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ADVANCES IN PEDIATRICS

The Optic Nerve Hypoplasia Spectrum

Review of the Literature and Clinical Guidelines

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Keywords

• Optic nerve hypoplasia • Septo-optic dysplasia • Epidemiology • Hypopituitarism • Hypothalamic-pituitary dysfunction • Clinical presentation • Diagnosis • Management

Key points

- Optic nerve hypoplasia (ONH) is a complex congenital disorder of unknown etiology and is the leading cause of permanent, congenital visual impairment in children in the western world.
- The causes of ONH are complex and multifactorial, with most cases being sporadic. Further studies are necessary to elucidate the causes of ONH.
- ONH is frequently associated with congenital brain malformations, hypothalamic-pituitary dysfunction, neurocognitive disability, obesity, and autism spectrum disorders.
- Hypothalamic-pituitary dysfunction in ONH occurs independently of brain malformations and may evolve over time, necessitating long-term evaluation and follow-up.

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INTRODUCTION

Optic nerve hypoplasia (ONH) is a common complex congenital disorder of unknown cause, involving a spectrum of anatomic malformations and clinical manifestations ranging from isolated hypoplasia of 1 or both optic nerves, with a variable degree of visual impairment, to extensive brain malformations, hypothalamic-pituitary dysfunction, neurocognitive disability, and/or autism spectrum disorders (ASDs) [1,2]. ONH is the second leading cause of congenital visual impairment, superseded only by cortical visual impairment [3,4]. According to the United States (US) Babies Count registry for children with visual impairment from birth to age 3 years, ONH carries a worse visual prognosis compared with cortical visual impairment, retinopathy of prematurity, and albinism [5]. It is the single leading cause of permanent legal blindness in children in the western world [3].

Owing to early observations of co-occurrence with agenesis of the septum pellucidum and hypopituitarism [6,7], ONH has long been recognized as part of the septo-optic dysplasia (SOD) syndrome, a clinically inaccurate term that attributes prognostic importance of the hypothalamic-pituitary dysfunction development to the absent septum pellucidum and/or other midline brain malformations. More recent, larger studies have demonstrated ONH to be an independent risk factor for hypothalamic-pituitary dysfunction, with abnormalities of the septum pellucidum having no prognostic value [1,8–11].

Currently, there are no consensus or clinical practice guidelines available for evaluation and management of children with ONH. This article focuses on the current state of knowledge about the prevalence, causes, and associated clinical features of the ONH spectrum, including their presentation, diagnosis, and management. The authors recommend a family-centered, multidisciplinary approach to caring for all children with ONH. Herein, are presented comprehensive guidelines for clinical evaluation and management based on an extensive literature review and the authors' clinical experience.

EPIDEMIOLOGY

The prevalence of ONH has increased substantially since the 1980s. The Swedish Register of Visually Impaired Children reported a fourfold increase in prevalence between 1980 and 1999 [12]. In an epidemiologic study conducted between 1944 and 1974, the prevalence of ONH in British Columbia, Canada, was reported to be 1.8 per 100,000 [13]. In 1997, Blohme and Tornqvist [4] reported that 7.1 per 100,000 children younger than 20 years of age with visual impairment or blindness in Sweden had ONH. The most recent estimates from the United Kingdom reported a prevalence of 10.9 per 100,000 in children younger than 16 years of age [14] and, from Stockholm, Sweden, 17.3 per 100,000 children younger than 18 years of age [2]. In another 2014 report using data derived from a registry of children with severe visual impairment in New Zealand, ONH was found in 6.3% of cases of children younger than 16 years of age [9]. This finding most likely underestimates the true prevalence because mild and/or unilateral cases are not consistently enrolled in the registry.

In the US, the prevalence of ONH in visually impaired children is not exactly known. According to the 2007 US Babies Count, ONH was the cause of blindness in 9.7% of children with vision impairment [5]. Among 3070 students from schools for the blind in 2012, ONH was the cause of blindness in 15%, more than double that reported in 1999 (7%) [3]. This prevalence is most likely underestimated because schools for the blind may exclude children with functional vision, unilateral ONH, or severe developmental disabilities. In fact, in the US, only about 13% of visually impaired children attend schools for the blind; all others attend mainstream schools [3]. In 2013, the Mayo Clinic College of Medicine analyzed medical records of all known cases of ONH in Olmsted County, Minnesota, between 1984 and 2008, generating an annual incidence of 2.4 per 100,000 children younger than 19 years of age (1 in 2287 live births) [15].

CAUSES AND RISK FACTORS

Prenatal factors and maternal age

Although the causes of ONH are not known, retrospective and prospective studies have consistently reported young maternal age and primiparity as predominant, independent prenatal factors associated with ONH [9,16–22]. In a 2012 study of 88 subjects with SOD, first-trimester bleeding was more common compared with the general population [18]. The investigators supported a previously proposed hypothesis that ONH may be due to a vascular disruption sequence, perhaps involving the anterior cerebral artery during a critical period of neuroembryogenesis [18,23]. Early gestational vaginal bleeding was also noted and introduced as a potential etiologic factor by a large prospective study of more than 200 children [16].

Recent reports have pointed to factors of deprivation and geographic differences associated with higher rates of ONH, especially in areas of lower socioeconomic status [9,14,18]. Garcia-Filion and colleagues [16] found an association of poor prenatal maternal weight gain or weight loss, suggesting a contributory role for prenatal nutrition.

High-risk behaviors, such as smoking, alcohol use, and recreational and/or prescription drug use, have been associated with higher rates of ONH [14,19,24–26]. However, these findings, specifically alcohol and drug exposures, were not supported by larger, prospective studies [16,17,21]. At this time, young maternal age and primiparity remain the most consistent risk factors, although more studies are needed to elucidate the mechanisms by which these factors contribute to the pathogenesis of ONH.

Genetics

Genetic causes and familial cases of ONH are uncommon, with most cases being sporadic [27–29]. Current understanding of the basis for ONH points towards environmental effects contributing to the congenital development of ONH during a vulnerable period of neuroembryogenesis. However, familial cases of ONH exist, including 1 set of monozygotic twins [30–33]. *HESX1* mutations have been identified in patients with SOD and/or hypopituitarism with

and without midline malformations, though not necessarily with ONH [34]. In the cases with ONH, *HESX1* mutations were rarely found [28,33,35,36]. In 1 series of 850 subjects with SOD, with or without ONH, mutations of *HESX1* were found in less than 1% of cases, supporting the rarity of mutations of this gene in a heterogeneous cohort of subjects [28]. In the literature, there is 1 case of *OTX2* gene mutation and another in *PROKR2*; however, in both cases, ONH was diagnosed by MRI without direct ophthalmologic examination [37,38]. It is also unclear how these mutations may be involved in the pathogenesis of ONH, and there are no genotype-phenotype correlations or animal models to establish the causation.

In the prospective, clinical registry of children with ONH established in 1992 at Children's Hospital Los Angeles, there is 1 set of monozygotic twins and 1 pair of brothers, among more than 320 enrolled subjects. Although it remains possible that a genetic cause or predisposition underlies ONH, perhaps involving various genes that affect similar biological pathways, the disease most likely has a multifactorial etiology with predominantly environmental causes. Next-generation genomic sequencing studies of children and families with ONH are an important future step to gaining a better understanding of a possible genetic basis.

CLINICAL APPROACH TO CHILDREN WITH OPTIC NERVE HYPOPLASIA

The wide spectrum of anatomic malformations and clinical presentations in patients with ONH necessitates a comprehensive guide to optimize care for these medically complex individuals. Table 1 summarizes neuroanatomical, neuroendocrine, cognitive, and behavioral features of ONH, their known frequencies, and previously reported correlations [1,2,8–11,17,18,39–54]. To date, there are no well-established predictive factors that can guide clinicians in the care and counseling of patients with ONH and their families. The presence of ONH alone, independent of laterality or neuroanatomical abnormalities, poses an increased risk for hypothalamic-pituitary dysfunction, seen in approximately 60% to 80% of cases [8,10,18,40,43,48,51–53], which, if unrecognized, may lead to significant morbidity and mortality [55]. Growth hormone (GH) deficiency (GHD) is the most common hypothalamic-pituitary abnormality in children with ONH presenting alone or in combination with other hormone deficiencies (see Table 1). Early recognition, diagnosis, treatment, and diligent surveillance using a family-centered, multidisciplinary approach is imperative to maximize the well-being of these patients. Timely evaluation is contingent on recognition of age-dependent presenting features of ONH, and should involve hypothalamic-pituitary and ophthalmologic assessments along with brain and sella imaging (Fig. 1, Table 2).

Clinical presentations and associated features in optic nerve hypoplasia

Neonatal period to infancy

Table 2 describes presenting clinical signs and symptoms in patients with ONH by age. Visual problems usually do not become apparent until 1 to 3 months of age [1]. Presentation with hypothalamic-pituitary dysfunction is

Table 1
Clinical features of optic nerve hypoplasia by frequency and correlations

Major associated features	Frequencies (%)	Correlations
ONH		Young maternal age and primiparity
Bilateral	55–80	Higher risk of hypothalamic-pituitary dysfunction, developmental delay
Unilateral	20–45	—
Hypothalamic-pituitary dysfunction	60–80	Higher in bilateral ONH, pituitary gland abnormalities
GHRH or GHD	70	Hyperprolactinemia
TRH-TSH deficiency	35–43	Developmental delay, worse visual outcomes
CRH-ACTH deficiency	17–27	GH deficiency
ADH deficiency	4–5	Unknown
Hyperprolactinemia	49–72	GHRH-GH deficiency
Pubertal abnormalities[a]	Unknown	Unknown
Other hypothalamic dysfunction		
Overweight or obesity	20–44	Unknown
Autonomic dysfunction	Unknown	Unknown
Disordered sleep	30	Severe visual impairment, developmental delay, and multiple hormone deficiencies
Neuroanatomical malformations	46–82	—
Hypoplasia of corpus callosum	51	Developmental delay
Absent septum pellucidum	38	Unknown
Pituitary gland abnormality[b]	6–64	Hypothalamic-pituitary dysfunction
Other major malformations[c]	22	Developmental delay, focal deficits, or seizures
Behavioral or developmental abnormalities	71	Bilateral ONH, hypoplasia of corpus callosum, and other major malformations
ASDs	25	Severe visual impairment

Abbreviations: ACTH, adrenocorticotrophic hormone; ADH, antidiuretic hormone; GHD, growth hormone deficiency; TSH, thyroid-stimulating hormone; GHRH, growth hormone releasing hormone; TRH, thyrotropin releasing hormone, CRH, corticotropin releasing hormone.

[a]Central precocious puberty, rapid tempo puberty, delayed puberty, and arrested or absent development.

[b]Absent pituitary, ectopic neurohypophysis, absent neurohypophysis, and/or adenohypophysis abnormality.

[c]Cortical heterotopia, schizencephaly, polymicrogyria, pachygyria, cerebellar hypoplasia, white matter hypoplasia, hydrocephalus, and/or ventriculomegaly.

common in infants and children subsequently diagnosed with ONH [8,22,56,57]. This phenotype is characterized by the typical manifestations of congenital GHD or hypopituitarism, which include transient or permanent hypoglycemia (which may be attributed to GHD and/or adrenal insufficiency), micropenis, and/or cryptorchidism in boys, prolonged hyperbilirubinemia after birth due to cholestasis resulting in a usually reversible form of giant-cell

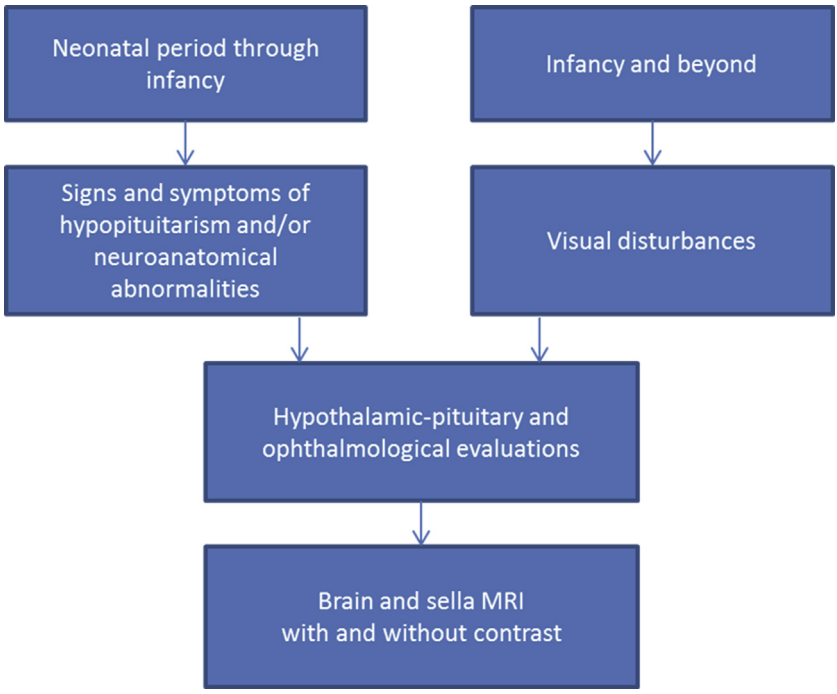

Fig. 1. Algorithm for initial evaluation of suspected ONH based on clinical presentation by age. Presenting clinical features detailed in Table 2.

Table 2
Clinical presentation by age

Neonatal period through infancy[a]	Infancy and beyond
Prolonged jaundice with or without giant-cell hepatitis	Unilateral or bilateral visual disturbances
Hypoglycemia	Nystagmus
Micropenis and/or cryptorchidism (boys)	Strabismus
Lethargy	Amblyopia
Poor feeding	Growth failure
Failure-to-thrive	Polyuria[b]
Polyuria	Polydipsia[b]
Irritability	
Neurologic deficits	
Seizures	
Vital sign instability	

[a]These features may occasionally be presenting signs during infancy and beyond.
[b]Polydipsia and polyuria may be psychogenic due to dysregulation of thirst to water balance in hypothalamus, or be a presenting feature of diabetes insipidus.

hepatitis, and/or poor linear growth that may begin at birth or, more likely, later in the first year of life [58–63]. The presence of any 1 or a combination of these findings should incite prompt investigation of the hypothalamic-pituitary axis and central nervous system, and referral to a pediatric endocrinologist and ophthalmologist, preferably a pediatric neuro-ophthalmologist (see Fig. 1). Timely hormonal replacement alleviates hypoglycemia and facilitates treatment of giant-cell hepatitis due to cholestasis [63]. In 62 cases of biopsy-confirmed neonatal giant-cell hepatitis, 16% were due to hypopituitarism [64]. Importantly, in 1 series of cases of neonatal hepatitis with significant delay in treatment until 5 years of age, cirrhosis and liver failure developed, necessitating liver transplant [62].

Central congenital hypothyroidism is often missed on newborn screening (NBS) in states that use initial thyroid-stimulating hormone (TSH) testing to detect the more commonly seen primary form of congenital hypothyroidism [65]. In a study of 135 subjects with ONH, approximately 50% who had low-normal TSH on NBS were diagnosed with central hypothyroidism on subsequent testing [66]. In this cohort, initial NBS TSH was significantly lower in those subsequently diagnosed with hypothyroidism compared with those who remained euthyroid (3.2 vs 4.5 μIU/mL; $P = .006$). In addition, subjects with hypothyroidism were found to have significantly worse vision outcomes compared with the euthyroid group [66]. Receiver-operating characteristic analysis suggested an optimal NBS TSH cut-off of 3.3 μIU/mL, over which there were relatively better vision outcomes. The study concluded that children with ONH and lower TSH levels on NBS are more likely to develop central hypothyroidism and poorer vision than those with higher TSH values.

Polyuria and polydipsia, as manifestations of diabetes insipidus (DI) due to a deficiency of antidiuretic hormone (ADH), also may occur, though posterior pituitary dysfunction in children with ONH is relatively uncommon [67]. The presence of DI in patients with ONH, similar to other forms of congenital DI, increases the risk for morbidity and mortality during the neonatal period because diagnosis and management in neonates are particularly challenging [67]. Patients with DI are also at increased risk for developing anterior pituitary hormone deficiencies during the neonatal period or later [67].

Infancy and beyond

Poor visual behavior in infants with ONH, presenting most commonly with wandering (searching) nystagmus, typically becomes evident at 1 to 3 months of life (see Table 2). In unilateral cases, strabismus (usually esotropia) is the main presenting feature, which typically develops in the first year of life. Unilateral cases are often diagnosed at later ages and have better visual function but possess significant risk for hypothalamic-pituitary dysfunction, though less than in bilateral cases [8,10,53]. Visual acuity in children with ONH ranges from functional vision to complete blindness. Vision impairment is nonprogressive and, in fact, improvement in vision, mainly in the first years of life, has been reported [1,66]. This is thought to be related to improvement in

superimposed cortical visual impairment, continuing optic nerve myelination, and/or thyroid status [1]. Approximately 80% of cases of ONH are bilateral, and most are legally blind [9,16,49].

Hypothalamic-pituitary dysfunction, most commonly presenting with growth failure due to GHD alone or in combination with other hormone deficiencies (see previous discussion), may present in infancy or evolve over time [9,10,40,68]. Normal linear growth velocity despite GHD is a documented phenomenon in children with ONH, though deceleration eventually occurs in most such cases, starting around age 3.5 years [48,69]. In the registry study, the authors examined the prevalence of endocrinopathies in 47 children at the time of enrollment (mean age 15.2 $\pm$ 10.6 months) and followed their subsequent growth patterns over time (until 59.0 $\pm$ 6.2 months of age) [8]. The overall prevalence of hypothalamic-pituitary dysfunction was 72%, with 64% of subjects having GHD, 49% hyperprolactinemia, 35% hypothyroidism, 17% adrenal insufficiency, and 4% DI. This hierarchy of hormonal dysfunction, with GHD being most common, is similar to that seen with other causes of congenital hypopituitarism, although the prevalence of TSH, adrenocorticotrophic hormone (ACTH), and ADH deficiencies may be greater in patients with ONH as suggested by 1 prior study [70]. An array of pubertal disturbances, including delayed, absent, precocious, and unduly rapid tempo variants, can occur, with the former 2 much more common than the latter 2, and typically only discernible after 10 years of age [45,71–76]. In addition, the authors' unpublished data show pubertal abnormalities may be present in children with no prior endocrinopathies; thus, long-term follow-up through adolescence is necessary. The prospective findings confirm or exceed the high prevalence of hypothalamic-pituitary dysfunction in children with ONH reported in previous retrospective studies [57,74].

Overweight or obesity is another manifestation of hypothalamic dysfunction and a major source of lifelong morbidity in patients with ONH. The prevalence of overweight (body mass index [BMI] $>$ 85th percentile) in the registry was found to be 44% and was higher in children with co-existing GHD (52%) [8]. Mild hyperprolactinemia often occurs in subjects with disorders of the hypothalamus as a reflection of loss of normal inhibitory dopaminergic control of prolactin secretion. In a study of 125 children (age 13.2 $\pm$ 9.3 months) with ONH, 72% of subjects had elevated initial serum prolactin levels. By age 5 years, 60% of subjects with hyperprolactinemia had hypopituitarism, 31% were overweight, and 20% were obese. Though early hyperprolactinemia correlated with the presence of GHD, it did not predict future endocrinopathies or overweight or obesity [39].

Developmental delay and behavioral abnormalities are common but usually are not the main presenting features of ONH (see Table 1). In the registry, developmental delay was found in 71% of subjects and was associated with hypoplasia of the corpus callosum, hypothyroidism, and laterality of ONH (unilateral 39% vs bilateral 78%) [10]. In a recent population-based study of children younger than 18 years of age in Stockholm, Sweden, behavioral

problems were also more common in cases of bilateral ONH compared with unilateral ones [2]. In addition, ASDs, which are over-represented in the visually impaired population [54,77], are prevalent in children with ONH [77,78]. In 1 study, 31% of children with ONH or SOD had a clinical diagnosis of ASDs, which was more common in patients with profound visual impairment [79]. However, given the overlapping behavioral characteristics of ONH and ASDs (including echolalia, pronoun reversal, stereotypic motor movements, and delays in developing imaginative play) [77], along with the inadequacy of current methods for diagnosing ASDs in visually-impaired children, the true prevalence in the ONH population is unknown.

Other common presenting features in ONH, including vital sign dysregulation (most notably temperature), hyperphagia or hypophagia with oral aversion, and disordered wake-sleep cycles, are thought to be due to hypothalamic dysfunction affecting critical regions or nuclei in the hypothalamus [1]. In a prospective study of 23 children with ONH, abnormal wake-sleep cycles were present in 30%, which correlated with severity of visual impairment, developmental delay, and hypothalamic-pituitary dysfunction [42].

Seizures and neurologic deficits have been described in patients with ONH with major neuroanatomical abnormalities on MRI, specifically, schizencephaly, polymicrogyria, and hydrocephalus [1]. Hypoplasia of the corpus callosum with or without an absent septum pellucidum has been associated with developmental delay and is the most common neuroanatomical malformation found in ONH (Fig. 2A) [10]. Similarly, in a recent evaluation of 94 children with ONH in New Zealand, neuroanatomical abnormalities were found in 60% of cases and were associated with a higher incidence of developmental delay [9].

There persists an assumption that the presence of various anatomic abnormalities of the brain in patients with ONH, most notably absence of the septum

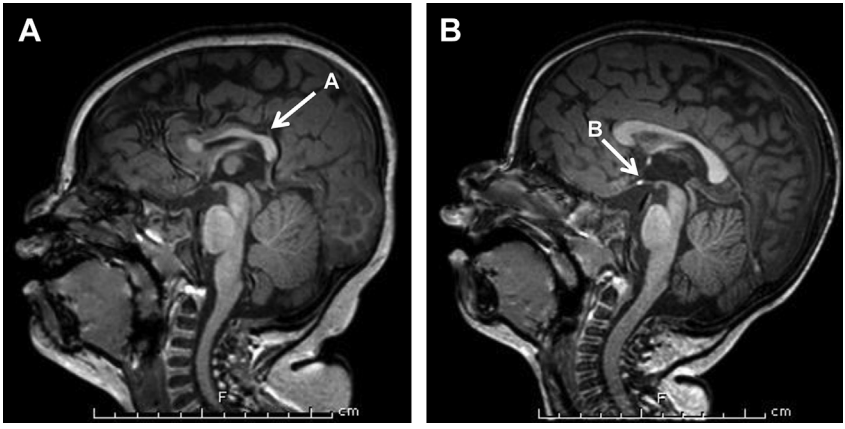

Fig. 2. ONH is commonly associated with neuroanatomical abnormalities (*arrows*), including (*A*) hypoplasia of (*A*) the corpus callosum and (*B*) an ectopic neurohypophysis.

pellucidum, is predictive of hypothalamic-pituitary dysfunction in ONH. This belief also seems to underlie the schedule of biochemical evaluations of pituitary function used by many clinicians.

In the registry study, Garcia-Filion and colleagues recently evaluated the spectrum of brain malformations by MRI and associations with hypopituitarism in children (personal communication, 2016). Subjects in the registry study undergo annual pituitary hormone testing until age 5 years and baseline neuroimaging. Noteworthy radiological findings in the cohort included abnormalities of the corpus callosum in 51%, the septum pellucidum in 38%, and the pituitary gland in 9% (see Fig. 2). Other major brain malformations affected 22% of the group and occurred independent of ONH laterality. In agreement with other reports [9,40,44], the study found that hypopituitarism was not associated with abnormalities of the corpus callosum, absent septum pellucidum, or other major brain malformations, except for malformations of the pituitary gland. Importantly, however, an intact pituitary gland and absence of neuroanatomical malformations do not preclude the development of hypothalamic-pituitary dysfunction [9,11,45,50,56] (personal communication, 2016). The authors' unpublished data show that, though all subjects with a pituitary gland malformation developed hypothalamic-pituitary dysfunction, 66% of patients with a normal pituitary gland on MRI also had hypothalamic-pituitary dysfunction (personal communication, 2016). The presence of ONH alone remains the main risk factor for the development of hypothalamic-pituitary dysfunction, independent of neuroradiographical findings.

An interesting but poorly explored observation is the occurrence of other systemic, non-neuroendocrine abnormalities occurring in as many as 47% of children with ONH as reported in a systematic retrospective review of 100 subjects [46]. The most commonly reported findings included facial dysmorphism, gastroesophageal reflux, cardiac or great vessel malformations, inguinal hernia, and hearing impairment. Several other case reports or series have described presence of gastroschisis, omphalocele, cleft lip or palate, and rare syndromes such as Williams and Donnai-Barrow syndromes [46,80–83]. The true prevalence and possible etiologic basis of these non-neuroendocrine abnormalities are not known. However, it is important to raise awareness that ONH may be found in patients with other systemic abnormalities or syndromes to avoid delayed diagnosis or treatment.

Evaluation and management of children with optic nerve hypoplasia

Vision

ONH is diagnosed by an ophthalmologist via direct ophthalmoscopy, confirming a small optic disc [1]. Fundus photographs are useful for confirming the diagnosis by measurement of the optic disc [1,2] (Fig. 3). A relative ratio of disc diameter to the distance between the macula and the temporal edge of the disc of less than 0.35 correlates with poor vision outcomes, though there is a gray zone of 0.30 to 0.35, in which normal vision has been reported [1,84]. Diagnosis in mild cases may be challenging but is improved by findings

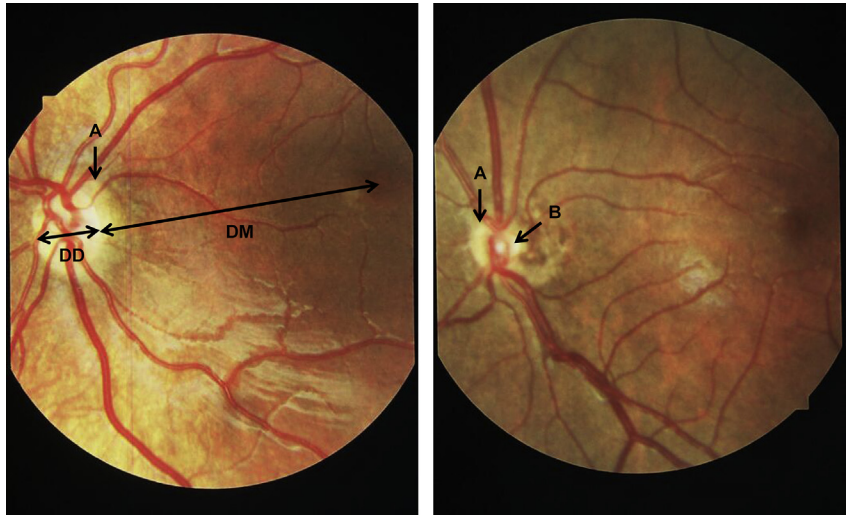

Fig. 3. Fundoscopic images of ONH. (*Left*) A mild case of ONH with disc diameter (DD) to disc to macula (DM) ratio of 0.22. (*Right*) A severely hypoplastic optic nerve (*B*). Both images display a hypopigmented double ring (*A*).

of tortuous retinal arterioles and/or venules, or abnormally straight retinal vessels with minimal branching [1]. Another common finding in ONH is a double-ring sign, which represents a hypopigmented or hyperpigmented area surrounding the disc, and is hypothesized to be due to a migrational defect of the sensory retina and/or pigment epithelium to the hypoplastic optic disc [53,85] (see Fig. 3). An MRI of the brain and orbits may be used as an adjunct to ophthalmoscopy in the diagnosis of ONH, though age needs to be taken into account when using MRI for this purpose [86].

ONH is an incurable congenital disorder. Though a growing number of international providers offer stem cell therapy for ONH, a small, case-controlled study showed no improvement in visual acuity in children who underwent stem cell therapy, the long-term risks of which are unknown [87]. Children with ONH should be monitored and treated by a neuro-ophthalmologist at least annually for refractive errors and amblyopia [1]. Children with unilateral or severely asymmetrical ONH should avoid patching. Strabismus surgery should be performed as early as possible in symmetric cases with good potential for binocular vision. Cosmetic surgery should be performed if psychosocial issues arise [1]. A referral to a teacher for the visually impaired may be beneficial to children with ONH at any age to help optimize residual vision.

Neuroanatomic malformations and neuropsychological abnormalities

An MRI of the brain and sella with and without contrast should be done on all patients with ONH. Severe major malformations, such as hydrocephalus and

schizencephaly and/or polymicrogyria, need to be evaluated and treated by a neurosurgeon and a neurologist, respectively, especially if seizures or neurologic deficits are present [53]. In addition to major brain malformations, the finding of a hypoplastic corpus callosum provides prognostic value for risk of delayed development (see Fig. 2).

All children with ONH should be referred to the local Early Head Start or Early Intervention program for early evaluation of deficits and, if needed, therapeutic services specific to visually impaired children. Physical therapy should focus on development of motor skills, especially ambulation. Oral aversions that make feeding a challenge may be remedied with occupational therapy focused on swallowing skills and tactile exposure. Speech therapy is often initiated to help with delays in communication development [1]. Orientation and mobility are critical for ambulatory patients to learn to safely navigate their environment. Behavioral therapy is frequently required in older children with emotional and behavioral problems related to ASDs, attention deficit disorders, or other neurologic dysfunction. A developmental pediatrician and/or neuropsychologist specializing in children with visual impairment should evaluate and treat children with ASDs and related developmental and learning challenges (Table 3).

Hypothalamic-pituitary axis

All children with a clinical presentation suggestive of hypothalamic-pituitary dysfunction or with a diagnosis of ONH should undergo hormonal testing and routine retesting to identify abnormalities in their earliest stages (see Fig. 1, Table 3). The authors suggest obtaining fasting blood tests, including cortisol, basic metabolic panel (for evaluation of fasting glucose and sodium), TSH, free T4, insulin-like growth factor (IGF)-I, IGF binding protein-3 (BP-3), and urine specific gravity at diagnosis. For young patients presenting with suspected hypoglycemia or DI, inpatient evaluation should be strongly considered. In children diagnosed between 3 weeks and 6 months of life, during the transient physiologic minipuberty period of infancy, initial blood testing should also include luteinizing hormone, follicle-stimulating hormone, and testosterone in boys or estradiol in girls. In addition, a prolactin level may be evaluated after 6 months of life (when the influence of normally higher physiologic levels in infancy is no longer an issue). Anthropometric measurements and morning screening blood tests should be obtained every 4 to 6 months in the first 3 years of life and annually thereafter for surveillance of evolving hypothalamic-pituitary dysfunction. Children with low levels of cortisol and/or IGF-I and IGFBP-3 on screening blood tests should undergo stimulation testing for corticotropin releasing hormone (CRH)-ACTH and growth hormone releasing hormone (GHRH)-GH deficiencies, respectively, which may be done simultaneously with a glucagon stimulation test [53].

Currently, there is no consensus on how long children with ONH and initially normal hypothalamic-pituitary function should be monitored. Some investigators have found that most children develop hypothalamic-pituitary

hormone dysfunction in the first 2 years of life [57]. However, other studies have demonstrated endocrinopathies may evolve at a later age [40,68]. Ma and colleagues [68] found a clinically significant number of children with ONH developed central hypothyroidism after normal thyroid function tests at an earlier age. Eight subjects with ONH developed central hypothyroidism between the ages of 20 to 51 months. One child at age 28 months developed central hypothyroidism within 4 months of prior normal thyroid test results. The study concluded that evolving central hypothyroidism, along with other hormonal aberrations, is a common occurrence in ONH and that ongoing surveillance testing is necessary throughout early childhood. This recommendation has been made in at least 1 other study [88]. Borchert [53] recommends continued monitoring until at least 4 years of age. Others have suggested that lifelong monitoring and surveillance may be necessary [9]. Because pubertal dysfunction in children with ONH is common and may manifest as precocious, rapid tempo, delayed, arrested, or absent pubertal development, the authors recommend that children with ONH be screened and closely monitored at least through adolescence. More studies are needed to investigate the incidence and risk of development of hypothalamic-pituitary dysfunction over time in children and adolescents with ONH. Children with diagnosed hormone deficiencies should be treated with appropriate hormonal replacement. The efficacy of hormonal therapy mimics that seen in other forms of congenital hypopituitarism. Interestingly, in children with ONH, initial growth may be normal despite documented GHD [48,53,69,89]. Children with ONH should have IGF-I and IGFBP-3 levels measured even with a normal growth pattern. The long-term growth phenotype of children with ONH includes an increased propensity toward obesity with a reported prevalence of up to 44% [8,22].

All children and families should receive counseling on hormonal abnormalities, their signs and symptoms, monitoring, and treatment from an endocrinologist or specially trained advanced practice provider. For those with adrenal insufficiency, proper education on glucocorticoid replacement and stress-dosing during illness or injury, including availability of emergency intramuscular hydrocortisone administration and an emergency letter describing the patient's diagnosis and treatment, should be provided to all patients and families. In addition, written instructions and emergency hydrocortisone should be provided to the child's school and major caregivers outside the home. Skills and knowledge should be reassessed at subsequent visits.

Other hypothalamic abnormalities

Children with ONH have a high prevalence of overweight or obesity [8,39], which may be due to hyperphagia and disordered leptin sensitivity in the hypothalamus [1]. Although some research suggests a connection between GHD and obesity, simply treating with GH has not been proven to mitigate the excess weight. A recent study evaluated the effects of GH replacement on body composition in 17 children with ONH and GHD, and found a modest reduction in body fat percentage but no improvement in BMI or weight-for-stature standard

Table 3
Guidelines for evaluation and management of children with optic nerve hypoplasia

Problem	Screening and referral	Timing of evaluations
Vision	Dilated direct ophthalmoscopic examination and evaluation for other visual deficits Ophthalmology referral	At diagnosis and yearly, and as clinically indicated for treatment of refractive errors, strabismus, and amblyopia
Neuroanatomical problems	MRI of the brain and sella with and without contrast Neurology and/or neurosurgery referral as needed	At diagnosis and as clinically indicated
Hormone deficiencies[a]	8 AM[b] fasting blood tests: BMP (CMP at diagnosis), serum osmolality, cortisol, TSH, free T4, IGF-I, and IGFBP-3, prolactin (>6 mo of age), and urine osmolality LH, FSH, and estradiol or testosterone[c] Bone-age radiograph[d] Endocrinology referral	At diagnosis, every 4–6 mo in the first 3 y of life, and yearly thereafter 3 wk–6 mo of life and as clinically indicated[c] As clinically indicated for growth and puberty Hormone replacement monitoring every 3 mo
Failure-to-thrive[a]	Nutritional evaluation and swallow testing OT and/or gastroenterology referral	When present as clinically indicated
Overweight or obesity[a]	Nutritional evaluation or weight management programs	When present as clinically indicated

Seizures[a]	EEG or MRI Neurology referral	At presentation of symptoms and signs
Sleep problems[a]	Counseling on bedtime routine and trial of melatonin Developmental pediatrician referral as needed	When present as clinically indicated
Developmental delay[a]	Developmental assessment tailored for visually impaired children Developmental pediatrician, psychologist, PT, OT, and/or speech therapy	Assessment at every visit by pediatrician
Behavioral problems or ASDs[a]	Behavioral or autism assessment Behavioral specialist or psychologist	As clinically indicated
School performance and quality-of-life	IFSP or IEP, counseling, and special needs assessment Early intervention, schools for blind children, and orientation and mobility referrals as needed	At diagnosis, when entering school and as needed

Abbreviations: BMP, basic metabolic panel; CMP, comprehensive metabolic panel; EEG, electroencephalogram; FSH, follicle stimulating hormone; IEP, individualized education program; IFSP, individual family service plan; IGFBP-3, insulin growth factor binding protein-3; IGF-I, insulin growth factor-I; GnRH, gonadotropin releasing hormone; LH, luteinizing hormone; OT, occupational therapy; PT, physical therapy; T4, thyroxine.

[a]At every visit, assess history, physical examination, vital signs, and growth with anthropometric data, including BMI and BSA.

[b]Before 6 months of age, screening tests may be done at any time of the day.

[c]Assessment of GnRH-LH-FSH function may be done during minipuberty, which is the physiologic, transient activation of hypothalamic-pituitary-gonadal axis of infancy. Subsequently, this assessment should be done when precocious puberty is suspected (signs of puberty <8 years in girls and <9 years of age in boys), or when delayed puberty is suspected (no signs of puberty in boys >14 years and girls >13 years), and/or with arrest of pubertal development.

[d]Delayed bone age is seen in GHD and/or delayed puberty, whereas advanced bone age is seen in precocious puberty. In children presenting concomitantly with GHD and precocious puberty, bone age as well as height velocity may be normal.

deviation scores [69]. Currently, as with other children who suffer from hypothalamic obesity, there is no effective treatment of this pernicious problem in children with ONH. Nutritional counseling for parents, early nutritional interventions, and weight management programs may be of some help.

Failure-to-thrive due to hypophagia and/or feeding challenges is seen in some children, and may necessitate nutritional and gastroenterological evaluations and management. DI should be evaluated in children presenting with failure-to-thrive and/or polydipsia because many young children with severe polydipsia may have poor growth and weight gain due to decreased caloric intake [90]. Additionally, water-seeking behavior is not uncommon and may be mistaken for DI. Conversely, some children with hypothalamic dysfunction may exhibit a diminished thirst mechanism, even in cases of DI.

Abnormal sleep-wake cycle and vital signs, including temperature dysregulation, may, in some instances, be managed through medical intervention. Disruption in these areas causes significant difficulties in daily life for the patients and families. Melatonin may be used to help with disordered sleeping, with low doses of 0.1 to 0.5 mg given daily before bedtime or higher doses of 3 to 5 mg for sporadic as-needed indications [91]. Vital sign dysregulation causing dysautonomia may pose a challenge for clinicians and families taking care of these children, especially in those with secondary adrenal insufficiency, frequently necessitating emergency room visits and glucocorticoid stress-dosing due to difficulty in objectively discerning true illness from dysautonomia.

SUMMARY

Overall, ONH is a complex condition of unknown causes with abnormalities of the septum pellucidum having no prognostic significance. The authors believe that the neuroendocrinologic manifestations of ONH require ongoing monitoring, even in those patients with normal brain imaging, and replacement of pituitary hormones when necessary (see Tables 1 and 3). Additionally, a long-term, family-centered multidisciplinary approach involving pediatric specialists in ophthalmology, endocrinology, neurology, and neuropsychology, as well as therapists and educators, is critical to optimize development and well-being of all children with ONH.

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