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Incidence and Associated Endocrine and Neurologic Abnormalities of Optic Nerve Hypoplasia

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Abstract

Purpose—To describe the incidence of optic nerve hypoplasia (ONH) and the rate of associated endocrine, neurologic, and developmental abnormalities among a population-based cohort of children.

Methods—The medical records of all children (< 19 years) who were residents of Olmsted County, Minnesota (95.7% Caucasian in 1990) when diagnosed with ONH from January 1, 1984, through December 31, 2008, were retrospectively reviewed.

Results—A total of 19 children were diagnosed with optic nerve hypoplasia during the 25- year study period, yielding an annual incidence of 2.4 (95% confidence interval 1.2 – 3.5) per 100,000 residents < 19 years of age, or 1 in 2287 live births. The mean age at diagnosis was 2.1 years, and 53% were male. Commonly associated perinatal conditions included primiparity in 8 (47%), premature birth in 6 (35%), and maternal diabetes mellitus in 3 (16%). Of the 19 study patients, 16 (84%) had bilateral involvement, 8 (47%) presented with decreased visual acuity, 8 (47%) had strabismus, and 5 (26%) had nystagmus. Systemic conditions included developmental delay in 12 (63%), neurologic deficits in 10 (53%), and endocrine dysfunction in 5 (26%).

Conclusions—This population-based study demonstrated an incidence of optic nerve hypoplasia of approximately 1 in 2287 live births. More than half of the patients had developmental and neurologic deficits while one-fourth were diagnosed with endocrine dysfunction.

Optic nerve hypoplasia (ONH) is one of the leading causes of childhood blindness and visual impairment in the United States.[1] It is a non-progressive congenital disease characterized histologically by a subnormal number of optic nerve axons in the optic nerve tracts resulting in small, pale optic discs.[2] ONH often occurs in association with a number of clinically important endocrine and central nervous system abnormalities as part of a spectrum of diseases known as septo-optic dysplasia (SOD), a congenital syndrome involving developmental abnormalities of the optic nerves, midline brain structures, and cerebral hemispheres.[3,4] Developmental delays are a common occurrence in children with ONH as well, and encompass a wide spectrum from mild communication delays to profound motor and global delays.[5]

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ONH has been an increasingly recognized cause of congenital blindness in children over the past 30 years. In 1981, Acers estimated the incidence of ONH to be 2 per 100,000.[3] More recently, the incidence of ONH in Sweden has been estimated at 6.3 per 100,000,[6] and incidence estimates in England had risen to 10.9 per 100,000 in 2006.[7] However, there are no known incidence reports of ONH in North America. The purpose of this study was to report the incidence and associated endocrine and neurologic abnormalities observed in a population-based cohort of children less than 19 years of age diagnosed with ONH using a medical record-retrieval system.

Subjects and Methods

The medical records of all pediatric (< 19 years) patients residing in Olmsted County when diagnosed with optic nerve hypoplasia from January 1, 1984, through December 31, 2008, were retrospectively reviewed. Potential cases of optic nerve hypoplasia were identified using the resources of the Rochester Epidemiology Project (REP), a medical record linkage system designed to capture data on any patient-physician encounter in Olmsted County, Minnesota.[8] The racial distribution of Olmsted County residents in 1990 was 95.7% Caucasian, 3.0% Asian-American, 0.7% African-American, and 0.3% Native American. In the year 2000, 91.1% (compared to 80.4% in the entire United States) of Olmsted County residents possessed a high school diploma or higher, 34.7% (24.4% nationally) had a bachelor's degree or higher, the mean household income was $51,000 ($42,000 nationally), and 3.8% (9.2% nationally) of families were below the poverty level.[9] The population of this county (106,470 in 1990) is relatively isolated from other urban areas, and virtually all medical care is provided to residents by Mayo Clinic or Olmsted Medical Group and their affiliated hospitals.

This study was approved by the Institutional Review Boards of Mayo Clinic and Olmsted Medical Group. The medical records of all patients < 19 years who were diagnosed with optic nerve hypoplasia, septo-optic dysplasia and DeMorsier's Syndrome during the 25-year study period were reviewed. Optic nerve hypoplasia was defined in this study as an abnormally small optic nerve as determined by the examining clinician. Incident cases included only those patients who had an initial diagnosis during the study period and were residing in Olmsted County at the time of their diagnosis. All diagnoses are carefully entered into the Rochester Epidemiology Project database and residency status was verified by specially-trained personnel. The complete medical records for all incident cases were abstracted by the medical student investigator to include information on demographics, prenatal risk factors, initial visit information, diagnoses, and follow-up visit information. Each diagnosis was confirmed by a pediatric ophthalmologist (BGM) who reviewed the medical record. Children not living in Olmsted County at the time of their diagnosis were excluded.

The incidence and prevalence of ONH was estimated using the age- and sex-specific population figures from Olmsted County, Minnesota. Yearly incidence rates for each age and sex group were determined by dividing the number of incident cases within their respective group by the estimated total Olmsted County resident population of the group for that given year. Population figures for 1990 and 2000 were obtained from the United States census data and population figures for the intercensus years were estimated using a linear interpolation.

Results

A total of 19 cases of ONH were identified during the 25-year study period, yielding an annual incidence of 2.4 (95% C.I.: 1.2 – 3.5) per 100,000 residents less than 19 years of age,

or 1 in 2287 live births. The incidence during the first five years of the study (1984–1988) was 1.52 (95% C.I.: 0.00 – 3.25), compared to 3.05 (95% C.I.: 0.79 – 5.30) per 100,000 patients for the final five years (p=0.32). The demographic characteristics of the 19 subjects are described in Table 1. There was no predilection for gender and the mean age at diagnosis was 2.1 years (range, birth to 17.6 years). There were 3 (16%) African American patients which was significantly different from the study population (p<0.001) of only 2.7%. One set of identical twins was identified. Six (35%) of the 19 study patients were born prematurely, and 8 (47%) were first-born. One patient had intra-uterine growth retardation, and 3 (16%) were born to mothers with gestational diabetes mellitus.

The ocular characteristics of the 19 children identified in this study are described in Table 2. Sixteen patients (84%) had bilateral involvement, and 3 (16%) had unilateral involvement of the right eye. Nine (47%) had decreased visual acuity at the initial visit, 8 (42%) had strabismus, 5 (26%) presented with nystagmus and 1 (6%) with amblyopia. Eleven patients had other ocular abnormalities as shown in Table 2.

The associated endocrine and neurologic abnormalities of the 19 study patients are described in Table 3. Five patients (26%), all with bilateral ONH, had an endocrine abnormality, including 4 with pituitary gland abnormalities on neuroimaging. One patient had panhypopituitarism, while 3 patients had varied pituitary dysfunction, including 2 with growth hormone deficiency, 2 with thyroid hormone deficiency, 2 with diabetes insipidus, and one with adrenal insufficiency. The fifth patient had isolated central precocious puberty. Three developed endocrine abnormalities within 6 weeks of birth, while two had identifiable endocrine dysfunction by around 7 years of age.

Twelve (63%) of the 19 study patients were evaluated by neuroimaging. Ten (53%) had an underlying neurologic abnormality either clinically or on imaging, and all ten had bilateral ONH. The most common neurologic abnormalities identified were cerebral palsy and microcephaly, with 3 (16%) patients each. Two patients (11%) had agenesis of the septum pellucidum, and 2 (11%) had corpus callosum abnormalities. Twelve (63%) of the 19 study patients were also diagnosed with developmental delay, with the most common deficits being profound mental retardation and motor and communication delays.

Optic nerve hypoplasia was also diagnosed in conjunction with assorted systemic disorders. One patient died shortly after birth, and was diagnosed with Trisomy 13 and bilateral ONH at autopsy. Another patient had epidermal nevus syndrome, while a third had Zellweger (cerebrohepatorenal) syndrome, both with bilateral ONH. One set of identical twins was diagnosed with bilateral ONH and oculocutaneous albinism.

The mean length of follow-up for the cohort was 2.2 years (range, 0 to 12.4 years). Table 4 describes the ophthalmologic, endocrine, and neurologic management of the 19 study patients. Eight patients required glasses for vision and one for strabismus. Two patients underwent strabismus surgery, and 2 were treated for amblyopia. Of the 5 patients with endocrine abnormalities, 2 required growth hormone replacement, 3 steroid hormone, 3 thyroid hormone, and one was treated with a gonadotropin releasing hormone agonist. Three patients died within the follow-up period.

Discussion

This study describes a population-based incidence rate of optic nerve hypoplasia (ONH) and the prevalence of associated endocrine and neurologic abnormalities from a cohort of children residing in Olmsted County, Minnesota. Optic nerve hypoplasia occurred in approximately 1 in 2287 live births. Associated findings included significant ocular

comorbidity in 65%, developmental delay in 63%, neurologic abnormalities in 53%, and 26% with confirmed pituitary dysfunction.

To our knowledge, this is the first study to describe the incidence of ONH in a North American population. In 1981, Acers estimated the incidence of ONH to be 2 cases per 100,000 people based on his incomplete review of 45 patients in the "state community" of Oklahoma.[3] A more recent study from Sweden estimated an incidence of 6.3 per 100,000,[6] and the incidence in England was estimated to be higher yet, at 10.9 per 100,000 persons.[7] Several recent studies have suggested that the incidence of ONH has been rising, possibly due to enhanced awareness of the condition.[10] Due to the small number of cases in this study, we were unable to demonstrate any statistically significant changes in incidence over time. However, it is worth noting that the incidence rate during the final five years of the study was twice that of the first five years. Additionally, we were only able to identify three additional cases of optic nerve hypoplasia between 1965 and 1984, demonstrating that, although not statistically significant in this small study, more cases have been diagnosed in the most recent years of the study.

While our incidence rate is significantly lower than other recent estimates, the populations studied may explain this finding. The residents of Olmsted County during the years of this study were 95% white, predominantly middle-class, and were more likely to possess a college degree and have a higher mean household income than the national average. The much higher estimate in England by Patel et al[7] was observed in a predominantly urban area in which they found an increased risk of ONH in three districts with high population densities, unemployment, and teenage pregnancies. They suggested that the development of ONH is associated with environmental or lifestyle factors linked to deprivation in this population.[7] The significance of the increased rate of ONH in this study among African Americans relative to their percentage within Olmsted County is unknown, but may be due in part to small sample size.

Multiple studies have suggested an association of ONH with various gestational and environmental conditions, particularly primiparity, prematurity, young maternal age, gestational diabetes mellitus, and alcohol and tobacco abuse.[2,11,12,14–17] The most common conditions associated with ONH in this study were primiparity and prematurity. Thirteen percent of affected infants were born to mothers with a history of perinatal alcohol or tobacco abuse, consistent with prior estimates. Contrary to previous reports indicating an association of young maternal age with ONH,[12–14] the average maternal age at delivery in this cohort was 30 years. Interestingly, one set of twins with ONH was identified in this group, suggesting that a common genetic or gestational factor may play a role in the development of the disorder.

Sixteen (84%) of the 19 incident cases of ONH in this study were bilateral, consistent with previous estimates, ranging from 75 to 93%.[3,5,17,18] The most common ocular findings at initial presentation were decreased visual acuity (47%), strabismus (42%), and nystagmus (26%). One child had amblyopia at initial exam, but was not diagnosed with ONH until 4 years of age. A second was diagnosed with ONH at birth, but developed amblyopia at a later age. This highlights the importance of not only early screening and diagnosis of ONH, but proper ophthalmologic management to curtail the development of treatable sequelae such as amblyopia.

There has been significant discord regarding the prevalence of endocrine abnormalities among patients with ONH. Several retrospective studies have reported endocrine dysfunction to vary from 6 to 81%.[11,18,20–23] In a prospective study, comprised of 46 children with ONH, Ahmad et al found 71.7% to have developed endocrine dysfunction by

five years of age.[18] However, all prior reports were performed in large medical referral centers. In this study, five patients (26%) were found to have developed endocrine abnormalities by seven years of age.

Ten (53%) of the study patients were found to have neurologic abnormalities, either clinically or by neuroimaging. Three patients (16%) had cerebral palsy, an association that, to our knowledge, has only been described once previously.[11] Twelve patients (63%) were diagnosed with developmental delay in this study. There was a broad range of developmental phenotypes in these patients, from normal intellect to profound mental retardation, as is often the case among children with ONH.[11] The most common deficits included profound mental retardation and motor and communication delays. These findings were consistent with previous estimates of neurodevelopmental deficits in children with optic nerve hypoplasia.[5,11]

Several studies have suggested that children with bilateral involvement are more likely to develop endocrine and neurodevelopmental deficits, [5,11,12,18,19,21] and this study further reinforces that hypothesis. All five patients with endocrine deficits and all ten patients with neurologic abnormalities had bilateral ONH. All but one patient with developmental abnormalities were bilaterally affected as well. Of the three children with unilateral ONH, only one had an additional diagnosis (developmental delay).

One set of identical twins with oculocutaneous albinism and bilateral ONH were identified in this cohort, supporting the findings of others. Spedick and Beauchamp described ONH in six eyes of four patients in a review of twelve patients with ocular or oculocutaneous albinism,[24] while Charles et al found ONH in 29 of 148 eyes of patients with albinism.[25] More recently, Schmitz et al reported a significant difference in optic nerve diameter by magnetic resonance imaging among patients with albinism compared to controls.[26]

There are several limitations to the findings in this study including its retrospective design and imprecise follow-up. The study design may not have captured all patients and all episodes of disease, as some patients with ONH may have sought care outside of Olmsted County or avoided an evaluation altogether. Additionally, because of the potential for misdiagnosis or miscoding, or because some children with ONH may have never developed visual, endocrine, or neurologic deficits, the incidence of ONH may have been underestimated in this population. While the mean duration of follow-up in this cohort should be sufficient to allow for the detection of endocrine, neurologic, or developmental abnormalities, it is possible that we underestimated the rate of these disorders among this cohort of patients. The absence of neuro-imaging in 7 of the 19 study patients may further underestimate this rate.

This study is further limited by the region in which it was performed. Because the ethnic composition of Olmsted County was 95% white during the years of the study, we are unable to extrapolate our findings to populations not represented by this cohort. Recognizing these weaknesses and assuming a population of 76,620,000 citizens younger than 19 years of age (2000 US Census), we estimate 1,838 new cases of optic nerve hypoplasia each year in the United States. Although relatively uncommon, each child diagnosed with ONH should receive specialized neurologic and endocrine evaluations given their high rate of having developmental delay (63%), neurologic deficits (53%), and endocrine dysfunction (26%).

This study found that approximately 1 in 2287 children developed optic nerve hypoplasia in Olmsted County over a 25-year period. Our data suggests that, although limited by small sample size, the incidence of ONH has remained stable in this U.S. population. A majority of patients with ONH have associated neurodevelopmental or endocrine deficits, necessitating early diagnosis and proper management of children with the disorder.

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Table 1

Demographic characteristics and prenatal risk factors in 19 children with optic nerve hypoplasia in Olmsted County, Minnesota, 1984 to 2008.

Characteristic	Value
Age at diagnosis in years (range)	2.1 (0 to 17.6)
Gender	
Male	10 (53%)
Female	9 (47%)
Ethnicity	
White	16 (84%)
Black	3 (16)%
Mean maternal age in years (range)	30 (19 to 36)
Mean birth weight in grams (range)	3085 (1233 to 3875)
Prematurity	6 (32%)
Primiparity	8 (44%)
Intrauterine growth retardation	1 (6%)
Maternal diabetes mellitus	3 (16%)
Gestational tobacco abuse	2 (13%) †
Gestational alcohol abuse	2 (13%) †
Gestational medication use	3 (20%) ‡

† Gestational tobacco and alcohol abuse status was known in 15 of 19 patients; 4 patients did not respond to clinical surveys.

‡ Gestational prescription medication use was known in 17 of 19 patients; 2 patients did not respond to clinical surveys.

Table 2

Ocular characteristics at initial presentation of 19 children diagnosed with ONH in Olmsted County, Minnesota, 1984 to 2008.

Characteristic	Value (%)
Visual Acuity[†]	
Normal	8 (42)
Decreased	9 (47)
Refractive Error[‡]	
Normal	8 (42)
Myopia	4 (21)
Hyperopia	3 (16)
Astigmatism	2 (11)
Ocular Alignment[*]	
Normal	8 (42)
Esotropia	4 (21)
Exotropia	4 (21)
Amblyopia	
Normal	8 (42)
OD	1 (6)
OS	1 (6)
Nystagmus	
Normal	13 (68)
OU	4 (21)
OS	1 (6)
OD	0
Optic Nerve Hypoplasia	19
OU	16 (84)
OS	0
OD	3 (16)
Other Ocular Abnormality[**]	
OU	5 (26)
OD	1 (6)
OS	0

[†]Decreased visual acuity was defined as ≤ 20/40 and determined to be the result of ONH. Visual acuity could not be assessed in 2 of 19 patients who died soon after birth

[‡]Myopia was defined as ≥ −0.75 diopters. Hyperopia defined as ≥ +4.0 diopters.

[*]Ocular alignment could not be assessed in 3 patients; 2 died soon after birth, and a third had an incomplete eye exam at birth and died before a follow-up exam could be done.

** Other ocular abnormalities included one patient each with bilateral congenital ptosis, Marcus Gunn pupil, bilateral oculomotor apraxia, bilateral lid colobomata and lipodermoid corneas as part of epidermal nevus syndrome, and two identical twins with oculocutaneous albinism.

Table 3

Endocrine, neurologic, and developmental disorders among 19 patients diagnosed with ONH in Olmsted County, Minnesota, 1984 to 2008.

Characteristic	Value (%)
Endocrine Abnormality	5 (26)
Hypopituitarism	1 (6)
Growth hormone deficiency	3 (16)
Diabetes Insipidus	2 (11)
Hypothyroidism	3 (16)
Adrenal Insufficiency	1 (6)
Precocious Puberty	1 (6)
Neurologic Abnormality	10 (53)
Corpus callosum hypoplasia	2 (11)
Septum pellucidum aplasia	2 (11)
White matter hypoplasia	2 (11)
Hydrocephalus	2 (11)
Microcephaly	3 (16)
Cerebral palsy	3 (16)
Trisomy 13	1 (6)
Developmental Abnormality	12 (63)
Motor	4 (21)
Language	4 (21)
Social	1 (6)
Mental Retardation	3 (16)

Table 4

Management of 19 children diagnosed with ONH in Olmsted County, Minnesota, 1984 to 2008.

Management	Value(%)
Ophthalmologic	
Glasses for visual acuity	8 (42)
Glasses for strabismus	1 (6)
Strabismus surgery	2 (11)
Amblyopia treatment	2 (11)
Endocrine Replacement	
Growth hormone	2 (11)
Steroid hormone	3 (16)
Thyroid hormone	3 (16)
Gonadotropin releasing hormone agonist	1 (6)
Neurologic surgery †	2 (11)

† Included a left temporal lobectomy in one patient and a rhizotomy in another.