of lack of cooperation due to age or gravity of the patient's health.

Optic nerve diameter measurements were made with the Bronson A-scan in both the horizontal and vertical planes. For the horizontal diameter the probe was placed near the temporal equator and the beam directed posteriorly. The beam was angled and shifted slightly in order to display a clear-cut defect in the orbital pattern, which corresponded to the optic nerve. Steeply rising, maximally high, double-peaked surface spikes on each side of the optic nerve indicate that the ultrasound beam is perpendicular to the surface of the nerve. The display of a maximally wide defect with such borders indicates the maximal width of the nerve. It was then measured on echogram photos with an electronic measuring scale calibrated in milliseconds and converted to millimeter values from a conversion table. The vertical diameter of the optic nerve was similarly measured with the probe placed inferiorly (Fig 2).

The computed tomographic studies were performed with the Varian V-360-3 CT scanner; and 12-second, high-resolution axial sections were taken through the orbits from floor to roof at 5-mm intervals along the canthomeatal plane. Scanning was continued through the brain to the vertex along the same plane with three-second exposures at 1-cm intervals. Magnification reconstructions of the optic nerve images were done and computer measurements made. Axial (horizontal) optic nerve diameters were obtained at the scleral level, midorbital, and at the apex of the orbit near the adit of the optic canal. Special attention was given to the midline brain structures, particularly the chiasm, diencephalon, mesencephalon, corpus callosum, and septum pellucidum.

The echographic area of the optic nerve was then calculated by the formula for determining the area of an ellipsoid, $\pi\ a \cdot b$; where a equals one-half the horizontal diameter and b equals one-half the vertical diameter. These area calculations were then compared with normal control figures (matched by general age groups), and expressed as a decimal ratio of normal. For example, if the nerve under study measured 2.30 × 2.36 mm, the optic nerve area would equal 3.14 × 1.50 × 1.18, or 5.5 sq mm. The matched normal control optic nerve measurements are horizontally 3.36 ± 0.33 (2 SD) and vertically 3.42 ± 0.35 (2 SD). The normal echographic area range therefore is from 7.25 to 10.92 mm with a mean normal area of 9.02 sq mm. The decimal ratio of normal for this particular patient would therefore equal 5.55 ÷ 7.25 or 0.76, using the lower limit of the normal range.

The computed axial tomographic diameter of the optic nerve was undimensional (horizontal) and was not corrected for magnification factor. It was also compared with a control normal optic nerve CT diameter with a normal range of 5.8 to 6.2 mm. Using the same example patients, the CT

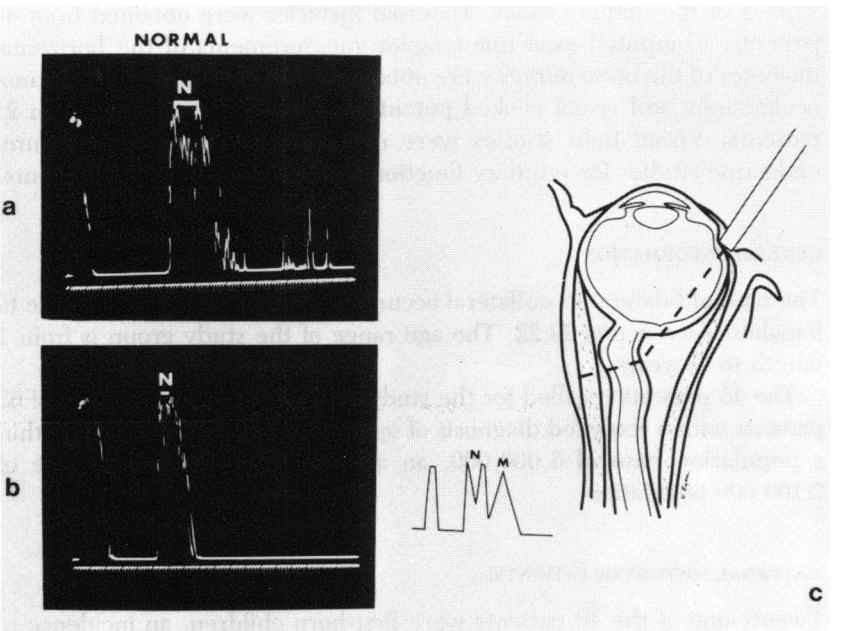


FIGURE 2
Optic nerve measurements: a, normal A-scan echogram; b, A-scan echogram of hypoplastic optic nerve; c, schematic illustration of ultrasound technique.

diameter measured 4.5 mm; therefore the decimal ratio of normal equals 4.5 ÷ 5.8, or 0.78.

Electroretinograms and visual evoked potentials were performed with the Nicolet CA-1000 averager and the Grass PS 22 photostimulator. Chloral hydrate sedation was routinely used in all the children under 5 years of age. Electro-oculograms were not performed on any patient under the age of 5 because of lack of cooperation.

Growth and development profiles were established on each child up to 3 years of age using the National Center for Health Statistics profile and the Denver Developmental Screening Test.

RESULTS

The total of 45 patients with optic nerve hypoplasia provides the subject base for this study. All 45 patients had complete ocular and general physical examinations; echographic measurements of the optic nerve diameters, horizontally and vertically; and computed axial tomographic

studies of the midline brain. Maternal histories were obtained from 40 patients. Computed axial tomographic measurements of the horizontal diameter of the optic nerves were obtained in 21 patients. Electroretinooculography and visual evoked potential studies were performed on 21 patients. Visual field studies were obtained on 17 patients. Neuroendocrine studies for pituitary function were performed on six patients.

GENERAL INFORMATION

The ratio of bilateral to unilateral occurrence is 40:5. The ratio of male to female occurrence is 23:22. The age range of the study group is from 1 month to 59 years.

The 45 patients recalled for the study were obtained from a total of 63 patients with a recorded diagnosis of optic nerve hypoplasia, from within a population base of 3,000,000, an approximate overall incidence of 2:100,000 population.

MATERNAL HISTORY (40 PATIENTS)

Twenty-one of the 40 patients were first-born children, an incidence of 52%.

The mean maternal age was 23.8 years, compared with a mean maternal age of 24.6 years in the general population of the state.

Five of the 40 were born to diabetic mothers, an incidence of 12.5%.

Significant illnesses or specific complications of pregnancy occurred in six cases (15%), including preeclampsia (two), hypertension (two), and kidney infection (two).

An admitted history of drug ingestion was reported in five cases (12.5%). In only one case, though, was the ingestion of an abortive agent recorded, and it was possibly quinine.

VISUAL FUNCTION

Twenty-one of the 45 patients were infants or preliterate children in whom only gross estimation of visual function could be made. Ten of these 21 (47%) appeared to have bilateral involvement with no light perception (response) or observable visual attention. Eight (38%) demonstrated varying degrees of visual attention or light responsiveness with bilateral involvement. Two demonstrated unilateral optic nerve hypoplasia with evidence of marked amblyopia in the involved eye. One had bilateral optic nerve hypoplasia with visual attention (response) in one eye

and not in the other. Electrophysiologic testing was done in all 21 of these children. The electroretinographic and electrooculographic studies were essentially normal in all patients tested. Visual evoked potential studies were also performed on all 21 patients in this age group. They were unrecordable in the ten patients without light perception or responsiveness and in the involved one eye of the two children with unilateral optic nerve hypoplasia, also without light perception or response. They were recordable in the remaining eight patients. The direct pupillary responses also were absent in the ten children without light perception bilaterally and present from mininal to normal response in the remaining 11 children (Tables I and II).

There were 24 patients in the literate age group. Visual acuity ranged from 20/30 to no light perception. Three of the 24 patients had no light perception bilaterally. Three patients had unilateral optic nerve hypoplasia with 20/20 vision in the normal eye and no light perception in the involved eye. Visual field studies were obtained on 17 of these patients and demonstrated bitemporal defects in seven, generalized constriction in six, central defects in one, binasal defects in one, and altitudinal defects in two. In the three unilateral cases the visual fields were normally full in the uninvolved eye and not obtainable in the involved amblyopic eyes in two; the third showed a central defect.

Six of these 24 patients demonstrated the vertical tilt-conus-ectasia syndrome, and three others the horizontal tilt-conus syndrome. One vertical tilt and one horizontal tilt patient were unilaterally affected and both eyes were deeply amblyopic. Five of the seven bilateral cases had visual acuity of 20/20 to 20/40 and two were in the 20/100 to 20/200 range. In this group of patients visual field studies were obtained in five patients, and the field defects invariably corresponded to the direction of tilt. Three patients with the inferior tilt-conus-ectasia demonstrated upper and predominantly temporal field defects that extended somewhat into the upper nasal quadrant. One patient with a superior tilt demonstrated lower altitudinal field defects. One patient with bilateral nasal tilt of the nerves demonstrated lower bitemporal field defects. One patient with bilateral temporal tilt of the nerves and 22 diopters of myopia demonstrated binasal field loss (Tables III and IV).

Also one patient with the tilt-conus-ectasia syndrome demonstrated an associated scaphocephaly.

OPTIC NERVE MEASUREMENTS

Echographic measurements of the horizontal and vertical diameters of the optic nerves and calculation of the optic nerve area were made on all 45

Table I
CLINICAL DATA

Patient	Age	Sex	Laterality		Gross Vision		Pupils		Nystagmus	Strabismus	Maternal History			General Medical Status
			OD	OS	OD	OS	OD	OS			gravida	age	illnesses	
1	2 1/2 yr	M	x	x	p	p	p	p	p	p				
2	3 1/2 yr	M	x	x	a	a	a	a	p	p	1	17		hypopituitarism
3	3 1/2 yr	M		x	p	a	p	a	a	p	3	25		hypopituitarism
4	1 yr	M	x	x	p	p	a	p	p	p	1	22		
5	5 mo	M	x	x	a	a	a	a	p	p	1	20		
6	6 mo	M	x	x	p	p	p	p	a	a	2	24		
7	2 mo	M	x	x	a	a	a	a	p	p	1	17		
8	3 1/2 yr	M	x	x	a	a	a	a	p	a	1	19	diabetes	neonatal seizures, hypoglycemia, hypopituitarism
9	3 mo	F	x	x	a	a	a	a	p	a	3	36		neonatal seizures, hypoglycemia, hypopituitarism
10	5 mo	M	x	x	a	a	a	a	p	a	2	20		
11	5 mo	F	x	x	a	a	a	a	p	a				cerebral palsy
12	2 yr	M	x	x	p	p	p	a	p	p	1	24		
13	4 mo	F	x	x	p	p	p	p	p	p	3	32		
14	2 mo	F	x	x	a	a	a	a	p	a	3	25	preeclampsia	hydrocephalus
15	3 mo	M	x	x	a	a	a	a	p	a	1	23		
16	1 yr	M	x	x	p	p	p	p	p		1	22	hypertension	
17	2 yr	F	x	x	p	p	p	p	p		1	22		
18	1 yr	F	x		p	a	p	a	a	a	1	20		prematurity
19	1 mo	F	x	x	a	a	a	a	p		1	17		
20	2 yr	F	x	x	p	p	p	p	a	a	1	24	diabetes	
21	14 mo	F	x	x	p	a	p	a	a	a	1		diabetes	

patients. The echographic areas ranged from 2.84 sq mm (decimal of normal 0.39) to 6.74 sq mm (decimal of normal 0.93) with a mean echographic area of 4.61 sq mm (decimal of normal 0.63). The nine patients with tilted nerves usually demonstrated a greater optic nerve area than the general group of optic nerve hypoplasia patients, but still less than a normal area. This group ranged from 4.41 sq mm area (decimal of normal 0.61) to 6.74 sq mm (decimal of normal 0.93) with a mean area of 5.44 sq mm (decimal of normal 0.75). The five unilateral cases had a mean echo-

Table II
ULTRASONOGRAPHY — TOMOGRAPHY DATA

	Ultrasonography						Tomography				
	Diameter (mm)		Area		Decimal		Diameter (mm)		Decimal		
Patient	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	Midline Defects
1	2.40 x 2.40	2.40 x 2.40	4.52	4.52	.62	.62					
2	2.41 x 2.70	2.40 x 2.70	5.11	5.09	.79	.78	4.0	4.0	.69	.69	absent septum pellucidum
3	2.30 x 2.70	2.30 x 2.70	4.87	4.87	.67	.67	3.8	3.8	.66	.66	absent septum pellucidum
4	2.30 x 3.10	2.30 x 3.10	5.60	5.60	.77	.77	5.3	5.0	.91	.86	
5	2.33 x 2.33	2.33 x 2.33	5.67	5.67	.78	.78	4.4	4.4	.76	.76	absent septum pellucidum
6	2.60 x 2.60	2.60 x 2.60	6.15	6.15	.85	.85	4.0	4.0	.69	.69	
7	2.17 x 2.17	2.25 x 2.25	3.70	3.97	.51	.55					suprasellar cyst, absent septum pellucidum
8	2.50 x 2.50	2.50 x 2.50	4.42	4.42	.61	.61	5.0	5.0	.86	.86	cerebral dysgenesis, absent septum pellucidum
9	2.10 x 2.20	2.10 x 2.20	3.63	3.63	.50	.50					third vent. divertic. absent septum pellucidum
10	2.70 x 2.70	2.40 x 2.40	5.72	4.52	.78	.62	4.0	4.0	.69	.69	absent septum pellucidum
11	2.33 x 2.00	2.33 x 1.94	3.66	3.55	.50	.49					third vent. divertic. absent septum pelludicum
12	2.70 x 3.10	2.70 x 3.10	6.67	6.67	.91	.91					
13	2.01 x 2.00	2.01 x 2.00	3.16	3.16	.44	.44					
14	2.70 x 2.70	2.70 x 2.70	5.72	5.72	.79	.79	4.4	4.4	.76	.76	hydrocephaly
15	2.71 x 2.71	2.71 x 2.71	5.76	5.76	.79	.79					
16	2.33 x 2.33	2.71 x 2.33	4.26	4.96	.59	.68	3.3	3.3	.57	.57	
17	2.88 x 2.88	2.75 x 2.75	6.51	5.94	.89	.82					
18	2.30 x 2.70	3.00 x 3.30	4.87	7.77	.67	1.00					absent septum pellucidum
19	2.55 x 2.70	2.60 x 2.60	5.38	6.15	.75	.85					
20	2.71 x 2.71	2.71 x 2.71	5.76	5.76	.79	.79	4.4	4.4	.76	.76	
21	2.33 x 2.33	3.33 x 3.33	4.26	8.65	.59	1.00					

graphic area of 5.12 sq mm (decimal of normal 0.71) in the involved eye and an echographic area in the normal eye of 7.57 sq mm (decimal of normal 1.0) (Tables 1 through 4).

Computed axial tomographic measurements of the horizontal diameter of the optic nerves were obtained in 21 of the 45 patients. They ranged

Table III
CLINICAL DATA

Patient	Age	Sex	Lateral		Vision		Pupils		Myopia	Tilt	Ectasia	Visual Fields	Maternal History			General Medical Information	Other Ocular Anomalies
			OD	OS	OD	OS	OD	OS					Grav Ids	Age	Medical History		
22	19	M	x	x	20/40	20/40	p	p	a	a		Lower bitemporal	1	21		growth retardation hypopituitarism	nasal tilt
23	8	F	x		NLP	20/20	a	p									vertical tilt OD
24	4	M	x	x	NLP	NLP	a	a	p	a			1	19			
25	8	F	x	x	20/100	20/100	p	p	a	a		general const.				cerebral palsy	myopia, tilt-conus-ectasia
26	33	M	x	x	20/400	20/40	a	p	p	p		upper bitemporal				growth retardation, hypopituitarism	
27	34	F	x	x	20/50	20/40	p	p	a	a		bitemporal					tilt-conus-ectasia
28	15	M	x	x	20/80	20/200	p	p	p	p		upper bitemporal	3	19			myopia, tilt-conus-ectasia
29	22	M	x	x	20/30	20/30	p	p	a	a		general const.	4	32			latent nystagmus
30	22	F	x	x	20/40	20/20	p	p	a	a		inferior alt.	1	21	dia betes		superior tilt-conus
31	5	F	x	x	NLP	NLP	a	a	p	p						epilepsy	
32	8	F	x	x	NLP	NLP	a	a	p	a			1	27			
33	14	F	x	x	20/400	20/20	a	p	a	a		upper alt.					inferior tilt-conus-ectasia coloboma
34	5	M	x	x	20/70	20/40	p	p	p	p			1	21		retarded	optic nerve tilt conus-ectasia
35	22	F	x	x	20/30	20/400	p	p	p	p		inferior nasal OU					superior-temporal tilt
36	13	F	x	x	20/30	20/100	p	p	a	a		general const.	3	20		retarded	scaphocephaly, Duane's Syndrome
37	40	F	x	x	20/40	20/40	p	p	a	a		lower bitemp.					optic nerve tilt-conus-ectasia
38	23	M	x	x	20/200	20/200	p	p	p	a		general const.				epilepsy	myopia
39	5	F		x	20/20	NLP	p	a	a	p							
40	6	F		x	20/400	20/40	p	p	a	a			1	18			
41	59	M		x	20/20	NLP	p	a	a	a		central defect					temporal tilt-conus
42	57	F	x	x	20/40	20/400	p	a	a	a		bitemporal					
43	8	M	x	x	HM	20/400	a	p	p	a		bitemporal	1	24			
44	26	M	x	x	20/200	20/200	p	p	p	a		general const.					
45	9	F	x	x	20/80	20/200	p	p	a	a		general const.	1	24	dia betes		temporal tilt

from 3.6 to 5.3 mm with a mean horizontal diameter of 4.2 mm. The normal control group ranged from 5.8 to 6.2 mm with a mean computed axial tomographic diameter of 6.0 mm, uncorrected for magnification (Tables I through IV).

The comparative data on echographic and computed tomographic optic nerve measurements is presented in Table V. It can be seen that the bidimensional echographic measurements are consistently greater than the unidimensional tomographic measurements, the difference varying from 1% to 48%. Because of the greater resolution and bidimensional recordings, one would assume that the echographic measurements are more precise. The potential factor of obliquity of projection exists for both modes of measurement, but is likely negated for statistical purpose by comparison with normal controls measured by the same techniques.

Table IV
ULTRASONOGRAPHY—TOMOGRAPHY DATA

	ULTRASOUND						TOMOGRAPHY				
Patient	Diameter (mm)		Area		Decimal		Diameter		Decimal		Midline Defects
	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	
22	2.70 x 2.70	2.70 x 2.70	5.72	5.72	.79	.79	4.0	4.0	.69	.69	Absent 1/3 septum pellucidum
23	2.70 x 2.70	3.00 x 3.10	5.72	7.32	.79	1.00	4.8	5.8	.68	1.00	
24	1.55 x 2.33	1.55 x 2.33	2.84	2.84	.39	.39	3.5	3.5	.60	.60	
25	3.00 x 2.30	3.00 x 2.30	5.42	5.42	.75	.75					
26	2.80 x 2.80	2.80 x 2.80	6.15	6.15	.85	.85					Absent anterior 1/3 septum pellucidum
27	2.80 x 3.00	2.80 x 3.00	6.59	6.59	.91	.91					
28	2.71 x 2.31	2.71 x 2.71	4.91	5.76	.68	.79	4.5	4.5	.78	.78	
29	2.71 x 2.71	2.71 x 2.71	5.76	5.76	.79	.79	4.5	4.5	.78	.78	
30	2.77 x 2.70	3.10 x 2.77	5.87	6.74	.80	.93	5.3	5.3	.91	.91	
31	2.33 x 2.33	2.06 x 2.06	5.67	3.33	.78	.46					
32	2.70 x 2.70	2.70 x 2.70	5.72	5.72	.79	.79	3.5	4.0	.60	.69	Absent septum pellucidum
33	3.02 x 2.02	3.02 x 2.02	4.79	4.79	.66	.66	4.0	4.2	.69	.72	
34	2.42 x 2.32	2.42 x 2.32	4.41	4.41	.61	.61	4.2	4.2	.72	.72	
35	2.70 x 2.70	2.70 x 2.70	5.72	5.72	.79	.79					
36	2.38 x 2.71	2.33 x 2.33	5.06	4.26	.70	.59	4.8	4.8	.83	.83	
37	2.30 x 2.70	2.30 x 2.70	4.87	4.87	.67	.67					
38	3.10 x 2.70	2.70 x 2.70	6.57	5.72	.91	.79					
39	3.00 x 3.20	2.33 x 2.33	7.53	4.26	1.00	.59	5.7	4.4	.98	.75	
40	3.08 x 3.08	2.71 x 2.33	7.44	4.96	1.00	.68					
41	2.99 x 3.10	2.65 x 3.05	7.15	6.40	1.00	.88					
42	2.80 x 3.00	2.60 x 3.00	6.59	6.12	.91	.84					
43	2.80 x 2.90	2.71 x 2.71	6.60	5.76	.91	.79					
44	3.10 x 2.70	2.70 x 2.70	6.57	5.92	.90	.79					
45	2.80 x 3.10	2.80 x 3.10	6.81	6.81	.93	.93					

COMPUTED AXIAL TOMOGRAPHY OF THE MIDLINE BRAIN

Computed axial tomographic studies of the midline brain structures were performed on all 45 patients. Twelve patients (27%) demonstrated midline anomalies and, specifically, partial or complete absence of the septum pellucidum. Three of the 12 also had other midline defects, including diverticulum of the third ventricle, optic vesicle cyst, and diffuse dysgenesis. None of the nine patients with the tilted optic nerve syndrome demonstrated a midline brain anomaly.

ASSOCIATED NEUROENDOCRINE DYSFUNCTION

Six of the 45 (13%) patients demonstrated associated neurologic defects, including epilepsy (two), cerebral palsy (two), and mental retardation (two).

Table V
COMPARISON OF ECHOGRAPHIC AND COMPUTED TOMOGRAPHIC MEASUREMENTS OF HORIZONTAL OPTIC NERVE DIAMETER

	Echographic Horizontal Diameters				Tomographic Axial Diameters				EDN /CTDN
	In mm		decimal of normal		In mm		decimal of normal		
Patient	OD	OS	OD	OS	OD	OS	OD	OS	
1	2.41	2.40	.80	.79	4.0	4.0	.69	.69	1.16
2	2.30	2.30	.76	.76	3.8	3.8	.66	.66	1.15
3	2.30	2.30	.76	.76	5.3	5.0	.91	.86	1.15
4	2.33	2.33	.77	.77	4.4	4.4	.76	.76	1.01
5	2.80	2.80	.92	.92	4.0	4.0	.69	.69	1.33
6	2.50	2.50	.83	.83	5.0	5.0	.86	.86	0.96
7	2.70	2.40	.89	.79	4.0	4.0	.69	.69	1.14
8	2.70	2.70	.89	.89	4.4	4.4	.76	.76	1.17
9	2.33	2.71	.77	.89	3.3	3.3	.57	.57	1.35
10	2.71	2.71	.89	.89	4.4	4.4	.76	.76	1.29
11	2.70	2.70	.89	.89	4.0	4.0	.69	.69	1.29
12	2.70	3.00	.89	.99	4.8	5.8	.61	1.00	1.46
13	1.55	1.55	.51	.51	3.5	3.5	.60	.60	0.85
14	2.71	2.71	.89	.89	4.5	4.5	.78	.78	1.14
15	2.71	2.71	.89	.89	4.5	4.5	.78	.78	1.14
16	2.77	3.10	.91	1.00	5.3	5.3	.91	.91	1.0
17	2.70	2.70	.89	.89	3.5	4.0	.60	.69	1.48
18	3.02	3.02	1.00	1.00	4.0	4.2	.69	.72	1.45
19	2.42	2.42	.80	.80	4.2	4.2	.72	.72	1.11
20	2.38	2.33	.79	.77	4.8	4.8	.83	.83	0.95
21	3.00	2.33	.99	.77	5.7	4.4	.98	.75	1.01

Six other patients in the study group demonstrated clinical evidence of pituitary hypofunction, including growth retardation in three and neonatal hypoglycemia with seizures in three. Four of the six patients received further neuroendocrine testing and all four demonstrated pituitary hypofunction, with diminished growth hormone (two), multiple trophic hormones (four), and hypoglycemia (two). One other case demonstrated borderline pituitary function but definite growth retardation at the age of

15. One of the six patients died before neuroendocrine studies were completed. All six of these patients had partial or total absence of the septum pellucidum demonstrated by computed axial tomography (Fig 3).

ASSOCIATED OCULAR ANOMALIES

Nystagmus was present in 21 cases, all with bilateral optic nerve hypoplasia. None of the optic nerve tilt patients demonstrated nystagmus. Seven of these 21 patients with bilateral optic nerve hypoplasia and nystagmus also had an associated strabismus.

Strabismus without nystagmus was present in two of the five unilateral cases.

Colobomas were present in three cases.

Latent nystagmus was present in one case, as was Duane's retraction syndrome in one and aniridia in one.

Scaphocephaly was present in one case of optic nerve hypoplasia with the tilt-conus-ectasia syndrome.

DISCUSSION

The prevailing opinion for almost a century (1864 to 1962) was that optic nerve hypoplasia was a rare and isolated ocular anomaly, characterized by a small, pale optic nerve and blindness.

During those almost 100 years, 18 cases of optic nerve hypoplasia were reported in the international literature.[4] By 1966, a review of the literature revealed 22 reported cases,[9] and until 1970 a total of 26 case reports had appeared.[11] Between the years 1970 and 1980 approximately 360 cases of optic nerve hypoplasia have either been reported or directly alluded to in the international literature. In this thesis I have referenced 290 cases, 205 of which are cited by four authors.[10,11,27-55] Another 69 cases have been documented in 18 unreferenced reports. This report will add an additional 45 cases for a total of 404 cases of optic nerve hypoplasia reported in approximately a ten-year span. The alleged rarity of optic nerve hypoplasia is obviously now refuted.

That same historical opinion also expressed that optic nerve hypoplasia was an isolated ocular anomaly. In 1941 the clinical association of optic nerve hypoplasia and absence of the septum pellucidum was reported in one case.[6] In 1956 this same association was documented at necropsy.[7] In 1962 an additional 35 necropsy cases with absence of the septum pellucidum had been reported,[8] and nine of these had significant optic nerve hypoplasia. The referenced reports herein record 22 cases of septo-optic

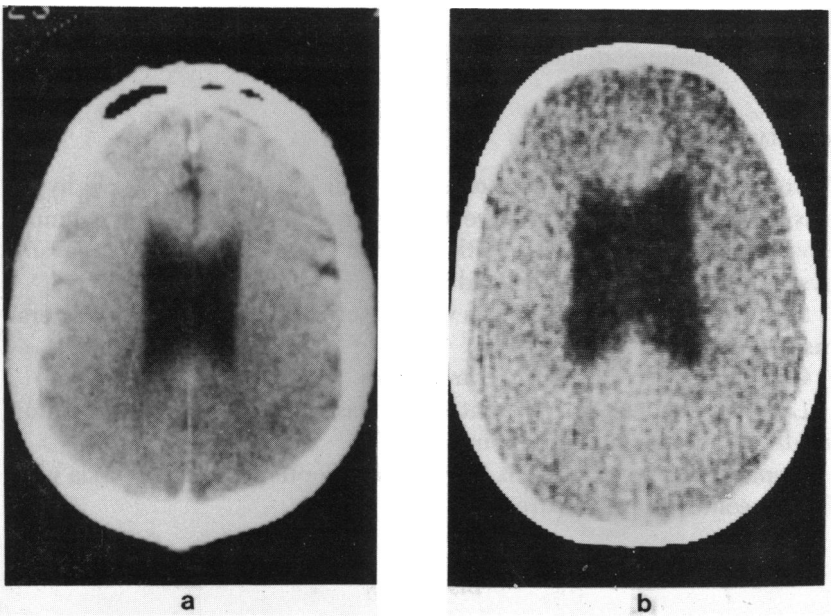


FIGURE 3
Computed axial tomographic studies: a, normal CT scan with intact septum pellucidum; b, absence of septum pellucidum.

dysplasia, and another 34 cases from unreferenced reports have been collected, between the years 1970 and 1980. This study adds another 12 cases demonstrating the association of optic nerve hypoplasia with absence of the septum pellucidum, providing a total of 68 cases of the septo-optic dysplasia syndrome reported in the last ten years.

If one hypothetically assumed that all 404 cases of optic nerve hypoplasia reported in this same time period had been evaluated for an associated septum pellucidum defect, then theoretically the overall incidence of the septo-optic dysplasia syndrome would approximate 22% of all reported cases of optic nerve hypoplasia. We know, of course, from the published data that the majority of cases of optic nerve hypoplasia were not studied in this manner. Prior to the advent of computed tomography and at the time most of these cases were reported, pneumoencephalography was the only technique available to demonstrate this anomaly.

The data from this study demonstrates that 12 out of 45 patients with optic nerve hypoplasia had computed tomographic evidence of partial or complete absence of the septum pellucidum, an incidence of 27%. None

of the nine patients with the tilt-conus-ectasia syndrome demonstrated such an associated defect. If we assumed that this subgroup indeed represents purely a localized ocular anomaly and for statistical purpose was deleted from the total group, then the incidence of associated septum pellucidum defects would increase to 33%, or 12 of 36 patients.

These correlative figures are also interesting if related back to the necropsy studies of DeMosier, wherein he reported that of 36 necropsy cases with absence of the septum pellucidum, nine had significant optic nerve hypoplasia, a converse correlation of 25%.

Since the coincidence of pituitary hypofunction and optic nerve hypoplasia was first documented in 1970, and the septo-optic-pituitary dysplasia syndrome described, closer diagnostic scrutiny had been practiced. In this ten-year period, 41 cases of pituitary hypofunction in association with optic nerve hypoplasia have been reported and 29 of these are herein referenced.[12-17] This study provides six more cases for a total of 47.

The true incidence of hypopituitarism in a large series of patients with optic nerve hypoplasia has not been determined. The data provided by this study indicates that out of 45 patients with documented optic nerve hypoplasia, six patients demonstrate clinical evidence of pituitary dysfunction, four of which had documented neurohormonal deficiences. Again, if the subgroup of nine patients with the optic nerve tilt syndrome (segmental hypoplasia) was deleted, and only those patients with diffusely small pale nerves were considered for statistical analysis, then six of the 36 patients in the larger group of optic nerve hypoplasia would demonstrate an associated pituitary dysfunction, an incidence of 16%. If this group with optic nerve hypoplasia is further narrowed to consider only that group of 12 patients with associated optic nerve hypoplasia and septum pellucidum defects, then the incidence of associated hypopituitarism would be 50%.

Some data is available regarding this consideration of the relationship of absence of the septum pellucidum and pituitary hypofunction. Several of the referenced reports[13-16] indicate that optic nerve hypoplasia and pituitary hypofunction may occur together with an intact septum pellucidum, and therefore the relationship is not inviolate. Only four of the 41 cases reported with associated optic nerve hypoplasia and hypopituitary function have not demonstrated absence of the septum pellucidum. Therefore the incidence of correlation is greater than 90%. It should be recalled, though, that these studies were performed with pneumoencephalography and not with the technique of computed tomography. A recent study by Manelfe and Rochiccioli[58] describes the increased facility and precision of computed tomography over pneumoencephalography in the study of

septo-optic dysplasia. Krause-Brucker and Gardner[53] presented the first series of patients with septo-optic-pituitary dysplasia studied with the aid of computed axial tomography. They described five children with the syndrome, and absence of the septum pellucidum was demonstrated in all five. It should be further noted that two of the cases in this study were diagnosed as having the septo-optic dysplasia syndrome with pituitary hypofunction prior to the availability of computed tomography, and both had "normal" pneumoencephalographic studies. As part of this study they then had computed tomographic studies and demonstrable absence of the anterior one third of the septum pellucidum. In the six cases herein reported with optic nerve hypoplasia and pituitary dysfunction, all had demonstrable partial or complete absence of the septum pellucidum. Conversely, six of the 12 patients (50%) with optic nerve hypoplasia and absence of the septum pellucidum did not demonstrate hypopituitarism. It would seem plausible, though, that one or more of the five infants less than 1 year of age, and with demonstrable absence of the septum pellucidum, may develop clinical evidence of hypopituitarism in future months or years. The final answer to this possible discrepancy regarding absence of the septum pellucidum will come from a larger series of similar patients who previously have had normal pneumoencephalographic studies and who are then restudied with computed tomography.

These data would also suggest that the tilted nerve syndrome is a distinct subgroup of optic nerve hypoplasia without associated CNS defects. If this is indeed true, then it would statistically appear that of the remaining subgroup of 36 patients with optic nerve hypoplasia (without tilt), 12 (33%) will demonstrate partial or complete absence of the septum pellucidum and six of these 12 (50%) will demonstrate clinical evidence of pituitary hypofunction or the complete septo-optic-pituitary dysplasia syndrome.

The last part of that previously accepted description denotes "small, pale optic nerves and blindness" as characteristic of optic nerve hypoplasia. This data suggests that this impression is only partly true, and then not without qualification. All patients in this study group had optic nerves that appeared to be, and echographically proved to be, smaller than normal. In general, but with significant variance, most of them were also more pale than normal (Fig 4). It can be noted from the data and Tables III and IV that the recorded visual acuities range from 20/20 to no light perception, and that the visual field defects also vary from one segment of field loss to another, depending on the direction of tilt or the segment of hypoplasia.

The calculated anatomic size (echographic area) varies from 39% of

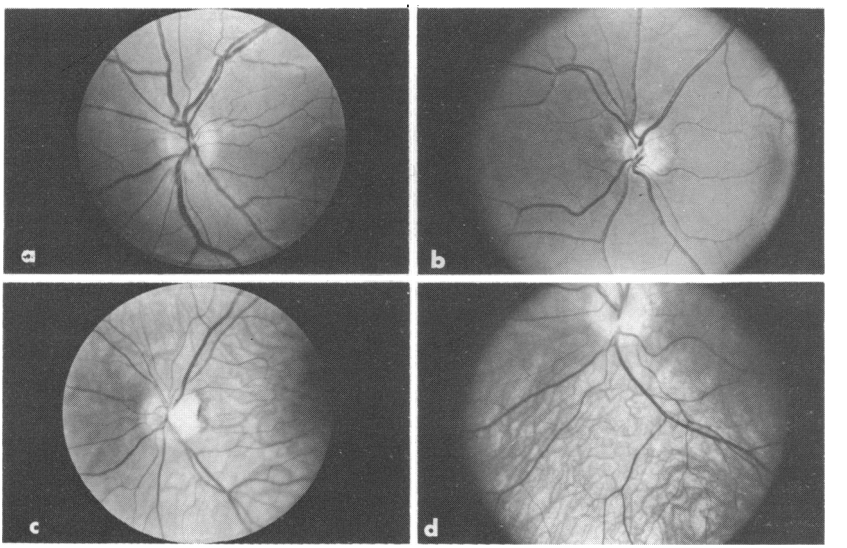


FIGURE 4
Optic nerves of patients in study: a, normal optic nerve; b, diffuse hypoplasia; c, segmental (temporal) hypoplasia; d, tilt-conus-ectasia.

normal area to 93%. Furthermore, there appears to be little correlation between size of the optic nerve and its visual function (Fig 5). Patient 24 demonstrated this in two ways. The echographic area of both optic nerves is calculated as being 39% of normal (the smallest optic nerves in the series), with a visual acuity of 20/80 in one eye and light perception only in the other eye. Patient 44 has an echographic area of the right optic nerve measuring 90% of normal with a visual acuity of 20/200, and 79% of normal area on the left with a visual acuity of 20/200. Patient 29 also has an echographic area of 79% of normal area in both eyes with visual acuity of 20/30 in each eye. Patient 32 also has an echographic area of 79% of normal in both eyes and no light perception in both eyes. Therefore there appears to be little correlation between the anatomic appearance or size of the optic nerve and its visual function.

Echographic measurements of the tilted nerve syndrome patients indicate that they, too, demonstrate structural hypoplasia of the optic nerves and visual dysfunction. The echographic areas in this group of nine patients ranged from 61% to 93% of normal. The echographic diameter of the nerve measured less in the direction of the tilt. For example, patient 41 demonstrates a unilateral temporal tilt of the left optic nerve. The horizontal echographic diameter is 2.63 mm and the vertical diameter is

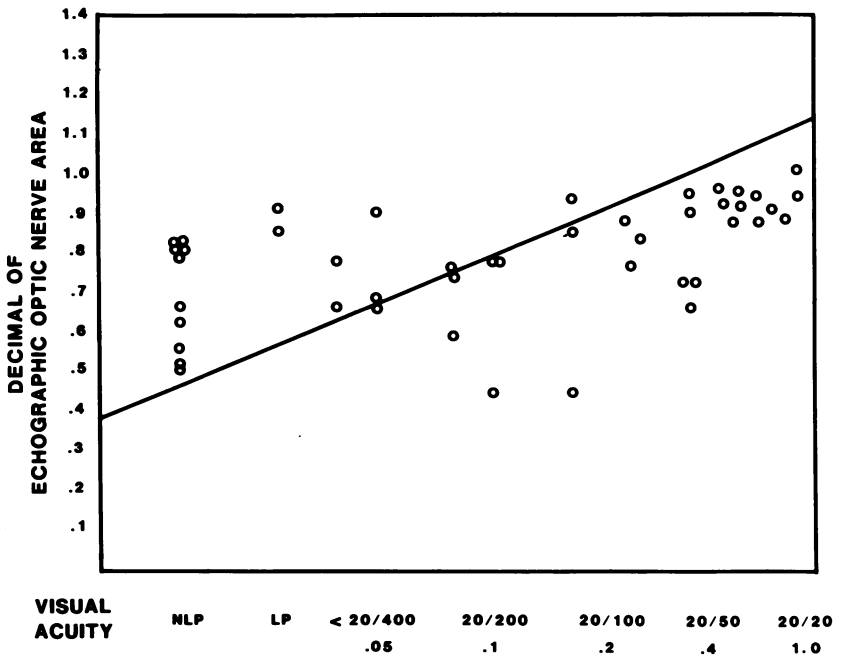


FIGURE 5
Correlation of echographic area of optic nerve with visual acuity demonstrating diffuse scatter.

3.1 mm with an echographic area of 88% normal. The vertically tilted nerves demonstrate the same disparity in diameter measurements in the opposite direction, as demonstrated by patient 35 with a superior tilt and inferior altitudinal field loss. The horizontal diameter of both nerves is 2.70 mm and the vertical diameters are 2.70 mm with an echographic area of 79% normal. The visual acuities in this group were generally good. The visual field defects almost always corresponded to the direction of the tilt. The five patients in this series with the tilt-conus-ectasia syndrome occasionally demonstrated some improvement in their field defects with increased myopic correction eccentrically placed in the direction of the ectasia.

The computed axial tomographic measurement of the optic nerve diameter was less precise, but did generally correlate with the echographic diameter, as outlined in Table V. As the computed tomographic technology is improved in its resolution capacity and more experience is obtained in coronal reconstruction studies of the optic nerve, its usefulness will undoubtedly increase.

This is the first large series of patients with optic nerve hypoplasia reported to utilize echographic and computed tomographic techniques to obtain in vivo measurements of the optic nerve. It is also the first study to document the absence of mutual correlation between the size of the optic nerve and its visual function.

These data further suggest that optic nerve hypoplasia is not only a component of a more diffuse syndrome, but itself can be subdivided into clinical subtypes. Thirty-two of the 45 patients fall into the segmental or incomplete optic nerve hypoplasia group characterized by small and pale or tilted optic nerves and variable visual function regarding visual acuity and visual fields. The tilt-conus-ectasia syndrome would fall into this subgroup. Thirteen patients demonstrate the diffuse or complete optic nerve hypoplasia subgroup characterized by small and pale optic nerves, amaurotic pupil response, absence of visual responsiveness, or blindness, alone or in combination.

The electrophysiologic testing performed on the 21 infants and preliterate-age children provided little useful information. The electroretinographic studies were uniformly normal, as previously documented by Francois and DeRouck.[59] The visual evoked potential recordings demonstrated what was clinically predictable; the children who were apparently blind and had absent direct pupillary response had no recordable visual evoked potential response. Those who responded to light or had evidence of visual attention and pupillary responses demonstrated visual evoked potential recordings at variable levels of recording. These tests therefore added little information over that gained from a carefully performed clinical examination.

COMMENTARY ON GENERAL INFORMATION DATA

Of the 45 cases herein reported, 40 (88%) were bilaterally affected and five (12%) unilaterally affected. It should be noted that 19 of these patients had previously been examined and nine of them were described as having unilateral optic nerve hypoplasia. On closer evaluation of these 19 patients, almost all of whom had been sedated in preparation for the echographic and computed tomographic studies, only two were unquestionably unilateral. The echographic and tomographic studies support this finding. Asymmetric but bilateral involvement was not uncommon in this series of patients. Two other large series of patients[10,11] report approximately 60% of the cases to be bilateral.

The male to female ratio in this series of patients was 23:22. The two previously cited series reported an incidence of predominance in males varying from 60% to 76%.[10,11]

The average maternal age in this study group was 23.8 years as compared with the average maternal age in the state of 24.6 years, not a significant statistical difference. Attention has recently been called to the incidence of young maternal age in a review group of these patients[49-51] with a mean maternal age of 19.25 years.

Twenty-one of the 40 patients on whom adequate information could be obtained were first-born children, an incidence of 52%. In Walton and Robb's study group,[11] 15 of 20 patients (75%) were first-born children.

Five of the 40 patients with adequate maternal information were born of diabetic mothers, all of whom were insulin-dependent, an incidence of 12.5%. Petersen and Walton[27] reported an incidence of 18%.

There were no familial cases in this series and only one possible maternal exposure to quinine used as an abortive agent. Six of the 45 patients did demonstrate other systemic neurologic problems other than hypopituitarism, including epilepsy, mental retardation, and cerebral palsy.

It is apparent from these data that optic nerve hypoplasia is not a rare and isolated ocular anomaly but is part of a spectrum of related developmental anomalies affecting the optic nerves and other structures in the CNS. It is a syndrome with disparate clinical expression.

The correlated embryologic and clinical factors involving the optic nerves, septum pellucidum, and hypophyseal-pituitary axis provide common ground for a classification system, which is supported by the data in this report. It is proposed as follows:

THE OPTIC NERVE HYPOPLASIA SYNDROME

Type I.	Optic Nerve Hypoplasia Simplex
	A. Diffuse
	B. Segmental
	C. Segmental with tilt
Type II.	Septo-optic dysplasia
Type III.	Septo-optic-pituitary dysplasia

It is readily acknowledged that, as with most rules, regulations, and classification systems, there must be exceptions and inconsistencies. The data presented here support the generalities of this classification system, and the possible exceptions are alluded to in the text.

SUMMARY

Forty-five patients with the common clinical factor of optic nerve hypoplasia are analyzed regarding their clinical appearance, echographic and

computed tomographic measurements of the optic nerves, and the correlation of anatomic size with visual function.

Computed axial tomographic studies of the midline brain were performed on all 45 patients to determine the incidence of correlated structural defects, especially the septum pellucidum, and neuroendocrine dysfunction.

Review of the spectrum of septo-optic-pituitary syndrome is separately developed to include historical background, embryogenesis, histopathology, and pathogenesis of the three major components of the syndrome.

In summary, 45 patients had optic nerve hypoplasia, 32 with evidence of segmental or partial hypoplasia and 13 with evidence of complete or diffuse hypoplasia—the optic nerve hypoplasia syndrome. Twelve of these patients demonstrated absence of the septum pellucidum by computed axial tomography—the septo-optic dysplasia syndrome. Of these 12 patients with partial or complete absence of the septum pellucidum, six demonstrated evidence of pituitary hypofunction—the septo-optic-pituitary dysplasia syndrome.

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