The Syndrome of Optic Nerve Hypoplasia

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The congenital malformation known as optic nerve hypoplasia (ONH) has been recognized in the past 30 years as an epidemic cause of congenital blindness. It was believed to occur either as an isolated anomaly or as a component of the syndrome of septo-optic dysplasia, which has evolved to include midline brain malformations and hypopituitarism. Evidence now suggests that ONH infrequently occurs in isolation. Most afflicted children will have hypothalamic dysfunction and/or neurodevelopmental impairment, regardless of MRI findings or severity of ONH. Adverse outcomes can often be ameliorated with early intervention. Thus, the syndrome of ONH should be suspected in all infants with signs of hypothalamic dysfunction or vision impairment.

Introduction

Optic nerve hypoplasia (ONH) is a congenital abnormality characterized by small optic discs affecting one or both eyes. It can occur in isolation or in combination with a myriad of functional and anatomic abnormalities of the central nervous system. Recently, ONH has been recognized as an increasingly frequent problem. Concomitantly, our understanding of this epidemic of neuronal dysgenesis and its diverse impact on growth and development has evolved considerably.

History and Epidemiology

Because of insufficient documentation, it is uncertain when the first case of ONH without associated microphthalmos or other ocular malformation was described. It dates to at least 1915 [1], but it may have been considerably earlier [2]. Nonetheless, prior to 1970, fewer than 30 cases had been reported in the English literature [3].

In 1941, Reeves [4] identified absence of the septum pellucidum in a 7-month-old girl with bilateral optic nerve hypoplasia. Fifteen years later, de Morsier [5] described an association of absent septum pellucidum with malformation of the optic chiasm in a single pathologic case of an 84-year-old woman. He provided no description of vision problems or ophthalmoscopic abnormalities, but he noted that the corpus callosum was normal. He also found a coexistence of unilateral or bilateral optic nerve abnormalities (or anophthalmia) with agenesis of the septum pellucidum in eight other radiology or pathology cases from the literature. He termed the association *septo-optic dysplasia*, despite the fact that descriptions of the optic nerve abnormalities were vague. It is important to note that de Morsier was collecting pathology cases of agenesis of the septum pellucidum and that ONH was coincidentally found in 1 of his 36 cases. Nonetheless, agenesis of the septum pellucidum was ascribed exaggerated clinical significance in much of the subsequent literature. It is now clear that absence of the septum pellucidum imparts no increased risk for the myriad of problems associated with ONH. It is also clear that these associated problems are largely due to miswiring of the brain, especially in the hypothalamus, that may not be detectable with neuroimaging. It is therefore suggested that the term *septo-optic dysplasia* be replaced with *syndrome of optic nerve hypoplasia*.

In 1970, Hoyt et al. [6] noted an association of pituitary dwarfism in nine cases of ONH, four of whom were found to be missing the septum pellucidum. They resurrected de Morsier's concept of septo-optic dysplasia and linked hypopituitarism to the syndrome. That same year, a similar case was described by Ellenberger and Runyan [7], and a series of 25 cases of ONH had numerous neurologic impairments without any described endocrine defects [8]. Because these reports preceded the era of CT scans, the prevalence of midline brain defects in these cases was unknown. In a subsequent large series of cases, hypopituitarism occurred at a high frequency and was present almost exclusively in bilateral severe cases, with or without agenesis of the septum pellucidum [9]. Other studies disputed whether or not laterality of ONH or radiographic evidence of midline brain abnormalities affects the risk for hypopituitarism [7,10–16]. Reports also recognized the frequent association of other problems, including seizures, mental retardation, behavioral problems, speech and motor deficits, neonatal jaundice,

and hypoglycemia [17,18]. Most of these reports suffered from selection bias and incomplete clinical documentation, making it difficult to distinguish definite from coincidental associations.

The prevalence of ONH in North America is unknown. Prior to 1970, it was considered rare. In fact, prior to 1962, only one case had been diagnosed (in British Columbia), but 20 cases were subsequently diagnosed by 1974, for an estimated prevalence of 1.8 per 100,000 [19]. Many authors have noted an increased incidence of reported cases [20,21]. In 1981, Acers [20] estimated an incidence of 2 per 100,000 live births. ONH was identified in 12% of blind infants in Harris County in Texas in the early 1980s [21]. Surveys of schools for the blind in the United States reveal a prevalence of ONH of 5.7% to 12.9% in blind students [22,23]. Such surveys underestimate the actual prevalence, because cognitive or behavioral impairments exclude most individuals with ONH from schools for the blind.

In 1997, ONH surpassed retinopathy of prematurity as the single leading cause of infant blindness in Sweden, with a prevalence of 6.3 per 100,000 [24]. Only cortical visual impairment was more common than ONH in blind children. But cortical visual impairment can be caused by many conditions, including trauma, ischemia, seizures, and hydrocephalus. The prevalence from each of these causes does not appear to exceed that of ONH. Between 1980 and 1999, the prevalence of ONH in Sweden rose fourfold to 7.2 per 100,000. This occurred while all other causes of childhood blindness declined [25]. By 2006, the prevalence of ONH in England had risen to 10.9 per 100,000 [26]. It is impossible to confirm whether or not the apparent increasing incidence of ONH in the past two decades is caused by increasing detection sensitivity. This seems unlikely because increasing prevalence has been reported from the same centers [25]. In addition, ONH is easily distinguishable by direct ophthalmoscopy, the method used almost exclusively prior to 1960, when ONH was rarely detected.

Prenatal Risk Factors

Genetic risks

Gene mutations affecting growth and transcription factors have been shown to have some impact on optic nerve or hypothalamic–pituitary axis development in humans and mice. These gene mutations affect netrin, *POUF1*, *PROP1*, *SF-1*, *PITX2*, *NeuroD1*, *GATA-2*, *LHX3*, *TPIT*, *SOX3*, *SOX2*, and *HESX1* [27–39]. Of these mutations, only *HESX1* is reported to affect optic nerve development as well as anterior pituitary gland formation in humans [40]. However, *HESX1* mutations were found to be present in less than 1% of a large sample of cases of ONH [41,42••]. Thus, a specific genotype/phenotype correlation has not yet been found to explain the majority of cases of ONH.

All ethnic groups are impacted by ONH, but in the United States the prevalence is lower in persons of Asian descent [43,44••]. To date, there have been few reports from Asian countries [45,46], so whether this is related to relative genetic protection or differences in environment or diet related to culture is uncertain.

Both male [47,48] and female [19,49] gender predisposition have been reported in some studies, whereas other studies have reported no sexual predilection for ONH [17,43,44••]

Gestational and exposure history

Numerous perinatal and prenatal risk factors for ONH have been reported: preterm birth; low birth weight [41,49]; intrauterine growth restriction [11]; twin-twin transfusion syndrome [50]; young maternal age [3,49]; primiparity [3,49]; prenatal exposure to smoking [49], alcohol [51], recreational drugs [52,53], antidepressants [11,18,49], anticonvulsants [54], antiemetics [14], antifungal agents, infertility treatment [49], and quinine [45,55]; and prenatal complications [53] including gestational diabetes [56], toxemia [3,19,50], viral infection [50], and maternal anemia [14,50]. All of these reports are retrospective or anecdotal and impacted by selection bias.

Although a broad spectrum of risk factors has been suggested, a paucity of maternal characteristics persists as potentially significant. The predominant enduring characteristics are young maternal age and primiparity [49]. The association of primiparity was reported by Tornqvist et al. [49] as a risk factor independent of maternal age. Gestational diabetes, a well-described risk factor, is firmly related to a unique and uncommon form of ONH known as superior segmental ONH [56]. Some researchers speculate about the role of lifestyle factors in the development of ONH [26,41,49] These purported associations are suspect because of isolated cases of exposures and the limitations of using nonsystematically collected data. The role of nutrition in the pathogenesis of ONH has not yet been studied.

Diagnosis

The diagnosis of ONH is made by ophthalmoscopic confirmation of a small optic disc. Morphometric techniques have been described for measurement of the optic disc based on photographs. Most of these have relied on measurement of disc area or diameter relative to other landmarks, such as retinal vessels or distance to the macula. In all normal children, the ratio of the horizontal disc diameter (DD) to the distance between the macula and the temporal edge of the disc (DM) has been greater than 0.35 (Fig. 1) [43,57,58]. DD/DM ratios less than 0.35 are generally described as ONH, although some patients with DD/DM ratios of 0.30 to 0.35 have normal vision.

De Silva et al. [59] found that the average DD/DM ratio of preterm, but otherwise normal, infants was 0.26 at birth. Compared with measurements made by other

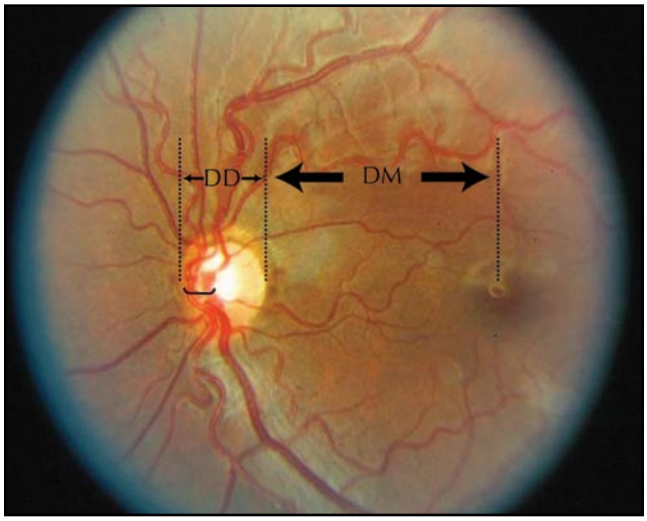

Figure 1. Example of borderline small optic disc wherein the ratio of disc diameter (DD) to disc-macula (DM) distance equals 0.36. Thus far, all patients with a DD/DM ratio greater than 0.35 have had normal vision and no other manifestations of the syndrome of optic nerve hypoplasia. Note that the DD is approximately 2.5 times larger than the width of the central retinal vessels (*bracket*).

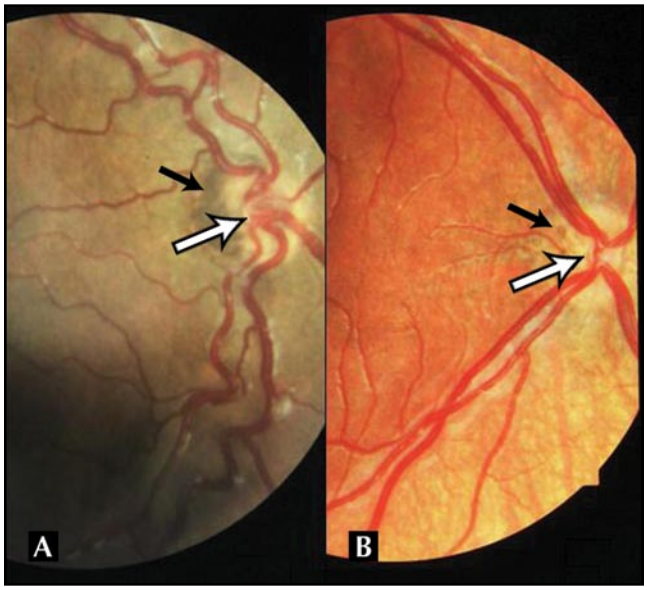

Figure 2. Examples of severely hypoplastic optic discs (*white arrows*) with partially pigmented double rings (*black arrows*). Optic nerve hypoplasia may be associated with tortuous retinal vessels (**A**) or straight, nonbranching (**B**) retinal vessels.

researchers from adults, they estimated that the DD increases 44% in a lifetime, whereas the DM distance increases only 11%. This results in increased DD/DM ratio with age, presumably occurring in the first 2 years of life, concomitant with maximal growth of the eye. Therefore, the age of the patient may need to be considered when measuring DD/DM ratios.

For practical purposes, morphometric measurements such as DD/DM ratio are not necessary to diagnose ONH. The clinician should note the overall area of the disc relative to the area of the retinal vessels overlying the disc. In equivocal cases, the width of the disc should be at least 2.5 to three times larger than the width of the central retinal vessels (Fig. 1).

In cases of ONH, a pigmented ring defining the area of the putative scleral canal often surrounds the disc (Fig. 2). This is presumably caused by migration of sensory retina and pigment epithelium from their original margin at the edge of the optic stalk to a new position at the border of the optic nerve that failed to fill, or regressed from, this area [60]. This "double ring" sign may also be unpigmented, partially pigmented, or absent altogether. Furthermore, the presence of a peripapillary ring does not define ONH, as it may be present in other common conditions.

Tortuous retinal vessels may accompany ONH (Fig. 2). This may affect arterioles, venules, or both. Alternatively, the vessels may be uncommonly straight with decreased branching (Fig. 2). Such a nonbranching vessel pattern has also been recognized in children with primary growth hormone (GH) deficiency [61]. It is not yet known if the anomalous vascular patterns in ONH correlate with the endocrine dysfunction.

Some authors have defined ONH broadly to include any optic disc with congenitally decreased neuronal area [62]. As such, those patients with a normal DD but with enlarged cups and thin rims would qualify as having ONH. Such an appearance typically occurs in premature infants suffering from periventricular leukomalacia [63]. Although such optic nerves may be technically hypoplastic in that they have fewer than the normal number of axons, these children are not at risk for the same developmental consequences as children with discs more typical of ONH, and therefore should not be considered in the same diagnostic category as the syndrome of ONH.

Histology

There are few histology reports from cases of human ONH because there is rarely a pathologic reason for enucleation. Most of the histopathologic reports have poor clinical documentation. The largest series identified 22 cases (35 eyes) from the Pathology Laboratory of the Wilmer Ophthalmological Institute [52]. Eighteen of the 22 cases were from autopsy, and all except one were stillbirths. The other died with meningitis and hydranencephaly at age 9 months. This was the only case with premorbid ocular fundus photographs documenting ONH, and it had been described previously [60]. Fifteen of the cases had anencephaly or craniorachischisis and nine of them had multiple somatic anomalies suggesting genetic causes of ONH. The reason for enucleation of the four nonautopsy eyes was not reported. In addition, the retinal vasculature was grossly hypoplastic in seven of the cases and five others had choroidal colobomas, features that are atypical for ONH. It is thus likely that few of the cases represented typical ONH. Nonetheless, there was

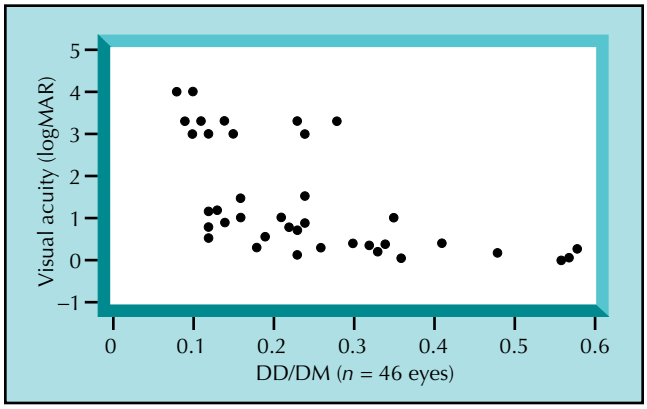

Figure 3. The base-10 logarithm of the minimum angle of resolution (logMAR) visual acuity (0 = 20/20; 3 = motion perception; 4 = no light perception) at age 5 years of the better eye roughly correlates with ratio of disc diameter (DD) to disc-macula (DM) distance (r = -0.7407; $P < 0.001$; Pearson's coefficient). Those eyes with a DD/DM ratio greater than 0.35 represent the normal eyes of unilaterally affected patients.

the common feature of absent or markedly reduced retinal ganglion cells and nerve fiber layer in all reported cases. Only four of the cases had any remaining axons in their optic nerves. The outer retinal layers appeared normal in the case that died at age 9 months [60], whereas others showed dysplasia with rosette formation.

There are reports of ONH in animals, particularly dogs, from which histopathologic information can be gleaned [64]. The nerves of these animals show malformed pial trabeculae, generally devoid of axons. Ganglion cells are few or absent whereas outer retinal elements are normal. It is uncertain whether such cases represent a good model for human ONH because they are usually unilateral, occur in select breeds, have no associated pituitary dysfunction, and are associated with retinal vasculature anomalies such as peripheral penetration into the vitreous and primary persistent hyperplastic vitreous.

Histopathologic reports from the brains of children with typical ONH are even scarcer. One report showed disorganization of myelinated axons within the hypothalamus [65].

Clinical Associations

Vision

Most children with ONH present with vision problems. Nystagmus usually develops at 1 to 3 months of age. They also present with strabismus, typically esotropia, in the first year of life. Children with markedly asymmetric or unilateral ONH may present primarily with strabismus rather than nystagmus.

Approximately 80% of children with ONH are bilaterally affected [44••]. Two thirds of those are asymmetrically affected. The unilateral cases are usually detected at a later age than those bilaterally affected (owing to better vision) unless they present with other problems related to hypothalamic dysfunction. Children with unilateral ONH are at significant risk for hypothalamic/pituitary dysfunction (69%) and developmental delay (39%), although they are at lower risk than those bilaterally affected (81% and 78%, respectively) [43,44••].

Visual acuity ranges from no light perception to near normal. More than 80% of bilateral cases are legally blind [47]. There is some, albeit imperfect, correlation of visual acuity with optic disc size (Fig. 3). It stands to reason that those with preserved axons of macular origin will have better vision regardless of the optic disc size (Fig. 4). Furthermore, some eyes may have worse vision than would be predicted based on optic disc size because of superimposed amblyopia due to strabismus or anisometropia.

Most affected children enjoy some improvement in their vision in the first few years of life. The reason for this is uncertain, because there is no reason to believe that there is any development of new axons. It is possible that improved axonal function due to optic nerve myelination that occurs in the first 4 years of life is responsible for this benefit [66]. Few children develop marked improvement in vision, but improvement from light perception to 1/200 is common.

Decline in vision due to ONH has not been reported. It is likely, however, that many patients develop superimposed amblyopia in one eye due to associated strabismus or anisometropia.

Electrophysiology

Electroretinograms (ERGs) to flash stimuli are typically normal in ONH [67,68]. This is consistent with the notion that retinal photoreceptors are normal in ONH. However, ERG abnormalities have been reported in some cases of ONH, suggesting retinal dysfunction distal to the ganglion cell layer [69–71]. It remains to be seen whether electroretinographic features now felt to be specific for ganglion cell function, such as the N95 peak of the pattern ERG, correlate with vision outcomes in patients with ONH [72].

Hypothalamic dysfunction

It is now clear that most of the clinical problems associated with ONH are related to dysfunction of the hypothalamus. This results in loss of regulation of homeostatic mechanisms controlling behavior and pituitary gland function.

Hypopituitarism

All pituitary hormones can be affected due to defects of the hypothalamus, infundibulum, or the pituitary gland itself. In a prospective study, hypopituitarism occurred in 75% to 80% of patients with ONH and was notably uncorrelated with laterality of disease [43]. GH deficiency was the most common pituitary endocrinopathy (70%), followed by hypothyroidism (43%), adrenal insufficiency (27%), and diabetes insipidus (5%) [44••]. This high prevalence of endocrinopathy is consistent with previous retrospective studies [53,73] and occurred in spite of the fact that only 7% of patients

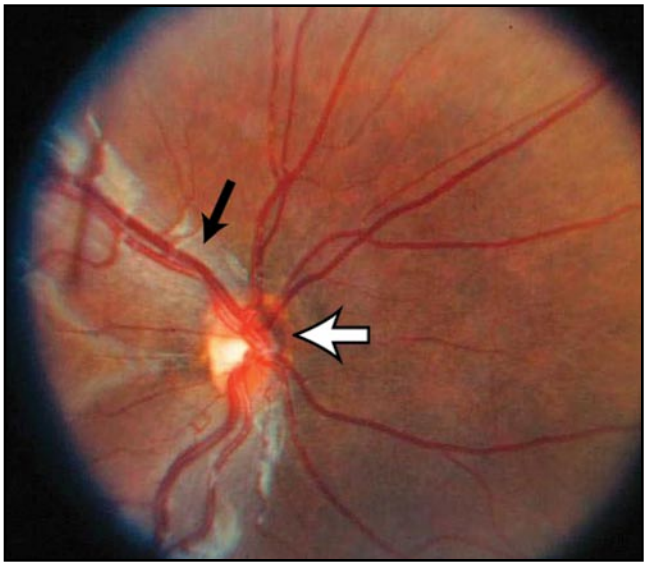

Figure 4. Optic nerve hypoplasia affecting nasal part of disc with partial double ring (*white arrow*) and preserved temporal and papillomacular fibers. Sheen from internal limiting membrane demarcating edge of preserved axons can be seen (*black arrow*). Such patients may have good visual acuity in spite of optic disc size.

were referred by endocrinologists, making ascertainment bias an unlikely explanation [44••].

The absence of GH is classically associated with short stature, although normal growth velocity with documented GH deficiency has been reported in patients with ONH [43]. Signs indicating an absence of GH include hypoglycemic events (including seizures) and prolonged jaundice, with or without giant cell hepatitis. Micropenis may be noted in boys, and delayed dentition may be seen later in boys and girls. Decreased levels of GH surrogates (insulin-like growth factor [IGF-1] and insulin-like growth factor binding protein 3 [IGFBP-3]) suggest GH deficiency.

Poor growth velocity, prolonged jaundice, delayed puberty, and delayed dentition can also be seen with central hypothyroidism. The critical importance of thyroid hormone on cerebral development and attainment of developmental milestones also necessitates close monitoring for this deficiency [44••]. Thyroid stimulating hormone levels may be low or normal in the context of a low level of free T4, and they can be missed by state screening programs that use an elevated thyroid stimulating hormone value as their detection method.

Documenting adrenocorticotropic hormone deficiency is essential because this can lead to cardiovascular collapse if an affected untreated patient encounters a stressful situation. This has been the presumed cause of sudden death in 2% of children afflicted with ONH [44••,74]. Hypocortisolism also causes neonatal cholestasis, jaundice, and hypoglycemia. More subtle clinical manifestations may include increased fatigue or irritability and increased duration of illnesses. In addition, both thyroid hormone and glucocorticoids are needed for free water excretion, and hyponatremia can result from a deficiency of one or both of these hormones [75,76].

The incidence of evolving pituitary dysfunction in children with ONH is not currently known, but cases of acquired hypopituitarism have been reported [73], and the authors have noted that this is especially true for hypothyroidism. Thus, the absence of a particular pituitary endocrinopathy does not imply absence of future pathology.

Pubertal development among children with ONH can be delayed because of GH deficiency, hypothyroidism, and/or deficiency of gonadotrophins, but can also occur prematurely because of a lack of inhibitory signals on gonadotrophin release from the hypothalamus [77].

Hyperprolactinemia occurs in 62% of children with ONH [44••]. As prolactin release is normally suppressed by dopamine release from the hypothalamus, the occurrence of hyperprolactinemia implies either hypothalamic dysfunction or a disconnection between the hypothalamus and pituitary gland. Hyperprolactinemia is not sufficient to cause galactorrhea but does correlate with the development of obesity in these children [43]. Whether this is an effect of hypopituitarism or related to malfunction of hypothalamic satiety centers is unknown.

Thirst/hunger

Ventromedial nuclei within the hypothalamus suppress hunger and eating in response to leptin, whereas lateral hypothalamic nuclei stimulate feeding behavior and regulate metabolism [78]. Thus, children afflicted with ONH frequently have feeding behaviors of hyperphagia with obesity or hypophagia with or without wasting. Some children have an aversion to certain textures of food. Water-seeking behavior is also common and may be mistakenly attributed to diabetes insipidus.

Sleep

The suprachiasmatic nuclei in the anterior hypothalamus are the site of a biological clock. They are located above the optic chiasm and receive optic nerve photic information to synchronize the clock to the 24-hour light-dark cycle. It is necessary to reset the circadian pacemaker each day with visual stimulation [79–81]. Disturbance of the circadian system can have significant and pernicious effects on physiology and behavior [79,82–84]. Many children with ONH have primary clock lesions with loss of rhythmicity and sleep or wakefulness distributed over the 24-hour day [82,85]. Alternatively, they may have inadequate retinohypothalamic input to daily entrain the circadian clock, resulting in sleep-wake cycles distinctly different than other family members. In either case, such sleep irregularities commonly result in behavioral difficulties and disruption to family life.

Temperature regulation

The medial preoptic region of the hypothalamus is involved in fine body temperature regulation and, through communication with the paraventricular nucleus, regulates fever response [86]. It is therefore not surprising that

many infants and children with ONH have problems with body temperature regulation and may be frequently hospitalized to rule out sepsis [54].

Development

Developmental delays are a common occurrence in children with ONH and encompass a wide clinical spectrum. Margalith et al. [3] in 1984 were the first to report a correlation with neuropsychiatric disorders, estimating handicaps in nearly three fourths of cases of ONH. Delayed development, based on neurologic examination, was estimated at a similar frequency by Burke et al. [50]. Observations of developmental delay in association with ONH range from isolated focal defects to global delay [48,87]. In a prospective study, overall adverse developmental outcomes with standardized testing were demonstrated in 71% of ONH patients. Motor delays were the most common (75%) and communication delays were the least common (44%) [44••]. Risk factors for significantly delayed development included hypoplasia of the corpus callosum and hypothyroidism but not absence of the septum pellucidum. Developmental delay can occur in unilateral (39%) as well as bilateral (78%) cases of ONH [44••].

Neuroimaging Associations

The syndrome of ONH may be suspected with neuroimaging. Hypoplasia of the corpus callosum, agenesis of the septum pellucidum, or pituitary malformations, especially if associated with thin optic nerves, may direct physicians toward clinical confirmation of the diagnosis. Attempts to diagnose ONH based on radiographic measurements of the optic nerve or chiasm have been promising but not definitive [88,89]. Such studies have been retrospective, lacked controls with normal and atrophic optic nerves, and failed to adjust for age in young patients. Nonetheless, it seems likely that high-resolution MRI could be used to distinguish ONH from optic atrophy once the appropriately controlled studies are done.

Because of the wide clinical spectrum of children with ONH, the use of neuroimaging in predicting the clinical phenotype has been investigated. The septum pellucidum is absent on neuroimaging in 38% of patients with ONH [44••]. Because it is common, easily diagnosed, and inextricably linked with the syndrome of septo-optic dysplasia, the impact of septum pellucidum agenesis has been the most frequently studied. Birkebaek et al. [11] looked retrospectively at 55 children with ONH from an endocrinology practice and concluded that the children at greatest risk for multiple pituitary hormone deficiencies were those who had both an absent septum pellucidum and an abnormal pituitary gland on MRI. However, absence of the septum pellucidum was not associated with hypopituitarism or developmental outcomes in a prospective study [44••]. Brodsky et al. [90] believe that absence of the septum pellucidum has no predictive value for hypopituitarism or other adverse outcomes, but that the pituitary abnormalities on MRI, including an ectopic posterior pituitary gland, are predictive of hormone dysfunction [91]. However, in a prospective observational study, Ahmad et al. [43] described a group of patients with ONH who had pituitary endocrinopathies despite both an intact septum pellucidum and normal pituitary gland on neuroimaging. In fact, despite the high prevalence of hypopituitarism, only 13% of children with ONH have an abnormal pituitary gland on neuroimaging [44••]. Uniquely, absence of the neurohypophyseal bright spot on MRI portends diabetes insipidus, whereas presence of the bright spot (ectopic or otherwise) seems to rule it out [92].

As previously described, hypoplasia of the corpus callosum is associated with adverse developmental outcomes, particularly in cognition, motor skills, and adaptive behaviors [44••]. Moreover, each decrement of 2 cm^2 in area measurements of the corpus callosum increased the risk for overall delay twofold, and it was even greater (odds ratio of 2.68; 95% CI, 1.45–5.86) for delayed cognition. However, corpus callosum hypoplasia was not associated with pituitary dysfunction.

Other structural abnormalities found on MRI that have an impact on development in children with ONH include schizencephaly, cortical heterotopia, white matter hypoplasia, pachygyria, and holoprosencephaly. Together, these affect less than 15% of patients [44••]. Arachnoid cysts are also common but of uncertain consequence.

Management Recommendations

The syndrome of ONH is a condition of miswiring of the brain that is manifested in the optic nerves, especially in the hypothalamus. Consequently, physicians should be vigilant for signs of hypothalamic dysfunction along with any vision problems and vice versa. Therefore, all children with neonatal jaundice and recurrent hypoglycemia should have ophthalmoscopic evaluation, especially if the child has associated temperature instability. Similarly, all infants with poor visual behavior, strabismus, or nystagmus by 3 months of age should have an ophthalmoscopic examination.

Once ONH is confirmed ophthalmoscopically, MRI of the brain and endocrinologic studies should be obtained. The MRI can rule out treatable conditions such as hydrocephalus but can also be used to anticipate developmental delay associated with corpus callosum hypoplasia or other major malformations.

Endocrinologic work-up should include fasting morning cortisol and glucose, thyroid stimulating hormone, free T4, IGF-1, IGFBP-3, and prolactin. If the child is less than 6 months of age, leuteinizing 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.

Children should be monitored at least semiannually for growth. With growth deceleration, thyroid function tests should be repeated and a GH stimulation test should be performed. These should also be done in the first 3 years of life if IGF-1 or IGFBP-3 is low, even if the child is growing normally. Free T4 should be rechecked annually for at least 4 years.

If fasting AM cortisol is low, it should be repeated or provocative testing for cortisol should be done. This can often be done simultaneously with provocative GH testing. Children with inadequate cortisol response to provocative tests should be given cortisol for administration during illness or physical stress.

Occupational, physical, and/or speech therapy are frequently needed by children with ONH. Attention should especially be given to early development of oral motor skills and acclimation to textured foods for those children resistant to eating. Incorporating words into song can sometimes ameliorate delayed verbal communication.

Sleep dysregulation can sometimes be alleviated by entraining the circadian clock with low doses (0.1–0.5 mg) of melatonin in the evening or, alternatively, with soporific doses (3–5 mg) at bedtime [85].

The vision of young children with ONH should be monitored at least annually, and any refractive errors should be treated when the visual acuity reaches a functional level. Patching of the better eye can result in improvement of vision in the worse eye. However, if the ONH is asymmetric, maintenance of improved vision requires prolonged patching that can be disruptive to development in a child with many other handicaps. Thus, amblyopia therapy should be reserved for those cases in which the potential vision in each eye is felt to be fairly good.

Early surgical correction of strabismus is warranted for children who have symmetrical functional vision in the eyes, and thus some potential for binocularity. Otherwise, correction of strabismus should be deferred until it is an impending psychosocial issue.

Conclusions

The syndrome of ONH encompasses multiple systemic problems related to miswiring of the central nervous system. This miswiring affects the majority children with ONH, regardless of radiographic findings. The absence of septum pellucidum is not a reliable marker for the syndrome. Management of ONH requires a multidisciplinary team approach.

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Disclosures

No potential conflicts of interest relevant to this article were reported.

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- • Of importance
- •• Of major importance

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