Introduction

Congenital anomalies of the optic disc underlie many cases of decreased vision, strabismus, and nystagmus in childhood. A comprehensive evaluation necessitates an understanding of the ophthalmoscopic features, associated neuro-ophthalmologic findings, pathogenesis, and appropriate ancillary studies for each anomaly. The subclassification of different forms of “colobomatous” defects on the basis of their ocular and systemic associations has further refined our ability to predict the likelihood of associated central nervous system (CNS) anomalies solely on the basis of the appearance of the optic disc. The widespread availability of modern neuroimaging has refined our ability to identify subtle associated CNS anomalies and to prognosticate neurodevelopmental and endocrinological problems. Genetic analysis has now advanced our understanding of some anomalies.

Four clinical axioms can be used to guide the general evaluation and management of children with congenital optic disc anomalies:

1. Children with bilateral optic disc anomalies generally present with poor vision and nystagmus in infancy, while those with unilateral optic disc anomalies may present later in the preschool period with sensory esotropia.
2. CNS malformations are common in patients with malformed optic discs. Small discs are associated with a variety of malformations involving the cerebral hemispheres, pituitary infundibulum, and midline intracranial structures (e.g., septum pellucidum, corpus callosum). Large optic discs of the morning glory configuration are associated with the transsphenoidal form of basal encephalocele.
3. In contradistinction to the severe dyschromatopsia that characterizes most acquired optic neuropathies, color vision is relatively preserved in eyes with congenital optic disc anomalies.
4. Any structural ocular abnormality that reduces visual acuity in infancy may lead to superimposed amblyopia. A trial of occlusion therapy may be warranted in some patients with unilateral optic disc anomalies and decreased vision.

Optic Nerve Hypoplasia

Optic nerve hypoplasia is an anomaly that, until recently, escaped the scrutiny of even the most meticulous observers. It was not until the late 1960s that its clinical description became commonplace. Optic nerve hypoplasia is now unquestionably the most common optic disc anomaly encountered in ophthalmologic practice. This dramatic increase in prevalence primarily reflects a greater recognition by clinicians. Many cases of optic nerve hypoplasia that previously went unrecognized or were misconstrued as congenital optic atrophy are now correctly diagnosed. In addition, some investigators believe that parental drug and alcohol abuse, which have become more widespread in recent years, may also be contributing to an increasing prevalence of optic nerve hypoplasia. Teratogenic agents and systemic disorders that have been associated with optic nerve hypoplasia are summarized in Table 2.1.

Ophthalmoscopically, optic nerve hypoplasia appears as an abnormally small optic nerve head that may appear gray or pale in color and is often surrounded by a yellowish, mottled peripapillary halo, bordered by a ring of increased or decreased pigmentation (“double-ring” sign) (Fig. 2.1). The major retinal veins are often tortuous. When the nystagmus precludes accurate assessment of the optic disc size, this selective venous tortuosity provides an important clue to the diagnosis. Borchert and Garcia-Filion have noted that optic nerve hypoplasia may also be accompanied by unusually straight retinal vessels with decreased branching. This nonbranching pattern is also found in patients with primary growth hormone deficiency, raising the intriguing possibility that this variant vascular pattern may turn out to correlate with endocrine dysfunction in children with optic nerve hypoplasia.
Histopathologically, optic nerve hypoplasia is characterized by a subnormal number of optic nerve axons with normal mesodermal elements and glial supporting tissue. The double-ring sign has been found histopathologically to consist of a normal junction between the sclera and lamina cribrosa, which corresponds to the outer ring, and an abnormal extension of the retina and pigment epithelium over the outer portion of the lamina cribrosa, which corresponds to the inner ring.

Visual acuity in optic nerve hypoplasia ranges from 20/20 to no light perception, and the affected eyes show localized visual field defects, often combined with a generalized constriction of the visual fields. Because visual acuity is determined primarily by the integrity of the papillomacular nerve fiber bundle, it does not necessarily correlate with the overall size of the disc. The association of astigmatism with optic nerve hypoplasia warrants careful attention to correction of refractive errors. A classic Pulfrich phenomenon (illusory perception of elliptical motion in the frontal plane) was detected in a 12-year-old girl with normal acuity and asymmetrical optic nerve hypoplasia.

Table 2.1 Systemic and teratogenic associations with optic nerve hypoplasia. (Modified from Zeki and Dutton)

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<td>Klippel–Trenauney–Weber syndrome</td>
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Fig. 2.1 Optic nerve hypoplasia. (a) Optic nerve hypoplasia with selective retinal venous tortuosity. (b) Pseudo-normal optic disc in a child with optic nerve hypoplasia and no light perception. The disc appears normal at first glance, but shows complete absence of retinal nerve fiber layer. It is difficult to tell whether central white area corresponds to lamina cribrosa or to hypoplastic and atrophic optic disc. Surrounding area represents extension of retinal pigment epithelium over normal-sized lamina cribrosa, producing double-ring sign. (c) Optic nerve hypoplasia with nasal pallor and extension of RPE and choroid over temporal aspect of disc. (d) Black optic disc caused by optic nerve hypoplasia with congenital optic disc pigmentation.
Optic nerve hypoplasia has recently been implicated in the pathogenesis of amblyopia. Using optic disc photographs corrected for magnification, Lempert found smaller optic discs and smaller axial lengths in amblyopic eyes compared with their fellow eyes, and suggested that vision impairment in presumed amblyopia may be caused by optic nerve hypoplasia with relative microphtalmos. Archer questioned whether a small optic disc area could be associated with amblyopia by being correlated with hyperopia and anisometropia rather than being the cause of the decreased vision. In other words, small eyes may have small optic discs, and further study is needed to determine whether the small optic nerves or the associated hyperopia or anisometropia is causal. In a follow-up study, Lempert factored axial length into the calculation and found the optic disc areas of eyes with hyperopic strabismus (with and without amblyopia) to be smaller than those in hyperopic eyes without amblyopia or esotropia. More recently, OCT has demonstrated a normal nerve fiber layer in amblyopic eyes, effectively refuting the Lempert hypothesis.

Visual acuity remains stable throughout life unless amblyopia develops in one eye. However, Taylor has documented mild optic nerve hypoplasia in children with congenital suprasellar tumors, which can slowly enlarge to produce the confusing diagnostic picture of acquired visual loss in the child with optic nerve hypoplasia.

While moderate or severe optic nerve hypoplasia can be recognized ophthalmoscopically, the diagnosis of mild hypoplasia continues to be problematic in infants and small children, whose visual acuity cannot be accurately quantified. Several techniques have been devised to directly measure fundus photographs of the optic disc in an attempt to apply quantitative criteria to the diagnosis of optic nerve hypoplasia. Jonas et al have defined “microdiscs” statistically as the mean disc area minus two standard deviations. In their study of 88 patients, the mean optic disc area measured 2.89 mm² and the diagnosis of a microdisc corresponded to a disc area smaller than 1.4 mm. Romano has advocated the simple method of directly measuring the optic disc diameter using a hand ruler and a 30° transparency (both under magnification) and has concluded that a horizontal disc diameter of less than 3.4 mm constitutes optic nerve hypoplasia. This quick and simple technique is limited to eyes with minimal spherical refractive error.

Zeki et al have found that a disc-to-macula/disc diameter ratio of 2.94 provides a one-tailed upper population limit of 95%, while individuals with optic nerve hypoplasia have a mean ratio of 3.57. Calculation of this ratio has the important advantage of eliminating the magnification effect of high refractive errors (myopic refractive errors can make a hyperplastic disc appear normal in size, whereas hyperopic refractive errors can make a normal disc appear abnormally small). While the Zeki technique is especially useful in patients with high refractive errors, the notion that one can establish an unequivocal dividing line between the normal and hypoplastic disc strictly upon the basis of size is inherently flawed. As discussed later, large optic discs can be axonally deficient and small optic discs do not preclude normal visual function. In evaluating small optic discs, we have grown accustomed to drawing inferences about axon counts on the basis of size.

While it is reasonable to infer that an extremely small disc must be associated with a diminution in axons, the application of this reasoning to mild or borderline cases is limited by additional variables, including the size of the central cup, the percentage of the nerve occupied by axons (as opposed to glial tissue and blood vessels), and the cross-sectional area and density of axons. Furthermore, segmental forms of optic nerve hypoplasia (described later) may affect a sector of the disc without producing a diffuse diminution in size. As such, it would seem prudent to reserve the diagnosis of optic nerve hypoplasia for patients with small optic discs who have reduced vision or visual field loss with corresponding nerve fiber bundle defects.

The use of the term “hypoplasia” to describe a congenitally small, axonally deficient optic nerve implies that this abnormality necessarily results from a primary failure of optic axons to develop. The timing of other CNS anomalies, which often coexist with optic nerve hypoplasia, would suggest that some cases of optic nerve “hypoplasia” represent an intrauterine degenerative phenomenon rather than a primary failure of axons to develop. In human fetuses, Provis et al found a peak of 3.7 million axons at 16–17 weeks of gestation, with a subsequent decline to 1.1 million axons by the 31st gestational week. This massive degeneration of supernumerary axons (termed apoptosis) occurs as part of the normal development of the visual pathways and may serve to establish the correct topography of the visual pathways. Toxins or associated CNS malformations may, in some instances, augment or interfere with the usual processes by which superfluous axons are eliminated from the developing visual pathways.

A recent study by Garcia-Filion et al confirmed young maternal age and primaparity as significant risk factors. Preterm labor, gestational vaginal bleeding, low maternal weight gain, and weight loss during pregnancy were also prevalent in mothers of patients with optic nerve hypoplasia.

Optic nerve hypoplasia is often associated with a wide variety of CNS abnormalities. Septo-optic dysplasia (de Morsier syndrome) refers to the constellation of small anterior visual pathways, absence of the septum pellucidum, and thinning or agenesis of the corpus callosum. The clinical association of septo-optic dysplasia and pituitary dwarfism was documented by Hoyt et al in 1970. Growth hormone deficiency is the most common endocrinologic abnormality associated with optic nerve hypoplasia, followed by thyrotropin, corticotropin, and antidiuretic hormone (Fig. 2.2). Hypothyroidism, panhypopituitarism, diabetes insipidus, and hyperprolactinemia may also occur. Hyperprolactinemia is said to occur in 62%
of cases, and does not cause galactorrhea but contributes to the high incidence of obesity in these children.\textsuperscript{35} Neonatal hypothyroidism is a significant risk factor for developmental delay.\textsuperscript{110} Growth hormone deficiency may be clinically inapparent in the first 3–4 years of life because high prolactin levels may stimulate normal growth over this period.\textsuperscript{3,79} Growth hormone surrogates such as insulin-like growth factor (IGF-1) and insulin-like growth factor binding protein (IGFBP-3) can also be decreased in patients with growth hormone deficiency.\textsuperscript{35} Puberty may be precocious or delayed in children with hypopituitarism.\textsuperscript{133}

Because subclinical hypopituitarism can manifest as acute adrenal insufficiency following general anesthesia, it may be prudent to empirically treat children who have optic nerve hypoplasia with perioperative intravenous corticosteroids.\textsuperscript{273} Although the incidence of clinical hypopituitarism has been estimated at 15%,\textsuperscript{57} in a recent analysis of multiple hormone levels in children with optic nerve hypoplasia, Ahmad et al\textsuperscript{3} recently found a 72% prevalence of endocrinopathies, suggesting that subclinical pituitary involvement is common. Other retrospective studies support this higher incidence.\textsuperscript{129,251} According to Borchart and Garcia-Falion,\textsuperscript{35} "endocrinological workup should include fasting morning cortisol and glucose, thyroid-stimulating hormone (TSH), free T4, IGF-1, IGFBP-3, and prolactin. If the child is less than 6 months of age, luteinizing hormone, follicle-stimulating hormone, and/or testosterone levels should be checked in order to anticipate delayed sexual development. Beyond 6 months of age, sex hormones are not normally produced until puberty and thus cannot be tested. Micropenis can be treated with testosterone injections during infancy but is a harbinger of delayed puberty."\textsuperscript{17}

In an infant with optic nerve hypoplasia, a history of neonatal jaundice suggests congenital hypothyroidism, while neonatal hypoglycemia or seizures suggest congenital panhypopituitarism.\textsuperscript{192} A serum thyroxine level may be normal in children with secondary hypothyroidism. Because the adverse developmental effects associated with secondary hypothyroidism are irreversible by 15 months of age, it is advisable to also obtain the serum TSH level to rule out this treatable problem. Because of inherent difficulties in measuring normal physiologic growth hormone levels, which vary widely over a 24-h period, most patients with optic nerve hypoplasia are followed clinically and only investigated biochemically if growth is subnormal. However, when MR imaging shows posterior pituitary ectopia, or when a clinical history of neonatal jaundice or neonatal hypoglycemia is obtained, anterior pituitary hormone deficiency is probable, and more extensive endocrinologic testing becomes mandatory.\textsuperscript{241}

The eyes and neurohypophysis probably evolved as a single receptor which developed a complex of integrating and crosslinking external and internal stimuli. The pituitary gland serves as the neurochemical interface between internal homeostasis and the external world. The fact that it controls the critical survival functions of the organism (to eat, drink, reproduce, and respond to stress within the environment) may explain why it is seated in the middle of the head in a

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**Fig. 2.2** Magnetic resonance imaging in optic nerve hypoplasia. (a) T1-weighted coronal MR imaging in patient with left optic nerve hypoplasia. Black arrow denotes normal right optic nerve. White arrow denotes thin, attenuated signal corresponding to hypoplastic left optic nerve. Used, with permission, from Williams et al\textsuperscript{322} (b) T1-weighted coronal MR imaging demonstrating diffuse thinning of optic chiasm (arrow) in patient with absence of septum pellucidum and bilateral optic nerve hypoplasia. Used, with permission, from Brodsky et al\textsuperscript{54} Copyright 1990, American Medical Association
boney cage, where it is well protected. The electrochemical responses of the melanopsin-containing ganglion cells provide an external continuum to this function. Pituitary hormone levels show active circadian regulation that is controlled by the hypothalamus. Some patients with optic nerve hypoplasia have sleep disturbances with increased daytime napping. It remains to be determined whether some of these sleep disturbances are directly attributable to absence of melanopsin-containing retinal ganglion cells or to hypothalamic injury. These sleep disturbances are often responsive to oral melatonin (although it has been reported that oral melatonin may interfere with normal progression of puberty). Children with septo-optic dysplasia and corticotropin deficiency are at risk for sudden death during febrile illness. This clinical deterioration appears to be caused by an impaired ability to increase corticotropin secretion to maintain blood pressure and blood sugar in response to the physical stress infection. These children may have coexistent diabetes insipidus that contributes to dehydration during illness and hastens the development of shock. Some also have hypothalamic thermoregulatory disturbances signaled by episodes of hypothermia during the period when they are feeling healthy and high fevers during illnesses, which may predispose to life-threatening hyperthermia. Children with septo-optic dysplasia who are at risk for sudden death have usually had multiple hospital admissions for viral illnesses. These viral infections can precipitate hypoglycemia, dehydration, hypotension, or fever of unknown origin. Because corticotropin deficiency represents the preeminent threat to life in children with septo-optic dysplasia, a complete anterior pituitary hormone evaluation, including provocative serum cortisol testing and assessment for diabetes insipidus, should be performed in children who have clinical symptoms (history of hypoglycemia, dehydration, or hypothermia) or neuroimaging signs (absent pituitary infundibulum with or without posterior pituitary ectopia) of pituitary hormone deficiency.

Magnetic resonance (MR) imaging provides an excellent noninvasive neuroimaging modality for delineating associated CNS malformations in patients with optic nerve hypoplasia. MR imaging can be used to provide specific prognostic information regarding the likelihood of neurodevelopmental deficits and pituitary hormone deficiency in the infant or young child with unilateral or bilateral optic nerve hypoplasia. It also provides high-contrast resolution and multiplanar imaging capability, allowing the anterior visual pathways to be visualized as distinct, well-defined structures. In optic nerve hypoplasia, coronal and sagittal T1-weighted MR images show thinning and attenuation of the corresponding prechiasmatic intracranial optic nerve (Fig. 2.2). Coronal T1-weighted MR

![Fig. 2.3](image-url) Cerebral hemispheric abnormalities associated with optic nerve hypoplasia. (a) Axial T1-weighted inversion recovery MR image demonstrating schizencephaly in patient with optic nerve hypoplasia. Schizencephalic cleft (arrows) consists of abnormal band of dysmorphic gray matter in left cerebral hemisphere extending from cortical surface to lateral ventricle. (b) T2-weighted axial MR image demonstrating asymmetrical periventricular leukomalacia, worse in right hemisphere (left side of picture), in child with optic nerve hypoplasia. Note enlargement and irregular contour of posterior aspect of lateral ventricle. Black arrow denotes loss of posterior periventricular white matter, with direct apposition of cortical gray matter to trigone of lateral ventricle. White arrow indicates greater volume of posterior periventricular white matter in the left hemisphere. Used, with permission, from Brodsky et al. Copyright 1993, American Medical Association.
Fig. 2.4 Posterior pituitary ectopia. (a) T1-weighted sagittal MR image demonstrating normal hyperintense signal of posterior pituitary gland (lower black arrow), normal pituitary infundibulum (lower white arrow), optic chiasm (upper right arrow). Open arrow denotes normal corpus callosum. (b) T1-weighted sagittal MR image demonstrating posterior pituitary ectopia (upper white arrow), which appears as abnormal focal area of increased signal intensity at tuber cinereum. Note absence of pituitary infundibulum and absence of normal posterior pituitary bright spot (lower arrow). Upper white arrow denotes ectopic posterior pituitary gland. Child had normal septum pellucidum and corpus callosum (open arrow). Used, with permission, from Brodsky et al 52
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imaging in bilateral optic nerve hypoplasia shows diffuse thinning of the optic chiasm in bilateral optic nerve hypoplasia (Fig. 2.2) and focal thinning or absence of the side of the chiasm corresponding to the hypoplastic nerve in unilateral optic nerve hypoplasia.54 When MR imaging shows a decrease in intracranial optic nerve size accompanied by other features of septo-optic dysplasia, a presumptive diagnosis of optic nerve hypoplasia can be made.54

Because MR imaging often shows associated structural abnormalities involving the cerebral hemispheres and the pituitary infundibulum, septo-optic dysplasia can no longer be considered a monolith and is best viewed as a heterogeneous malformation syndrome.52,243 Cerebral hemispheric abnormalities are evident in about 45% of patients with optic nerve hypoplasia (Fig. 2.3).52 They may consist of hemispheric migration anomalies (e.g., schizencephaly, cortical dysgenesis) or intrauterine or perinatal hemispheric injury (e.g., periventricular leukomalacia, porencephaly),32 and other rare conditions such as intracranial arachnoid cysts.207 A recent prospective study found developmental delay in 78% of children with bilateral optic nerve hypoplasia and 39% of children with unilateral optic nerve hypoplasia at 5 years of age, with hypoplasia of the corpus callosum and hypothyroidism standing out as independent correlates.111

Evidence of perinatal injury to the pituitary infundibulum (seen on MR imaging as posterior pituitary ectopia) is found in about 15% of patients with optic nerve hypoplasia.52,180,217

Normally, the posterior pituitary gland appears bright on T1-weighted images, probably because of the chemical composition of the vesicles contained in it.52,243 In posterior pituitary ectopia, MR imaging demonstrates absence of the normal posterior pituitary bright spot, absence of the pituitary infundibulum, and an ectopic posterior pituitary bright spot where the upper infundibulum is normally located (Fig. 2.4).52,241

In the patient with optic nerve hypoplasia, posterior pituitary ectopia is virtually pathognomonic of anterior pituitary hormone deficiency, whereas cerebral hemispheric abnormalities are highly predictive of neurodevelopmental deficits.52 Absence of the septum pellucidum alone does not portend neurodevelopmental deficits or pituitary hormone deficiency.32 Thinning or agenesis of the corpus callosum is predictive of neurodevelopmental problems,52 probably by virtue of its frequent association with cerebral hemispheric abnormalities. The finding of unilateral optic nerve hypoplasia does not preclude coexistent intracranial malformations.52

Segmental Optic Nerve Hypoplasia

Optic nerve hypoplasia can be segmental.228 A superior segmental optic hypoplasia with an inferior visual field defect occurs in children of insulin-dependent diabetic mothers (Fig. 2.5).183,240 Despite the multiple teratologic effects of
maternal diabetes early in the first trimester, superior segmental optic hypoplasia is usually diagnosed in patients with no other systemic anomalies. The incidence of superior segmental optic hypoplasia has been estimated at approximately 8%. Kim et al have noted that the inferior visual field defects in superior segmental optic hypoplasia differ from typical nerve fiber bundle defects and questioned whether a regional impairment in retinal development could play a role in the pathogenesis. Superior segmental optic hypoplasia has also been documented in Japanese patients whose mothers were not diabetic, demonstrating that this anomaly is not pathognomonic for maternal diabetes. The teratologic mechanism by which insulin-dependent diabetes mellitus selectively interferes with the early gestational development of superior retinal ganglion cells or their axons is not established. Mice lacking EphB receptor guidance proteins exhibit specific guidance defects in axons originating from the dorsal or superior part of the retina, suggesting that developmental mechanisms that control the expression of axon guidance molecules along the dorsal-ventral axis of the retina may eventually explain this segmental hypoplasia.

Congenital lesions involving the retina, optic nerve, chiasm, tract, or retrogeniculate pathways are associated with segmental hypoplasia of the corresponding portions of each optic nerve (Fig. 2.6). Chiasmal hypoplasia produces focal loss of the nasal and temporal nerve fiber layer, with hypoplasia of corresponding portions of the optic nerve (Fig. 2.7). Hoyt et al 49 coined the term “homonymous hemioptic hypoplasia” to describe the asymmetrical form of segmental optic nerve hypoplasia seen in patients with unilateral congenital hemispheric lesions involving the postchiasmal afferent visual pathways. In this setting, the nasal and temporal aspects of the optic disc contralateral to the hemispheric lesion show segmental hypoplasia and loss of the corresponding nerve fiber layer. This hypoplasia may be accompanied by a central band of horizontal pallor across the disc. The ipsilateral optic disc may range from normal in size to frankly hypoplastic. Homonymous hemioptic hypoplasia in retrogeniculate lesions results from transsynaptic degeneration of the optic tract that is usually seen in the setting of a congenital hemispheric lesion.

Periventricular leukomalacia produces another segmental form of optic nerve hypoplasia. In 1995, Jacobson et al recognized that periventricular leukomalacia produces a unique form of bilateral optic nerve hypoplasia characterized by an abnormally large optic cup and a thin neuroretinal rim contained in a normal-sized optic disc. They attributed this morphologic characteristic to intrauterine injury to the optic radiations with retrograde transsynaptic degeneration of retinogeniculate axons after the scleral canals had established normal diameters. The large optic cups can simulate glaucoma, but the history of prematurity, normal intraocular pressure, and characteristic symmetrical inferior visual field defects all serve to distinguish periventricular leukomalacia from glaucomatous optic atrophy. Most authorities believe that this anomaly warrants classification as a prenatal form of optic atrophy because of its normal optic disc diameter. Patients with periventricular leukomalacia can also have typical optic nerve hypoplasia with small optic discs.

**Pathogenesis**

Several distinct mechanisms may be involved in the embryogenesis of optic nerve hypoplasia. Early investigators attributed optic nerve hypoplasia to a primary failure of retinal ganglion cell differentiation at the 13- to 15-mm stage of development.
Congenital Optic Disc Anomalies

Recent experiments have shown that a deficiency of axon guidance molecules at the optic disc can lead to optic nerve hypoplasia. Netrin-1 is an axon-guidance molecule that is involved in development of spinal commissural axons and is expressed by neuroepithelial cells at the developing optic nerve head. Retinal ganglion cells in vitro respond to netrin-1 as a guidance molecule. Mice with a targeted deletion of the netrin-1 gene exhibit hypoplasia of nasal and temporal nerve fiber layer bilaterally.

Fig. 2.6 Segmental optic nerve hypoplasia. (a) Segmental hypoplasia of temporal optic disc with focal absence of the temporal nerve fiber layer in patient with “macular coloboma.” (b) Subtle segmental hypoplasia of temporal portion of disc. Child was thought to have amblyopia with 20/400 OS but was refractory to occlusion therapy. (c and d) Chiasmal hypoplasia with congenital bitemporal hemianopia. Note segmental hypoplasia of nasal and temporal nerve fiber layer bilaterally. Courtesy of William F. Hoyt, M.D. (e and f) Homonymous hemiopic hypoplasia in patient with right occipital porencephalic cyst. Both optic discs are hypoplastic. Left optic disc (f) shows relative loss of disc substance and peripapillary nerve fiber layer nasally and temporally. Used, with permission, from Novakovic et al. Photographs courtesy of William F. Hoyt, M.D.
pathfinding errors at the optic disc, whereas retinal ganglion cells fail to exit into the optic nerve and instead grow inappropriately into the other side of the retina. As a result of this aberrant pathfinding, these mice exhibit optic nerve hypoplasia. In addition to defects in optic nerve formation, the lack of netrin-1 function during development also results in abnormalities in other parts of the CNS, such as agenesis of the corpus callosum and cell migration and axonal guidance defects in the hypothalamus. Thus, elimination of specific axon guidance molecules during development of the mouse nervous system results in a phenotype that bears striking resemblance to septo-optic dysplasia.

The timing of coexistent CNS injuries would also suggest that some cases of optic nerve hypoplasia may result from intrauterine destruction of a normally developed structure (i.e., an encephaloclastic event), whereas others represent a primary failure of axons to develop. In human fetuses, Provis et al found a peak of 3.7 million optic axons at 16 or 17 weeks of gestation, with a subsequent decline to 1.1 million axons by the 31st gestational week. This massive degeneration of supernumerary axons, termed “apoptosis,” occurs as part of the normal development of the visual pathways and may serve to establish the correct topography of the visual pathways. Toxins or associated CNS injury could augment the usual processes by which superfluous axons are eliminated from the developing visual pathways.

The common association of optic nerve hypoplasia with periventricular leukomalacia, which clearly cannot be reconciled with a deficiency of axon guidance molecules at the optic disc, demonstrates the importance of retrograde transsynaptic degeneration in the development of some forms of optic nerve hypoplasia.

**Genetics**

Reported cases of optic nerve hypoplasia in siblings have all been bilateral and without consanguinity. These cases are sufficiently rare that parents of a child with optic nerve hypoplasia can reasonably be assured that subsequent siblings are at little or no additional risk. While genetic mutations in the human netrin-1 and DCC genes have not been described, homozygous mutations in the HESX1 gene has been identified in two siblings with optic nerve hypoplasia, absence of the corpus callosum, and hypoplasia of the pituitary gland. Numerous additional mutations in HESX1 have recently been observed in children with sporadic pituitary diseases. Mutations have clustered in the DNA-binding region of the protein consistent with a presumed loss in protein function. Formal examination of homeobox genes with expression patterns similar to HESX1, such as SOX2 and SOX3, may yield additional genes responsible for both sporadic and familial septo-optic dysplasia. The targets and partners of the transcriptional factors involved in the development of forebrain structures involved in septo-optic dysplasia are unknown. Optic nerve hypoplasia may accompany other ocular malformations in patients with mutations in the PAX6 gene.

Recent studies suggest that mitochondrial disease may underlie some cases of optic nerve hypoplasia. Taban et al retrospectively reviewed 80 patients with nonsyndromic mitochondrial cytopathies and found 10 cases of optic nerve hypoplasia, leading them to question whether excessive apoptosis during embryonic ganglion cell and/or axonal development could result from abnormal mitochondrial function and cellular energy metabolism. Superoxide dismutase (SOD)-deficient mice with inactivation of SOD2 (the mitochondrial form of superoxide dismutase) produces multiple ocular and systemic abnormalities that are accompanied by optic nerve hypoplasia.

**Excavated Optic Disc Anomalies**

Excavated optic disc anomalies include optic disc coloboma, morning glory disc anomaly, and peripapillary staphyoma. The morning glory disc anomaly is a congenital, funnel-shaped excavation of the posterior fundus that incorporates the optic disc. It was so named by Kindler in 1970 because of its resemblance to the morning glory flower. Ophthalmoscopically, it is now clear that optic disc colobomas, morning glory optic discs, and peripapillary staphylomas are distinct anomalies, each with its own specific embryological origin, and not simply clinical variants along a broad phenotypic spectrum. Genetic mechanisms producing optic disc excavation have been associated with papilloreal syndrome, and others have been mapped to specific chromosomal sites.

**Morning Glory Disc Anomaly**

The morning glory disc anomaly is a congenital, funnel-shaped excavation of the posterior fundus that incorporates the optic disc. It was so named by Kindler in 1970 because of its resemblance to the morning glory flower. Ophthalmoscopically, the disc is markedly enlarged, orange or pink in color, and may appear to be recessed or elevated centrally within a funnel-shaped peripapillary excavation (Fig. 2.7). A wide annulus of chorioretinal pigmentary disturbance surrounds the disc.
within the excavation. A white tuft of glial tissue overlies the central portion of the disc. The blood vessels appear increased in number and often arise from the periphery of the disc. They often curve abruptly as they emanate from the disc, and then run an abnormally straight course over the peripapillary retina. It is often difficult to distinguish arterioles from venules. Close inspection occasionally reveals the presence of small peripapillary arterovenous communications (Fig. 2.8). The macula may be incorporated into the excavation (macular capture). Computed tomography (CT) scanning shows a funnel-shaped enlargement of the distal optic nerve at its junction with the globe (Fig. 2.9).

The morning glory disc anomaly is usually unilateral but can be bilateral. Visual acuity usually ranges from 20/200 to finger counting in the morning glory disc anomaly, but cases with 20/20 vision as well as no light perception have been reported. The fact that visual acuity tends to be near normal in bilateral cases suggests that functional amblyopia may contribute to visual loss in unilateral cases. Unlike optic disc colobomas that have no racial or gender predilection, morning glory discs are conspicuously more common in females and rare in African-Americans. With rare exceptions, the morning glory disc anomaly does not present as part of a multisystem genetic disorder.

Fig. 2.7 Morning glory optic disc. Large optic disc is surrounded by annular zone of pigmentary disturbance. Retinal vessels appear increased in number, emerge from periphery of disc, and have abnormally straight, radial configuration. There is radial folding of peripapillary retina. Note characteristic central white glial tuft. Arrow denotes focal yellowish discoloration that corresponds to macula lutea pigment (macular capture). Used, with permission, from Goldhammer et al Copyright 1975, American Medical Association. Photograph courtesy of Stephen C. Pollock, M.D.

Fig. 2.8 Morning glory disc anomaly with multiple retinal arteriovenous communications (denoted by arrows). Child was later found to have neurofibromatosis 2. Used, with permission, from Brodsky and Wilson Copyright 1995, American Medical Association

Fig. 2.9 CT scan of morning glory disc anomaly. Note calcified, funnel-shaped enlargement of distal optic nerve at its junction with globe. Used, with permission, from Brodsky
Excavated Optic Disc Anomalies

The association of morning glory disc anomaly with the transsphenoidal form of basal encephalocele is well established. Transsphenoidal encephalocele is a rare midline congenital malformation in which a meningeal pouch, often containing the chiasm and adjacent hypothalamus, protrudes inferiorly through a large, round defect in the sphenoid bone (Fig. 2.10). Children with this occult basal meningocele have a wide head, flat nose, mild hypertelorism, midline notch in the upper lip, and sometimes a midline cleft in the soft palate (Figs. 2.11 and 2.12). The meningocele protrudes into the nasopharynx, where it may obstruct the airway. Symptoms of transsphenoidal encephalocele in infancy may include rhinorrhea, nasal obstruction, mouth breathing, or snoring. These symptoms may be overlooked unless the associated morning glory disc anomaly or the characteristic facial configuration is recognized. A transsphenoidal encephalocele may present as a pulsatile posterior nasal mass or as a “nasal polyp” high in the nose; surgical biopsy or excision can have lethal consequences.

Transsphenoidal encephalocele can present initially by interfering with intubation during general anesthesia. Associated brain malformations include agenesis of the corpus callosum and posterior dilatation of the lateral ventricles. Absence of the chiasm is seen in approximately one-third of patients at surgery or autopsy. Most of the affected children have no overt intellectual or neurological deficits, but panhypopituitarism is common. Surgery for transsphenoidal encephalocele is considered by many authorities to be contraindicated, because herniated brain tissue may include vital structures, such as the hypothalamic-pituitary system, optic nerves and chiasm, and anterior cerebral arteries, and because of the high postoperative mortality reported, particularly in infants. As with other dysplastic optic discs (see Fig. 2.23 below), the finding of a discrete V- or tongue-shaped zone of infrapapillary depigmentation can be considered a clinical sign of transsphenoidal encephalocele.

With the advent of MR angiography, numerous reports have found ipsilateral intracranial vascular dysgenesis (hypoplasia of the carotid arteries and major cerebral arteries with or without Moyamoya syndrome) in patients with morning glory disc anomaly (Fig. 2.13). A retrospective multicenter study by Lenhart et al found cerebrovascular anomalies in nine of 20 patients (45%) with morning glory optic disc anomalies. Some patients also have duplication of the pituitary stalk. These findings underscore the need for MR angiography in the routine neurodiagnostic evaluation of patients with morning glory disc anomaly. It is unknown whether this congenital unilateral form of Moyamoya syndrome carries the same risk for progressive stenosis and cerebral ischemia that characterizes the more common bilateral progressive form in children. The coexistence of these intracranial vascular anomalies implicates a primary vascular dysgenesis with regional mesodermal dysgenesis.

Fig. 2.10 Transsphenoidal encephalocele. (a) T1-weighted sagittal MR image shows an encephalocele (delimited by open arrows) extending down through the sphenoid bone into the nasopharynx with impression on the hard palate (white arrow). (b) T1-weighted coronal MR image shows the third ventricle and hypothalamus (white arrowheads) extending inferiorly into the encephalocoele (delimited inferiorly by open arrows). Used, with permission, from Barkovich. Photographs courtesy of A. James Barkovich, M.D.
Congenital Optic Disc Anomalies

Holmström and Taylor documented the association of morning glory disc anomaly with ipsilateral orofacial hemangioma. Metry et al suggested that this association falls within the spectrum of the PHACE syndrome (posterior fossa malformations, large facial hemangiomas, arterial anomalies, cardiac anomalies and aortic coarctation, and eye anomalies), which occurs only in girls. We have confirmed that girls with infantile hemangiomas and ipsilateral morning glory disc anomalies (or peripapillary staphylomas) have PHACE syndrome with dysplasia of the ipsilateral carotid vasculature (Fig. 2.14). The morning glory disc anomaly has been reported in patients with neurofibromatosis 2 (Fig. 2.8), and in Okihiro syndrome.

Patients with morning glory disc anomaly are also at increased risk for acquired visual loss. Serous retinal detachments have been estimated to develop in 26–38% of eyes with morning glory anomalies optic discs. These detachments typically originate in the peripapillary area and extend through the posterior pole, occasionally progressing to total detachments. Although retinal tears are rarely evident, several reports have identified small retinal tears adjacent to the optic nerve in patients with morning glory disc-associated retinal detachments. Subretinal neovascularization may occasionally develop within the circumferential zone of pigmented disturbance adjacent to a morning glory disc. In addition to retinal detachments, careful fundus examination reveals nonattachment and radial folding of the retina within the excavated zone in a substantial percentage of the remaining cases. The sources of subretinal fluid may be multiple. Irvine et al reported a patient with a morning glory disc-associated retinal detachment who was treated with optic nerve fenestration followed by gas injection into the vitreous cavity. Following the procedure, gas was seen to bubble out through the dural window, demonstrating an interconnection between the vitreous cavity and the subarachnoid space through the anomalous disc. Chang et al also reported resolution of a morning glory-associated serous retinal detachment followingoptic nerve sheath fenestration. Spontaneous resolution of morning glory-associated retinal detachments have also been reported.

We and others have documented contractile movements in a morning glory optic disc. Pollock attributed the contractile movements in his case to fluctuations in subretinal fluid volume altering the degree of retinal separation within the confines of the excavation (Fig. 2.15). One child and one adult with unilateral morning glory disc anomalies had ipsilateral episodes of amaurosis accompanied by transient dilation of the retinal veins in an eye with a morning glory disc. In another child with a morning glory disc anomaly, MR angiography showed marked narrowing of the ipsilateral distal carotid artery, which resolved 6 months later, suggesting vasospasm.

The embryogenesis of the morning glory disc anomaly is poorly understood. Histopathological reports have, unfortunately, lacked clinical confirmation. Older reports mistakenly attributed the morning glory disc anomaly to defective closure of the embryonic fissure and considered it to be a phenotype a colobomatous (i.e., embryonic fissure-related) defect. More recent investigators have interpreted the

Fig. 2.11 Transphenoidal encephalocele. (a) Infant with transphenoidal encephalocele. Note hypertelorism, depressed nasal bridge, and mid upper lip defect. Photograph courtesy of Thomas P. Naidich, M.D. (b) Infant with cleft palate and intraoral transphenoidal encephalocele. Note midline cleft in upper lip. Photographs courtesy of William F. Hoyt, M.D.

Holmström and Taylor documented the association of morning glory disc anomaly with ipsilateral orofacial hemangioma. Metry et al suggested that this association falls within the spectrum of the PHACE syndrome (posterior fossa malformations, large facial hemangiomas, arterial anomalies, cardiac anomalies and aortic coarctation, and eye anomalies),
Excavated Optic Disc Anomalies

Clinical findings of a central glial tuft, vascular anomalies, and a scleral defect, together with the histological findings of adipose tissue and smooth muscle within the peripapillary sclera in presumed cases of the morning glory disc, to signify a primary mesenchymal abnormality. According to this interpretation, the associated midfacial anomalies in some patients further support the concept of a primary mesenchymal defect, because most of the cranial structures are derived from mesenchyme. Dempster attempted to reconcile these two views by proposing that the basic defect is mesodermal but that some clinical features of the defect may result from a dynamic disturbance between the relative growth of mesoderm and ectoderm. The observation that neural guidance molecules such as netrins also regulate angiogenesis may provide a clue to the molecular pathomechanism for this neurovascular anomaly.

Pollock has argued that the fundamental symmetry of the fundus excavation with respect to the disc implicates an anomalous funnel-shaped enlargement of the distal optic stalk at its junction with the primitive optic vesicle as the primary embryological defect. According to this hypothesis, the glial and vascular abnormalities that characterize the morning glory disc anomaly would be explainable as the secondary effects of a primary neuroectodermal dysgenesis on the formation of mesodermal elements that arise later in embryogenesis.

Optic Disc Coloboma

The term coloboma, of Greek derivation, means curtailed or mutilated. It is used only with reference to the eye. In optic disc coloboma, a sharply delimited, glistening white, bowl-shaped excavation occupies an enlarged optic disc (Fig. 2.16). The excavation is decentered inferiorly, reflecting...
the position of the embryonic fissure relative to the primitive epithelial papilla. The inferior neuroretinal rim is thin or absent, while the superior neuroretinal rim is relatively spared. Rarely, the entire disc may appear excavated; however, the colobomatous nature of the defect can still be appreciated ophthalmoscopically because the excavation is deeper inferiorly. The defect may extend further inferiorly to involve the adjacent choroid and retina, in which case...

Fig. 2.14  PHACE syndrome. (a) Large facial hemangioma. (b) Morning glory disc anomaly. (c) MR angiogram showing tortuosity of the right internal carotid artery (open arrow) and narrowing of the proximal right middle cerebral artery (closed arrow). Used with permission from Kneistdet al.

Fig. 2.15  Contractile morning glory optic disc. (a) Morning glory disc prior to contraction. Note minor retinal elevation with radial folding of the peripapillary retina. (b) Same morning glory disc during contraction. There is now greater elevation of retina and encroachment of peripapillary retinal folds on central glial tuft. Used with permission from Pollock. Photographs courtesy of Stephen C. Pollock, M.D.
Excavated Optic Disc Anomalies

Microphthalmia is frequently present. Optical disc colobomas may contain focal pit-like excavations. Iris and ciliary colobomas often coexist. Axial CT scanning shows a large crater-like excavation of the optic nerve at its junction with the globe (Fig. 2.17). Visual acuity, which depends primarily on the integrity of the papillomacular bundle, may be mildly to severely decreased and is difficult to predict from the appearance of the disc. Unlike the morning glory disc anomaly, which is usually unilateral, optic disc colobomas occur unilaterally or bilaterally with approximately equal frequency. As with uveal colobomas, optic disc colobomas may arise sporadically or be inherited in an autosomal dominant fashion. Ocular colobomas may also be accompanied by multiple systemic abnormalities in myriad conditions including, the CHARGE association, Walker-Warburg syndrome, Goltz focal dermal hypoplasia, Aicardi syndrome, Goldenhar sequence, and linear sebaceous nevus syndrome. Rarely, large orbital cysts can occur in conjunction with atypical excavations of the disc, which are probably colobomatous in nature. A communication between the excavation and the cyst was documented ultrasonographically in one case. Histopathological examination in optic disc coloboma has demonstrated the presence of intrascleral smooth muscle strands oriented concentrically around the distal optic nerve. This pathological finding may account for the contractility seen in rare cases of optic disc coloboma.
Eyes with isolated optic disc colobomas are prone to develop serous macular detachments, (Fig. 2.16) while those with retinochoroidal colobomas develop complicated rheumatogenous retinal detachments. In a clinicopathologic study of an optic disc coloboma and associated macular detachment in a rhesus monkey, Lin et al noted disruption of the intermediary tissue of Kuhnt, with diffusion of retrobulbar fluid from the orbit into the subretinal space. A variety of treatment modalities have been applied to the associated sensory retinal detachments, including patches, bedrest, corticosteroids, vitrectomy, scleral buckling procedures, gas-fluid exchange, and photocoagulation. Some have advocated waiting 3 months before treating coloboma-associated macular detachments, because spontaneous reattachment may occur. In patients with atypical optic disc colobomas, intraoperative drainage of subretinal fluid through the disc anomaly may be possible, or gas or silicone oil may be seen to migrate subretinally. The pressure differential required for migration of gas through a small defect in the roof of a cavitary lesion is within the range of expected fluctuations in cerebrospinal fluid pressure, suggesting the presence of interconnections between the vitreous cavity, subarachnoid space, and subretinal space. Perkins et al described three patients with macular schisis cavities who developed (noncolobomatous-appearing) optic disc cavitations concurrent with the resolution of the macular fluid. They proposed that a communication through dysplastic tissue could either allow liquified vitreous to migrate posteriorly into the perineural space or CSF to migrate intraretinally. They cautioned that, in cases of macular schisis in which an optic nerve excavation is not initially apparent, spontaneous resolution of the macular schisis cavity is possible.

Colobomatous malformations of the optic disc produce an inferior segmental hypoplasia of the optic nerve, with a C-shaped or quarter-moon-shaped neuroretinal rim confined to the superior aspect of the optic disc (Fig. 2.16). Colobomas constitute the most common segmental defect of optic nerve hypoplasia encountered in clinical practice. Coronal T1-weighted MR imaging confirms that the intracranial portion of the optic nerve is reduced in size. The nosological overlap between colobomatous derangement of the optic nerve and segmental hypoplasia reflects the early timing of colobomatous dysembryogenesis, which results in primary failure of inferior retinal ganglion cells to develop.

Unfortunately, many uncategorizable dysplastic optic discs are indiscriminately labeled optic disc colobomas. This practice continues to complicate the nosology of coloboma-associated genetic disorders. It is therefore crucial that the diagnosis of optic disc coloboma be reserved for discs that show an inferiorly decentered, white-colored excavation with minimal peripapillary pigmentary changes. For example, the purported association between optic disc coloboma and basal encephalocele is deeply entrenched in the literature; however, a critical review reveals only two photographically documented cases. In striking contrast to the numerous well-documented reports of morning glory optic discs occurring in conjunction with basal encephaloceles, cases of optic disc coloboma with basal encephalocele are conspicuous by their absence.

In the early 1900s, von Szily, in his monumental study of colobomas, stated “with certainty” that “all the true morphological malformations of the optic disc, including true colobomas . . . are only different manifestations of the same developmental anomaly, namely, a different form and degree of malformation of the primitive or epithelial optic papilla.” Despite the multiple ophthalmoscopic findings that distinguish optic disc coloboma from the morning glory disc anomaly (Table 2.2), many authors continue to treat these two anomalies as merely different phenotypic expressions of the same embryological defect, namely, failure of closure of the superior aspect of the embryonic fissure. Although the phenotypic profiles of optic disc coloboma and the morning glory disc anomaly may occasionally overlap, the ophthalmoscopic features of optic disc coloboma (Table 2.2) are most consistent with a primary structural dysgenesis involving the proximal embryonic fissure, as opposed to an anomalous dilatation confined to the distal optic stalk in the morning glory disc anomaly. The profound differences in associated ocular and systemic findings between the two anomalies (Table 2.3) lend further credence to this hypothesis.

<table>
<thead>
<tr>
<th>Table 2.2</th>
<th>Ophthalmoscopic findings that distinguish the morning glory disc anomaly from optic disc coloboma</th>
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<tr>
<td>Morning glory disc anomaly</td>
<td>Optic disc coloboma</td>
</tr>
<tr>
<td>Optic disc lies within the excavation</td>
<td>Excavation lies within the optic disc</td>
</tr>
<tr>
<td>Symmetrical defect (disc lies centrally within the excavation)</td>
<td>Asymmetrical defect (excavation lies inferiorly within the disc)</td>
</tr>
<tr>
<td>Central glial tuft</td>
<td>No central glial tuft</td>
</tr>
<tr>
<td>Severe peripapillary pigmentary disturbance</td>
<td>Minimal peripapillary pigmentary disturbance</td>
</tr>
<tr>
<td>Anomalous retinal vasculature</td>
<td>Normal retinal vasculature</td>
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<th>Table 2.3</th>
<th>Associated ocular and systemic findings that distinguish isolated optic disc coloboma from the morning glory disc anomaly</th>
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<tbody>
<tr>
<td>Morning glory disc anomaly</td>
<td>Optic disc coloboma</td>
</tr>
<tr>
<td>More common in females, rare in blacks</td>
<td>No sex or racial predilection</td>
</tr>
<tr>
<td>Rarely familial</td>
<td>Often familial</td>
</tr>
<tr>
<td>Rarely bilateral</td>
<td>Often bilateral</td>
</tr>
<tr>
<td>No iris, ciliary, or retinal colobomas</td>
<td>Iris, ciliary, and retinal colobomas common</td>
</tr>
<tr>
<td>Rarely associated with multisystem genetic disorders</td>
<td>Often associated with multisystem genetic disorders</td>
</tr>
<tr>
<td>Basal encephalocele common</td>
<td>Basal encephalocele rare</td>
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</tbody>
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the morning glory disc anomaly and optic disc coloboma are occasionally seen, these “hybrid” anomalies could easily represent instances of early embryonic injury involving both the proximal embryonic fissure and the distal optic stalk. Their existence should not obscure the fact that colobomatous and morning glory optic discs appear as clinically distinct anomalies in the great majority of cases. The concept of “an optic disc coloboma with a morning glory configuration” should be abandoned.

Coloboma can be sporadic or transmitted as an autosomal recessive, dominant, or X-linked trait.\textsuperscript{318} Mutations have been identified in the following genes: PAX6,\textsuperscript{13,119} CHX10,\textsuperscript{20,98} MAF,\textsuperscript{165} SHH,\textsuperscript{269} CHD7,\textsuperscript{176} GDF6,\textsuperscript{248} and SOX2.\textsuperscript{377} However, these genes account for only a fraction of colobomas,\textsuperscript{318} so there is no high-yield genetic test. In CHARGE syndrome, 60% have a mutation in CHD7 genetic testing is high yield.\textsuperscript{177} Because chromosomal abnormalities are more common in cases where coloboma is clearly syndromic, it is in the child who has systemic malformations involving the CNS, ears, spine or ribs, digits, or urogenital syndrome that genetic testing is most fruitful.

**Peripapillary Staphyloma**

Peripapillary staphyloma is a rare, usually unilateral anomaly, in which a deep fundus excavation surrounds the optic disc.\textsuperscript{62,277} In this condition, the disc is seen at the bottom of the excavated defect and may appear normal or shows temporal pallor (Fig. 2.18).\textsuperscript{244,326} The walls and margin of the defect may show atrophic pigmentary changes is the retinal pigment epithelium (RPE) and choroid.\textsuperscript{326} Unlike the morning glory disc anomaly, there is no central glial tuft overlying the disc, and the retinal vascular pattern remains normal, apart from reflecting the essential contour of the lesion.\textsuperscript{244} The staphylomatous excavation in peripapillary staphyloma is also notably deeper than that seen in the morning glory disc anomaly. Several cases of contractile peripapillary staphyloma have been documented.\textsuperscript{69,188,189,326} One patient had transient visual obscurations in an eye with an atypical peripapillary staphyloma.\textsuperscript{272}

Visual acuity is usually markedly reduced, but cases with normal acuity have also been reported.\textsuperscript{62} Affected eyes are usually emmetropic or slightly myopic.\textsuperscript{62} Eyes with decreased vision frequently have centrocecal scotomas.\textsuperscript{62}

Although peripapillary staphyloma is clinically and embryologically distinct from morning glory disc anomaly, these conditions are frequently transposed in the literature.\textsuperscript{40} Table 2.3 contrasts the ophthalmoscopic features that distinguish these two anomalies. Although peripapillary staphyloma is usually unassociated with systemic or intracranial disease, it has been reported in association with transsphenoidal encephalocele,\textsuperscript{146} PHACE syndrome,\textsuperscript{188} linear nevus sebaceous syndrome,\textsuperscript{56} and 18q- (de Grouchy) syndrome.\textsuperscript{163}

The relatively normal appearance of the optic disc and retinal vessels in peripapillary staphyloma suggests that the development of these structures is complete, prior to the onset of the staphylomatous process.\textsuperscript{244} According to Pollock,\textsuperscript{244} the clinical features of peripapillary staphyloma are consistent with diminished peripapillary structural support, perhaps resulting from incomplete differentiation of sclera from posterior neural crest cells in the fifth month of gestation. Staphyloma formation presumably occurs when establishment of normal intraocular pressure leads to herniation of unsupported ocular tissues through the defect.\textsuperscript{244} Thus, peripapillary staphyloma and the morning glory disc anomaly appear to be pathogenetically distinct both in the timing of the insult (5 months gestation vs. 4 weeks gestation) as well as the embryological site of structural dysgenesis (posterior sclera versus distal optic stalk).

**Megalopapilla**

Franceschetti and Bock originally assigned the term *megalopapilla* to a patient who had enlarged optic discs with no other morphological abnormalities.\textsuperscript{103} Since that time, *megalopapilla* or *congenital macrodiscs* have become generic terms that connote an abnormally large optic disc that lacks the inferior excavation of optic disc coloboma or the numerous anomalous features of the morning glory disc anomaly. In its current usage, megalopapilla comprises two phenotypic variants. The first is a relatively common variant in which an abnormally large optic disc (greater than 2.1 mm in diameter) retains an otherwise normal configuration.\textsuperscript{62,173} This form of megalopapilla...
is usually bilateral and often associated with a large cup-to-disc ratio, which almost invariably raises the diagnostic consideration of normal-tension glaucoma (Fig. 2.16). However, the optic cup is usually round or horizontally oval with no vertical notching or encroachment, so that the quotient of horizontal-to-vertical cup-to-disc ratio remains normal, in contradistinction to the decreased quotient that characterizes glaucomatous optic atrophy. Jonas et al have emphasized that the most important parameter in distinguishing megalopapilla from glaucoma may be the inferior-superior-nasal-temporal rule of the normal physiologic shape of the neural retinal rim.170,174,176 Because the axons are spread over a larger surface area, the neuroretinal rim may also appear pale, mimicking optic atrophy.63 Less commonly, a unilateral form of megalopapilla is seen in which the normal optic cup is replaced by a grossly anomalous noninferior excavation that obliterates the adjacent neuroretinal rim (Fig. 2.19). The inclusion of this rare variant under the rubric of megalopapilla serves the nosologically useful function of distinguishing it from a colobomatous defect with its attendant systemic implications. Cilioretinal arteries are more common in megalopapilla.175 A high prevalence of megalopapilla has been observed in natives of the Marshall Islands.209

Two reports have documented large optic discs in patients with optic nerve hypoplasia associated with a congenital homonymous hemianopia.211,246 This combination of findings suggests that a prenatal loss of optic nerve axons leading to optic nerve hypoplasia may not always alter the genetically predetermined size of the scleral canals.246 Visual acuity is usually normal but may be mildly decreased in some cases of megalopapilla. Visual fields are usually normal, except for an enlarged blind spot, allowing the examiner to effectively rule out normal tension glaucoma or compressive optic atrophy. However, Jonas et al175 reported the exceptional case of a three-year-old boy with congenital megalopapilla and normal neuroretinal rims who developed a glaucomatous optic neuropathy 10 years later. Colobomatous discs are distinguished from megalopapilla by their predominant excavation of the inferior optic disc. Aside from glaucoma and optic disc coloboma, the differential diagnosis of megalopapilla includes orbital optic glioma, which in children can cause progressive enlargement of a previously normalized optic disc.126

Pathogenetically, most cases of megalopapilla may simply represent a statistical variant of normal. However, it is likely that megalopapilla occasionally results from altered optic axonal migration early in embryogenesis, as evidenced by a report of megalopapilla in a child with basal encephalocele.153 The rarity of this association, however, would suggest that neuroimaging is unwarranted in megalopapilla, unless midfacial anomalies (e.g., hypertelorism, cleft palate, depressed nasal bridge) coexist.

Optic Pit

An optic pit is a round or oval, gray, white, or yellowish depression in the optic disc (Fig. 2.20). Optic pits commonly involve the temporal optic disc but may be situated in any sector.60 Temporally located pits are often accompanied by adjacent peripapillary pigment epithelial changes. One or two cilioretinal arteries are seen to emerge from the bottom or the margin of the pit in greater than 50% of cases.62,303 Although optic pits are typically unilateral, bilateral pits are seen in 15% of cases.62 Histologically, optic pits consist of herniations of dysplastic retina into a collagen-lined pocket extending posteriorly, often into the subarachnoid space, through a defect in the lamina cribrosa.62,99,161 Numerous reports of familial optic pits suggest an autosomal dominant mode of transmission.172,249,287
Excavated Optic Disc Anomalies

In unilateral cases, the involved disc is slightly larger than the normal disc. Visual acuity is typically normal in the absence of subretinal fluid. Although visual field defects are variable and often correlate poorly with the location of the pit, the most common defect appears to be a para-central arcuate scotoma connected to an enlarged blind spot. With rare exceptions, optic pits do not portend additional CNS malformations. Acquired depressions in the optic disc that are indistinguishable from optic pits have been documented in normal-tension glaucoma.

Serous macular elevations have been estimated to develop in 25–75% of eyes with optic pits. Optic pit-associated maculopathy generally becomes symptomatic in the third or fourth decade of life. Vitreous traction on the margins of the pit and tractional changes in the roof of the pit may be the inciting events that ultimately lead to late-onset macular detachment.

Until recently, all optic pit-associated macular elevations were thought to represent serous detachments. Studies by Lincoff et al have led to a better understanding of optic pit-associated maculopathy. These investigators have proposed that careful stereoscopic examination of the macula in conjunction with kinetic perimetry demonstrates the following progression of events:

1. A schisis-like inner-layer retinal separation initially forms in direct communication with the optic pit, which produces a mild, relative, centrocecal scotoma.
2. An outer-layer macular hole develops beneath the boundaries of the inner-layer separation and produces a dense central scotoma.
3. An outer-layer retinal detachment develops around the macular hole (presumably from influx of fluid from the inner-layer separation). This outer-layer detachment ophthalmoscopically resembles an RPE detachment but fails to hyperfluoresce on fluorescein angiography.
4. The outer-layer detachment may eventually enlarge and obliterate the inner-layer separation. At this stage, it is no longer ophthalmoscopically or histopathologically distinguishable from a primary serous macular detachment.

Figure 2.20 depicts the retinal findings that can be observed in the evolution of an optic pit-associated macular detachment. The finding of a sensory macular detachment in histopathologically studied eyes with optic pits presumably represents the end stage of this sequence of events. Optical coherence tomography has confirmed this mechanism.

The risk of optic pit-associated macular detachment is greater in eyes with large optic pits and in eyes with temporally located pits. Perhaps because of age-related differences in vitreopapillary traction, optic pit-associated serous maculopathy in children may have a tendency toward spontaneous resolution. Spontaneous reattachment is seen in approximately 25% of adult cases. Early reports of spontaneous resolution of most optic pit-associated macular detachments with good visual recovery differ from the experience of subsequent investigators who have noted permanent visual loss in untreated patients, even when spontaneous reattachment occurs. Bedrest and bilateral patching have led to retinal reattachment in some patients, presumably by decreasing vitreous traction.

Fig. 2.20 Optic pit showing each stage in evolution of serous macular detachment. (a) Abnormal radial striations between disc and macula (delimited by large arrows) correspond to schisis-like inner-layer retinal separation. There is also outer-layer hole (open arrow) surrounded by outer-layer macular detachment (delimited by small arrows). (b) Black and white photograph demonstrating inner-layer separation (delimited by large arrows), macular hole (open arrow), and outer-layer sensory detachment (delimited by small arrows). Used with permission from Lincoff et al. Copyright 1988, American Medical Association. Photograph courtesy of Harvey Lincoff, M.D.
Laser photoocoagulation to block the flow of fluid from the pit to the macula has been largely unsuccessful, perhaps due to the inability of laser photoocoagulation to seal a retinoschisis cavity.\textsuperscript{34,80,113,194,203,265,284} Vitrectomy with internal gas tamponade laser photoocoagulation has produced long-term improvement in acuity.\textsuperscript{3,113,142,203,216,265} Although the aim of this treatment is to compress the retina at the edge of the disc to enhance the effect of laser treatment, Linzoff et al\textsuperscript{219} have postulated that internal gas tamponade functions to mechanically displace subretinal fluid away from the macula, allowing a shallow, inner-layer separation to persist, which is associated with a mild scotoma and relatively good visual acuity. On the basis of clinical and perimetric observations following treatment, Linzoff et al have concluded that laser photocoagulation probably does not contribute to the success of this procedure.\textsuperscript{204}

The source of intraretinal fluid in eyes with optic pits is controversial. Possible sources include (1) vitreous cavity via the pit, (2) the subarachnoid space, (3) blood vessels at the base of the pit, and (4) the orbital space surrounding the dura. Although fluorescein angiography shows early hypofluorescence of the pit followed in many cases by late hyperfluorescent staining, optic pits do not generally leak fluorescein, and there is no extension of fluorescein into the subretinal space toward the macula.\textsuperscript{60} The finding of late hyperfluorescent staining has been shown to correlate strongly with the presence of cilioretinal arteries emerging from the pit.\textsuperscript{304} Careful slit-lamp biomicroscopy and OCT\textsuperscript{914} often reveal a thin membrane overlying the pit\textsuperscript{60} or a persistent Cloquet’s canal terminating at the margin of the pit.\textsuperscript{6}

Although active flow of fluid from the vitreous cavity through the pit to the subretinal space has been demonstrated in collie dogs, this mechanism has never been conclusively demonstrated in humans.\textsuperscript{61} Friberg and McLellan\textsuperscript{295} demonstrated a pulsatile communication of fluid between the vitreous cavity and a retrobulbar cyst through an optic pit. Theodossidasidis et al\textsuperscript{196} described a similar optic nerve sheath cyst that compressed and displaced the nerve, producing optic pallor. On the other hand, Dithmar et al\textsuperscript{217} reported progressive migration of oil into the subretinal space following retinal detachment surgery in an eye with a pit, suggesting that a communication between the vitreous cavity and the subretinal space through the pit can also cause retinal detachment. Rarely, macular holes can develop in eyes with optic pits or optic disc colobomas and lead to rhegmatogenous retinal detachment.\textsuperscript{29,293}

Although the pathogenesis of optic pits is unclear, they have historically been viewed as the mildest variant in the spectrum of optic disc colobomas.\textsuperscript{6,60,113,161,190,201,208,253,258,265,292,293} It should be noted, however, that this widely accepted hypothesis is inconsistent with the preponderance of clinical evidence:

1. Optic pits are usually unilateral, sporadic, and unassociated with systemic anomalies. Colobomas are bilateral as often as unilateral, commonly autosomal dominant, and may be associated with a variety of multisystem disorders.
2. It is rare for optic pits to coexist with iris or retinochoroidal colobomas.
3. Optic pits usually occur in locations unrelated to the embryonic fissure.

Following a review of 75 eyes with optic pits, Brown et al concluded that “the sparsity of inferonasal pits (none among our cases) casts doubt as to whether the pits are truly colobomas resulting from incomplete closure of the embryonic fissure. Certain authors have thought that pits are colobomas, and the finding of pits in three of our patients in association with true optic nerve colobomas, along with similar reports by others, indicates more than an incidental relationship. However, if pits are colobomatous defects, they are certainly atypical.”\textsuperscript{663} While it is true that colobomas may contain focal crater-like deformations that resemble optic pits,\textsuperscript{9,122} and that the distinction between an inferiorly located pit and a small optic disc coloboma is difficult at times, there appears to be sufficient evidence to conclude that most optic pits are fundamentally distinct from colobomas in their pathogenesis. The observation that one or more cilioretinal arteries emerge from the majority of optic pits suggests that this finding must somehow be pathogenetically related.\textsuperscript{50,140}

**Papillorenal Syndrome**

*(The Vacant Optic Disc)*

The papillorenal syndrome, previously known as renal-coloboma syndrome, was first described by Rieger in 1977.\textsuperscript{254} This syndrome was initially considered to be a rare autosomal dominant disorder consisting of bilateral optic disc anomalies associated with hypoplastic kidneys.\textsuperscript{230} Associated retinal detachments were described, as was eventual renal failure. In 1995, Sanyanusin et al discovered mutations in the developmental gene \textit{PAX2}, the human homologue of the mouse gene \textit{PAX2} in two affected families.\textsuperscript{266} Schimmenti et al\textsuperscript{168} identified three additional families with \textit{PAX2} mutations with similar ophthalmologic features and a wider spectrum of renal abnormalities, which may include hypoplasia, variable proteinuria, vesiculoureteral reflux, recurrent pyelonephritis, microhematuria, echogenicity on ultrasound, or high resistance to blood flow on Doppler ultrasound.

Parsa et al have since determined that the papillorenal syndrome is characterized by a distinct optic disc malformation that bears no relationship to coloboma.\textsuperscript{217} In this syndrome, the excavated optic disc is normal in size, and may be surrounded by variable pigmented disturbances.\textsuperscript{237} Unlike in colobomatous defects, the excavation is centrally positioned (Fig. 2.18). According to Parsa et al, the defining feature is the presence of multiple cilioretinal vessels that emanate from the periphery...
of the disc, and variable attenuation or atrophy of the central retinal vessels (Fig. 2.21). Color Doppler imaging has confirmed the absence of central retinal circulation in patients with papillorenal syndrome. Visual acuity is usually 20/20 but may occasionally be severely diminished secondary to choroidal and retinal hypoplasia and, in some cases, to later-onset serous retinal detachments. Peripheral visual field defects corresponding to areas of retinal hypoplasia are often present. The central optic disc excavation and peripheral field defects can simulate coloboma as well as normal tension glaucoma. Follow-up examination has shown renal disease in some patients who were originally reported as having isolated familial autosomal dominant “coloboma.” In infants, the bilateral optic disc excavation can simulate congenital glaucoma, but the diagnosis can be established clinically by recognizing the characteristic optic disc morphology.

This malformation is attributed to a primary deficiency in angiogenesis involved in vascular development. In these patients, there is a failure of the hyaloid system to convert to normal central retinal vessels. The absence of a well-defined central retinal artery or vein in several adult mammalian species, including lemurs and cats, suggests that this malformation could be considered analogous to an evolutionary regression to a feline pattern of circulation. Because ocular tissues and renal cortex are the most highly perfused tissues of the body, both develop a significant portion of their vasculature by means of angiogenesis (budding) in addition to vasculogenesis. These tissues may thus be particularly susceptible to anomalies in vascular development, resulting in hypoplasia or anomalies of associated structures. Many patients with papillorenal syndrome have no detectable mutations in the PAX2 gene.

Honkanen et al recently described a four-generation pedigree with progressive optic nerve head cupping, anomalous vasculature (often emerging from the periphery of the disc), and serous macular detachments in some patients and mapped the chromosomal location of the disease-causing gene to chromosome 12q. These patients may have had undiagnosed papillorenal syndrome. In patients with the vacant optic disc, we routinely check blood pressure and order serum BUN and creatinine levels, urinalysis for hematuria, and Doppler renal ultrasound to look for structural defects such as renal hypoplasia.

**Congenital Tilted Disc Syndrome**

Nonspecific tilting of the optic discs is a rather frequent anomaly found in 1.6–1.7% of population-based surveys. The tilted disc syndrome is a nonhereditary bilateral condition in which the superotemporal optic disc is elevated and the inferonasal disc is posteriorly displaced, resulting in an oval-appearing optic disc, with its long axis obliquely oriented (Fig. 2.22). This configuration is accompanied by situs inversus of the retinal vessels, congenital inferonasal conus, thinning of the inferonasal RPE and choroid, and bitemporal hemianopia. The anomalous optic disc appearance is secondary to a posterior ectasia of the inferonasal fundus and optic disc. Because of the regional fundus ectasia, affected patients have myopic astigmatism, with the plus axis oriented parallel to the ectasia. Corneal topography studies indicate that an irregular corneal curvature contributes to the associated astigmatism. The cause of the condition is unknown, but the inferonasal or inferior location of the excavation is at least vaguely suggestive of a pathogenetic relationship to retinochoroidal coloboma.
Familiarity with the tilted disc syndrome is crucial for the ophthalmologist, because affected patients may present with bitemporal hemianopia or optic disc elevation that simulates papilledema.\(^7,40\) The bitemporal hemianopia in affected patients, which is typically incomplete and confined primarily to the superior quadrants, represents a refractive scotoma, secondary to regional myopia localized to the inferonasal retina. Unlike the visual field loss from chiasmal lesions, the field defects seen in the tilted disc syndrome fail to respect the vertical meridian on careful kinetic perimetry. Furthermore, the superotemporal depression is selectively confined to the midsize isopter, while the large and small

Fig. 2.22 Congenital tilted disc syndrome. (a) and (b) Optic discs appear obliquely oval. There is elevation of superonasal discs and posterior displacement of inferonasal disc. Note subtle inferonasal peripapillary crescent, albinotic appearance of inferonasal retina, and situs inversus of vessels as they emerge from disc. (c and d) Goldmann visual field of right eye demonstrates superotemporal visual field defect confined to midperipheral isopter that does not respect horizontal meridian. (e and f) Axial CT scan showing “tilted eyeballs” with posterior protrusion of both globes. Courtesy of Klara Landau, M.D.
Congenital Optic Disc Pigmentation

isopters remain fairly normal due to the marked ectasia of the midperipheral fundus. Repeat perimetry after addition of a −4.00 lens often eliminates the visual field abnormality, confirming the refractive nature of the defect. In some cases, retinal sensitivity may be decreased in the area of the ectasia, and the defect persists to some degree despite appropriate refractive correction.129

It should be emphasized that the tilted disc syndrome has been associated with true bitemporal hemianopia in several patients who were found to harbor a congenital suprasellar tumor. As with optic nerve hypoplasia, these two seemingly disparate findings may reflect the disruptive effect of the suprasellar tumor on optic axonal migration during embryogenesis.301 This sinister association makes neuroimaging mandatory in any patient with a tilted disc syndrome whose bitemporal hemianopia either respects the vertical meridian or fails to preferentially involve the midperipheral isopter on kinetic perimetry.178,231 Tilted discs without retinal ectasia occur in patients with transsphenoidal encephalocele.55,64 The tilted disc syndrome has also been reported in patients with X-linked congenital stationary night blindness.137,144 In eyes with tilted discs or the full tilted disc syndrome, anomalies at the junction of the staphyloma or at the junction between the peripapillary retina and the altered disc margin may cause serous macular detachments.43,76,307 Crowding and elevation of the superotemporal portion of the tilted disc may predispose to the formation of optic disc drusen118 and to central retinal vein occlusion.117

The congenital tilted disc syndrome can also be complicated by choroidal neovascularization, which develops at the inferotemporal edge of the staphyloma,116 serous macular detachment and subretinal leakage,59 and polypoidal choroidal vasculopathy.215

Optic Disc Dysplasia

The term optic disc dysplasia should be viewed not as a diagnosis but as a descriptive term that connotes a markedly deformed optic disc that fails to conform to any recognizable diagnostic category (Fig. 2.23). The distinction between an un categorizable “anomalous” disc and a “dysplastic” disc is somewhat arbitrary and based primarily on the severity of the lesion. In the past, the term optic disc dysplasia has been applied to cases that are now recognizable as the morning glory disc anomaly.123,132 Conversely, many dysplastic optic discs have been indiscriminately labeled optic disc colobomas.40 It is likely that additional variants of optic disc dysplasia will be recognized and identified as distinct anomalies.

A discrete infrapapillary zone of V- or tongue-shaped retinochoroidal depigmentation has been described in five patients with dysplastic optic discs and transsphenoidal encephalocele (Fig. 2.24).55 These juxtapapillary defects differ from typical retinochoroidal colobomas, which widen inferiorly and are not associated with basal encephalocele. Unlike the typical retinochoroidal coloboma, this distinct juxtapapillary defect is associated with minimal scleral excavation and no visible disruption in the integrity of the overlying retina. In patients with dysplastic optic discs, the finding of this V- or tongue-shaped infrapapillary retinochoriald anomaly should prompt neuroimaging to look for transsphenoidal encephalocele.55

Congenital Optic Disc Pigmentation

Congenital optic disc pigmentation is a condition in which melanin deposition anterior to or within the lamina cribrosa imparts a gray or black appearance to the optic disc (Fig. 2.25).50 True congenital optic disc pigmentation is extremely rare, but it has been described in a child with an interstitial deletion of chromosome 17 and in Aicardi syndrome.50 Congenital optic disc pigmentation is compatible with good visual acuity but may be associated with coexistent optic disc anomalies that decrease vision.50 Silver and Sapiro276 have demonstrated that, in developing mice and rats, a transient zone of melanin in the distal developing optic stalk influences migration of the earliest optic nerve axons. The effects of abnormal pigment deposition on optic nerve embryogenesis could explain the frequent coexistence of congenital optic disc pigmentation with other anomalies, particularly optic nerve hypoplasia. In some cases, congenital optic disc pigmentation may be
Infrapapillary retinochoroidal depigmentation associated with transsphenoidal encephalocele. (a) V-shaped defect with inferior segmental optic hypoplasia. Photograph courtesy of William F. Hoyt, M.D. (b) Tongue-shaped infrapapillary depigmentation with dysplastic optic disc. Used with permission from Brodsky et al.55

Congenital optic disc pigmentation. (a) Right optic disc. Circular area of patchy pigmentation surrounds severely hypoplastic, elevated, central tuft of optic nerve substance, producing appearance of gray optic disc. Arteries and veins overlying disc are anomalous. (b) Left optic disc. Disc is elevated and uniformly gray in appearance. Note anomalous superior vasculature and anomalous venous trunk along 2 o’clock meridian of disc. Used with permission from Brodsky et al.50

difficult to distinguish from melanocytoma of the optic disc. This distinction is assisted by the fact that melanocytoma is generally a unilateral condition and rarely associated with other optic disc anomalies.56

The great majority of patients with gray optic discs do not have congenital optic disc pigmentation. For reasons that are poorly understood, optic discs of infants with delayed visual maturation and albinism may have a diffuse gray tint when
viewed ophthalmoscopically (Fig. 2.26). In these conditions, the gray tint often disappears in the first year of life without visible pigment migration. Beauvieux observed gray optic discs in premature infants and in albinotic infants who were apparently blind but who later developed good vision as the gray color disappeared.\(^{21,22}\) He attributed the gray appearance of these neonatal discs to delayed optic nerve myelination with preservation of the “embryonic tint.” It should be noted, however, that gray optic discs may also be seen in normal neonates and are therefore a nonspecific finding of little diagnostic value, except when accompanied by other clinical signs of delayed visual maturation or albinism.

Despite their fundamental differences, “optically gray optic discs” and congenital optic disc pigmentation have, unfortunately, been lumped together in many reference books. These two conditions can usually be distinguished ophthalmoscopically, because melanin deposition in true congenital optic disc pigmentation is often discrete, irregular, and granular in appearance.\(^{50}\)

**Aicardi Syndrome**

The Aicardi syndrome is a cerebroretinal disorder of unknown etiology. Its salient clinical features are infantile spasms, agenesis of the corpus callosum, a characteristic electroencephalographic pattern termed hypsarrhythmia, and a pathognomonic optic disc appearance consisting of multiple de-pigmented “chorioretinal lacunae” clustered around the disc (Fig. 2.27).\(^{67,92,155}\)

Histologically, chorioretinal lacunae consist of well-circumscribed, full-thickness defects limited to the RPE and choroid. The overlying retina remains intact, but is often histologically abnormal.\(^{67}\)

Congenital optic disc anomalies, including optic disc coloboma, optic nerve hypoplasia, and congenital optic disc pigmentation, may accompany chorioretinal lacunae.\(^{67,73}\) Other ocular abnormalities include microphthalmos, retrolubular cyst, pseudoglioma, retinal detachment, macular scars, cataract, pupillary membranes, iris synechiae, and iris colobomas.\(^{73,155}\) The most common systemic findings associated with the Aicardi syndrome are vertebral malformations (e.g., fused vertebrae, scoliosis, spina bifida) and costal malformations (e.g., absent ribs, fused or bifurcated ribs).\(^{67,73,155}\) Other systemic associations include muscular hypotonia, microcephaly, dysmorphic facies, auricular anomalies, and gastrointestinal dysfunction.\(^{120}\) A constellation of facial anomalies, including a prominent premaxilla, upturned nasal tip, decreased angle of the nasal bridge, and sparse lateral eyebrows may assist in the diagnosis of the Aicardi syndrome.\(^{203}\) Various skin lesions are also present in 20% of cases.\(^{201}\) Severe mental retardation is almost invariable.\(^{57,155}\)

CNS anomalies in the Aicardi syndrome include agenesis of the corpus callosum, cortical migration anomalies (e.g., pachygyria, polymicrogyria, cortical heterotopias), and
multiple structural CNS malformations (e.g., cerebral hemispheric asymmetry, Dandy–Walker variant, colpocephaly, midline arachnoid cysts) (Fig. 2.28).5,15,67,121,131,152,160 An overlap between the Aicardi syndrome and septo-optic dysplasia has been recognized in several patients.67 The intriguing association between choroid plexus papilloma and the Aicardi syndrome has been documented in five patients.297 No gene has been identified for the Aicardi syndrome, but several observations support the hypothesis that the Aicardi syndrome is caused by de novo mutations of a gene on the

![Fig. 2.28 MR imaging in Aicardi syndrome. (a) Sagittal T1-weighted MR image demonstrating agenesis of corpus callosum (upper solid arrow denotes normal position of corpus callosum), arachnoid cyst in region of quadrigeminal cistern (open arrow), and hypoplasia of cerebellar vermis with cystic dilatation of fourth ventricle (Dandy–Walker variant) (white arrow). (b) Coronal T1-weighted image demonstrating absent corpus callosum (black arrow denotes normal position of corpus callosum) and chiasmal hypoplasia (white arrow). (c) Coronal inversion recovery image (arrow) demonstrating pachygyria (thickened dysmorphic cortex with decreased cortical gyri and sulci). (d) Axial T1-weight MR image demonstrating gray matter heterotopias in right temporal lobe (upper arrow), small areas of probable polymicrogyria just medial to occipital poles (greater in left hemisphere), dilatation of posterior horns of lateral ventricles (also known as colpocephaly) (open arrows), and arachnoid cyst in region of quadrigeminal cistern (lower arrow). Used with permission from Carney et al.67]
Doubling of the Optic Disc

X-chromosome that is subject to X-chromosomal inactivation and that is lethal in males. Parents should therefore be asked about a previous history of miscarriages. All but four affected individuals have been female and, except for one pair of sisters, all reported cases are sporadic. At least six pairs of twins that are discordant for Aicardi syndrome are known. Five of these are confirmed to be dizygotic, which excludes the possibility that the etiology is a prenatal toxic or other disruptive event. With a single exception, all males confirmed to have Aicardi syndrome had a 47XXY karyotype. In 1986, Chevrie and Aicardi suggested that all cases of Aicardi syndrome represent fresh gene mutations, because no cases of affected siblings had been reported. A report of Aicardi syndrome in two sisters challenged the notion that Aicardi syndrome always results from a de novo mutation in the affected infant and indicates that parental gonadal mosaicism for the mutation may be an additional mechanism of inheritance.

Although early infectious CNS insults can lead to severe CNS anomalies, tests for infective agents have been consistently negative. No teratogenic drug or other toxin has yet been associated with the Aicardi syndrome. On the basis of the pattern of cerebroretinal malformations in the Aicardi syndrome, it is speculated that an insult to the CNS must take place between the fourth and eighth week of gestation.

The neurodevelopmental prognosis of Aicardi syndrome is extremely poor, with most children having seizures that are intractable despite therapy, and 91% attaining milestones no higher than 12 months. However, some do well; one girl reportedly never had seizures, and her psychomotor and language development were normal for her age. One study found the presence of large chorioretinal lacunae to correlate with poor neurodevelopment. The ability of new medications such as vigabatrin and lamotrigine, which are more effective in controlling infantile spasms, have also improved the neurodevelopmental outcome and obviated the need for treatment with adrenocorticotropic hormones and prednisone.

Persistence of fetal vasculature between gestational weeks 9 and 12 may provide a unifying hypothesis for the embryogenesis of the Aicardi syndrome. On the basis of the presence of associated intraocular malformations such as microphthalmos, persistent pupillary membrane, persistent hyperplastic primary vitreous, vascular loops on the optic disc, and epiretinal glial tissue, a persistence of fetal vasculature between gestational weeks 9 and 12 may provide a unifying hypothesis for the embryogenesis of the Aicardi syndrome.

Doubling of the Optic Disc

Doubling of the optic disc is a rare anomaly in which two discs appear to be in close proximity to one another. This ophthalmoscopic finding is presumed to result from a duplication or separation of the distal optic nerve into two fasciculi. Most reports describe a “main” disc and a “satellite” disc, each with its own vascular system (Fig. 2.29). Doubling of the optic disc is usually unilateral and associated with decreased vision in the involved eye.

Most clinical reports antedate the era of high-resolution neuroimaging and have relied upon the roentgenographic demonstration of two optic nerves in the same orbit, results of fluorescein angiography, synchronous pulsations of each major disc artery, dual blind spots, and angioscotomas to provide indirect evidence of optic nerve diastasis. In many cases, an apparent doubling of the optic disc results from a

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**Fig. 2.29** Doubling of optic disc (a) Note superior retinal vasculature arising from upper disc and inferior retinal vasculature arising from lower disc, with interconnecting vessels between two discs. (b) Major optic disc and superotemporal “accessory optic disc” (right eye). Note “bridging tissue” between discs. Used with permission from Donoso et al. Photographs courtesy of Larry Donoso, M.D.
focal, juxtapapillary retinochoroidal coloboma that displays an abnormal vascular anastomosis with the optic disc.\textsuperscript{93,312}

Separation of the optic nerve into two or more is rare in humans but common in lower vertebrates.\textsuperscript{33} However, separation of various portions of an intracranial or orbital optic nerve has been documented in a handful of autopsy cases.\textsuperscript{77,108,230,279,282} High-resolution orbital MR imaging should allow in vivo confirmation of optic nerve diastasis. In one recent case, retinal examination disclosed distinct vasculatures, OCT and ultrasound permitted in vivo imaging confirmation of two distinct optic nerve heads.\textsuperscript{252} Acquired optic nerve splitting has been described after trauma and penetration by an aneurysm.\textsuperscript{90,178} Occasionally, coronal MR imaging can produce the appearance of optic nerve diastasis.\textsuperscript{114}

**Optic Nerve Aplasia**

Optic nerve aplasia is a rare nonhereditary malformation that is usually seen in a unilaterally malformed eye of an otherwise healthy person.\textsuperscript{320} In its current usage, the term optic nerve aplasia comprises complete absence of the optic nerve (including the optic disc), retinal ganglion and nerve fiber layers, and optic nerve vessels.\textsuperscript{313a} Histopathological examination usually demonstrates a vestigial dural sheath entering the sclera in its normal position, as well as retinal dysplasia with rosette formation (Fig. 2.30).\textsuperscript{320} Some early reports of optic nerve aplasia actually described patients with severe hypoplasia at a time when the latter entity was not clearly recognized.\textsuperscript{205,213a}

Ophthalmoscopically, optic nerve aplasia may take on any of the following appearances\textsuperscript{32}:

- Absence of a normally defined optic nerve head or papilla in the ocular fundus, without central blood vessels or macular differentiation
- A whitish area corresponding to the optic disc, without central vessels or macular differentiation
- A deep avascular cavity in the site corresponding to the optic disc, surrounded by a whitish annulus

Optic nerve aplasia seems to fall within a malformation complex that is fundamentally distinct from that seen with optic nerve hypoplasia, as evidenced by its tendency to occur unilaterally and its frequent association with malformations that are otherwise confined to the involved eye (microphthalmia, malformations in the anterior chamber angle, hypoplasia or segmental aplasia of the iris, cataracts, persistent hyperplastic primary vitreous, colobomas, and retinal dysplasia), as opposed to the brain.\textsuperscript{32,115,154,250} The pathogenesis of optic nerve aplasia is unknown. When it occurs bilaterally, optic nerve aplasia is usually associated with other CNS malformations,\textsuperscript{19,289,327} although rare exceptions exist.\textsuperscript{252} One infant with bilateral optic nerve aplasia was found to have congenital hypopituitarism and posterior pituitary ectopia.\textsuperscript{49}

In patients with unilateral optic nerve aplasia, the intracranial course of the “intact” optic nerve may vary. One patient with unilateral anophthalmos had optic nerve aplasia associated with a congenital giant suprasellar aneurysm.\textsuperscript{147} The remaining optic nerve was identified at craniotomy as passing posteriorly as a single cord to form an optic tract with no adjoining chiasm. It was speculated that the absent optic nerve and chiasm may have formed initially and then degenerated in a retrograde fashion. Autopsy findings from a patient with a Hallerman–Streiff-like syndrome and left optic nerve hypoplasia showed normal geniculate bodies and optic tracts with only a single nerve that emerged anteriorly from a chiasm that deviated to the right.\textsuperscript{153} In another patient with unilateral optic nerve aplasia and microphthalmos, MR imaging disclosed optic nerve aplasia and hemichiasmal hypoplasia on the
affected side. Visual evoked cortical responses demonstrated increased signals over the occipital lobe contralateral to the intact optic nerve, suggesting chiasmal misdirection of axons from the temporal retina of the normal eye, as seen in albinos. The authors speculated that this abnormal decussation may represent an atavistic form of neuronal reorganization. Optic nerve aplasia and its associated chorioretinal lacuna may occasionally overlap with the autosomal dominant microcephaly-lymphedema-chorioretinal dysplasia syndrome.

Myelinated (Medullated) Nerve Fibers

Myelination of the afferent visual pathways begins at the lateral geniculate body at 5 months of age and terminates at the lamina cribrosa at term or shortly thereafter. Oligodendrocytes, which are responsible for myelination in the CNS, are not normally present in the human retina. Histological studies have confirmed the presence of presumed oligodendrocytes and myelin in areas of myelinated nerve fibers and their absence in other areas. Myelinated retinal nerve fibers have been found in approximately 1% of eyes examined at autopsy and in 0.3–0.6% of routine ophthalmic patients. Ophthalmoscopically, myelinated nerve fibers usually appear as white striated patches at the upper and lower poles of the disc (Fig. 2.31). In this location, they may simulate papilledema, both by elevating the involved portions of the disc and by obscuring the disc margin and the underlying retinal vessels. Distally, they have an irregular fan-shaped appearance that facilitates their recognition. Small slits or patches of normal-appearing fundus color are occasionally visible in an area of myelination. Myelinated nerve fibers are bilateral in 17–20% of cases, and clinically, they are discontinuous with the optic nerve head in 19%. Isolated patches of myelinated nerve fibers in the peripheral retina are rarely found nasal to the optic nerve head.

The pathogenesis of myelinated nerve fibers remains largely speculative, but several recent hypotheses advanced by Williams provide a useful conceptual framework and seem particularly plausible in light of recent reports. It is known that animals with little or no evidence of lamina cribrosa tend to have deep physiological cups and extensive myelination of retinal nerve fibers, while animals with a well-developed lamina cribrosa tend to show fairly flat nerve heads and no myelination of retinal nerve fibers. Williams has used this animal model to question whether the following factors could play a critical role in the pathogenesis of myelinated nerve fibers:

1. A defect in the lamina cribrosa may allow oligodendrocytes to gain access to the retina and produce myelin there.
2. There may be fewer axons relative to the size of the scleral canal, producing enough room for myelination to proceed into the eye. In eyes with remote, isolated peripheral patches of myelinated nerve fibers, an anomaly in the formation or timing of formation of the lamina cribrosa permits access of oligodendrocytes to the retina. These cells then migrate through the nerve fiber layer until they find a region of relatively low nerve fiber layer density, where they proceed to myelinate some axons.
3. Late development of the lamina cribrosa may allow oligodendrocytes to migrate into the eye. The sclera begins to consolidate in the limbal region, then proceeds posteriorly toward the lamina cribrosa. As Williams stated, “in a sense, it is possible to imagine a race going on, with the oligodendrocytes myelinating their way toward the retina and the mesodermal tissue consolidating its way to make the lamina cribrosa. If scleral consolidation is retarded, then some retinal myelination may occur.”

Extensive unilateral (or, rarely, bilateral) myelination of nerve fibers can be associated with high myopia and severe amblyopia (Fig. 2.32). Unlike other forms of unilateral high myopia that characteristically respond well to occlusion therapy, many children with myelinated nerve fibers are notoriously refractory to rehabilitation. In such patients, myelin envelops most or all of the circumference of the disc, and the disc may have a dysplastic appearance. In addition, the macular region (although unmyelinated) usually appears abnormal, showing a dulled reflex or pigment dispersion. The appearance of the macula may be the best direct correlate of response to occlusion therapy. Schmidt et al proposed that myelinated retinal nerve fibers could blur
retinal images and induce visual deprivation.\textsuperscript{270} Regarding the pathogenesis of the syndrome, it is unclear whether increased axial length of the eye predisposes to retinal myelination or whether retinal myelination causes myopia.\textsuperscript{269,299} Myelinated nerve fibers may be familial, in which case the trait is usually inherited in an autosomal dominant fashion.\textsuperscript{105} Isolated cases of myelinated nerve fibers have also been described in association with abnormal length of the optic nerve (oxycephaly),\textsuperscript{27} effects in the lamina cribrosa (tilted disc),\textsuperscript{23} anterior segment dysgenesis,\textsuperscript{322} and NF-2.\textsuperscript{125} Although myelinated nerve fibers are purported to be associated with neurofibromatosis,\textsuperscript{125} many authorities feel that this association is questionable at best.\textsuperscript{322}

Myelinated nerve fibers also occur in association with the Gorlin (multiple basal cell nevi) syndrome.\textsuperscript{84} This autosomal dominant disorder can often be recognized by the finding of numerous tiny pits in the hands and feet that produce a “sandpaper” irregularity. Multiple cutaneous tumors develop in the second or third decade, but they may occasionally develop in the first few years of life. When present in childhood, these lesions remain quiescent until puberty, then increase in number and demonstrate a more rapid and invasive growth pattern.\textsuperscript{179} Additional features include jaw cysts (which are found in approximately 70% of patients and often appear in the first decade of life) and mild mental retardation.\textsuperscript{84} Rib anomalies (bifid ribs, splaying, synostoses, and partial agenesis) are found in approximately 50% of patients. Facial characteristics include hypertelorism, prominent supraorbital ridges, frontoparietal bossing, a broad nasal root, and mild mandibular prognathism.\textsuperscript{84} Ectopic calcification, especially of the falx cerebri, is an almost constant finding. Medulloblastomas have developed in several children with this condition. This disorder should be considered in children with myelinated nerve fibers, because small lesions can be treated with curettage, electrophotocoagulation, cryosurgery, and topical chemotherapy to forestall the development of aggressive and invasive lesions.\textsuperscript{179}

Traboulsi et al\textsuperscript{307} described an autosomal dominant vitreoretinopathy characterized by congenitally poor vision, bilateral extensive myelination of the retinal nerve fiber layer, severe vitreal degeneration, high myopia, a retinal dystrophy with night blindness, reduction of the electroretinographic responses, and limb deformities.

Rarely, areas of myelinated nerve fibers are acquired after infancy and even in adulthood.\textsuperscript{1,14} Trauma to the eye (a blow to the eye in one patient and an optic nerve sheath fenestration in the other) seems to be a common denominator in these cases. Williams has suggested that “perhaps there was sufficient damage to the lamina cribrosa in these patients to permit oligodendrocytes to enter the retina, whereupon they moved to the nearest area of relatively loose nerve fibers and myelinated them.” Myelinated nerve fibers have also been known to disappear as a result of tabetic optic atrophy, pituitary tumor, glaucoma, central retinal artery occlusion, and optic neuritis.\textsuperscript{222}

The Albinotic Optic Disc

The optic discs of albinos have a number of distinct ophthalmoscopic appearance that has gone largely unrecognized. Albino optic discs often have a diffuse gray tint when viewed ophthalmoscopically in the first few years of life. This discoloration must somehow be related to optical effects resulting from surrounding chorioretinal depigmentation, because it is no longer evident in older children and adults.

Schatz and Pollock\textsuperscript{356} have identified the following five ophthalmoscopic findings that characterize most albino optic discs: (1) small disc diameter; (2) absence of the physiological cup; (3) oval shape with long axis oriented obliquely; (4) origin of the retinal vessels from the temporal aspect of the disc; and (5) abnormal course of retinal vessels consisting of initial nasal deflection followed by abrupt divergence and reversal of direction to form the temporal vascular arcades (Fig. 2.33). The purported association between albinism and optic nerve hypoplasia is controversial. Although histopathological verification is lacking in humans, some circumstantial evidence supports this association. Clinically, it has been observed that the optic discs appear small in some human albinos.\textsuperscript{296} Because the macula is poorly developed in albinos, it is plausible that a decreased number of macular ganglion cells would reduce the total number of optic nerve axons from the papillomacular nerve fiber bundle.
Optic nerve hypoplasia would then be inevitable, unless other nerve fiber bundles contained a proportionately larger number of axons. Several histological studies have estimated that animals with albinism have approximately 7% fewer optic nerve fibers than their normally pigmented counterparts. These findings raise the possibility that optic nerve hypoplasia is a component of albinism. In one study, high-resolution MR imaging of the intracranial optic nerves in human albinos shows no diminution in size while a more recent study detected hypoplasia anterior visual pathways.

Clinically, the diagnosis of mild optic nerve hypoplasia is usually predicated on finding either subnormal visual acuity or visual field abnormalities, which are usually present in albinos by virtue of the associated macular hypoplasia and nystagmus. Because neither ophthalmoscopy nor MR imaging alone can definitively distinguish mild forms of optic nerve hypoplasia from variants of normal, resolution of this controversy awaits neuropathological examination of human albino optic nerves.

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