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Reappraisal of the Optic Nerve Hypoplasia Syndrome

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Background: Optic nerve hypoplasia (ONH) has been described as an increasingly prevalent cause of congenital blindness. Its association with hypopituitarism and absent septum pellucidum has been recognized for more than 40 years as "septo-optic dysplasia" or "de Morsier syndrome." More recent studies have suggested that these associations are independent of one another. This review was designed to assess the historical and recent evidence for associations of neuroradiologic, endocrinologic, and developmental problems in patients with ONH.
Evidence acquisition: Historical and contemporary literature review.
Results: The medical literature does not support the notion that Georges de Morsier ever described a case of ONH or recognized its association with hypopituitarism or missing septum pellucidum. Recognition of the critical association of ONH with hypopituitarism should be attributed to William Hoyt. Hypopituitarism and other more recently identified associations with ONH, such as developmental delay, hypothalamic dysfunction, and autism, are independent of septum pellucidum development. Other common neuroradiographic associations, such as corpus callosum hypoplasia, gyrus dysplasia, and cortical heterotopia, may have prognostic significance.
Conclusions: Children with ONH need to be monitored for many systemic, developmental, and even life-threatening problems independent of the status of the septum pellucidum. "Septo-optic dysplasia" and "de Morsier syndrome" are historically inaccurate and clinically misleading terms that should be abandoned.

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This review will summarize the state of knowledge on optic nerve hypoplasia (ONH) and reanalyze the historical literature that led to misunderstanding of its association with neurologic or endocrinologic abnormalities. The case will be made for abandonment of the terms septo-optic dysplasia (SOD) and de Morsier syndrome.

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HISTORICAL PERSPECTIVE

The first description of ONH is ascribed to Briere in 1877 (1), but the first artistic rendering of the optic disc appearance was by Schwarz in 1915 (2) (Fig. 1). The first recognition of an association of ONH with agenesis of the septum pellucidum was by Dr David Reeves at Children's Hospital Los Angeles in 1941 (3,4).

The purpose of Reeves' report was to demonstrate the youngest case of agenesis of the septum pellucidum diagnosed by air encephalogram (Fig. 2). The 4-month-old patient was coincidentally blind, and examination under anesthesia by Dr S. Rodman Irvine revealed "bilateral primary optic atrophy of undetermined origin, probably, however, on the basis of a congenital aplasia."

The association of ONH with absence of the septum pellucidum was later erroneously attributed to Georges de Morsier (Fig. 3), who coined the term, "la dysplasia septo-optique" (SOD) (5). However, the "optic dysplasia" recognized by de Morsier was not ONH. In his treatise on cranioencephalodysraphism, his third chapter highlighted his fascination with absence of the septum pellucidum that had incidentally been noted in postmortem brains. From this, he discovered that 1 brain had a unilaterally vertically rotated optic tract (Fig. 4). This was from a woman who died of pyelonephritis at the age of 84 years without any history of vision problems. He also described the case of a living 44-year-old alcoholic man who had "slight narrowing of the visual field with enlargement of the blind spot," but was incidentally discovered to be missing the septum pellucidum on air encephalogram. De Morsier supplemented these 2 cases with 34 others (11 autopsy cases and 23 radiographic cases) from the literature that had agenesis of the septum pellucidum, 8 of which had some other eye or optic nerve problem. These included 1 case of bilateral anophthalmia, 3 cases of bilateral optic atrophy (1 with Apert syndrome and 1 with osteogenesis imperfecta), and 3 cases of unilateral optic atrophy (2 systemically normal and 1 with

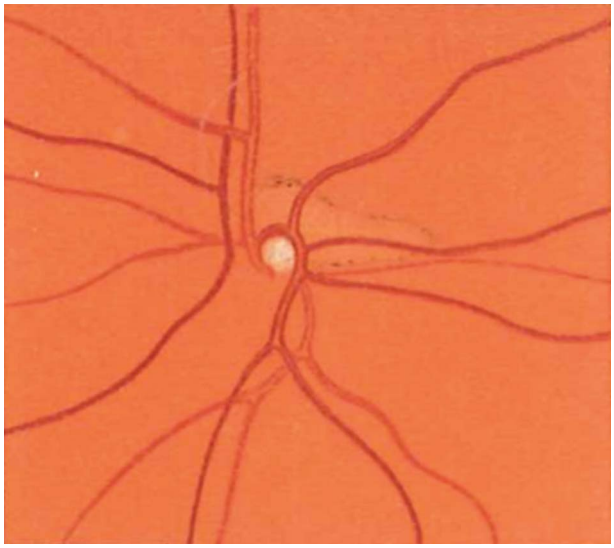

FIG. 1. Appearance of ONH rendered by Schwarz in 1915. Reproduced with permission from Schwarz (2).

FIG. 3. Photograph of Georges de Morsier (1894–1982) (courtesy of Avinoam Safran, MD, Geneva, Switzerland).

hemiparesis and mental retardation). The only case with definite ONH from the literature cited by de Morsier was the case that had been previously documented by Reeves (3). It was from this compilation of disparate cases that an association of eye problems with agenesis of the septum pellucidum (i.e., SOD) was postulated.

De Morsier believed that agenesis of the septum pellucidum and various ocular anomalies were "not fortuitous" associations (6). He hypothesized that the septum pellucidum served to connect the corpus callosum to the fornix and that lacking this supporting structure resulted in penetration of the chiasm by the third ventricle. This malformation of the chiasm then somehow led to optic nerve or ocular anomalies.

Three years following de Morsier's report, Gross and Hoff (7) reported their autopsy findings from 465 brains obtained from patients with severe neurologic problems or systemic malformations. They identified 13 brains with absence of the septum pellucidum. One of these had bilateral ONH and 7 (6 bilateral; 1 unilateral) had optic atrophy. They also

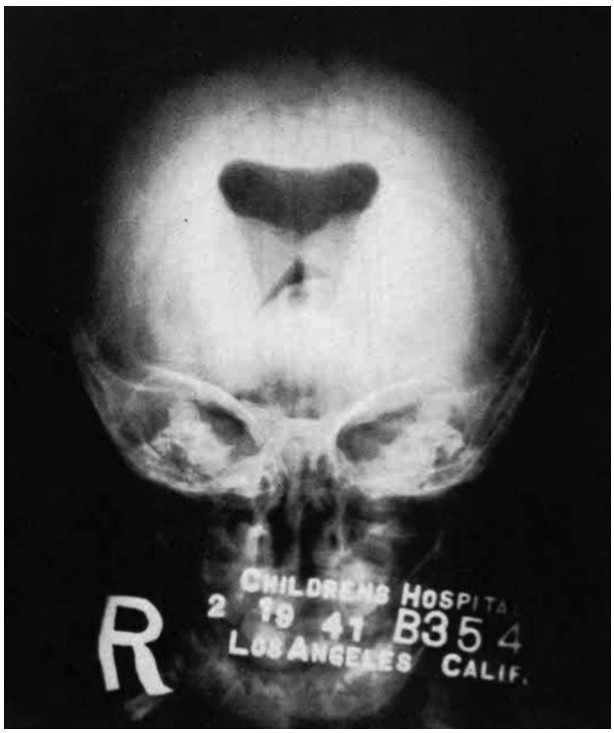

FIG. 2. Air encephalogram from first case documenting absence of septum pellucidum in a child with ONH in 1941. Reproduced with permission from Reeves (3).

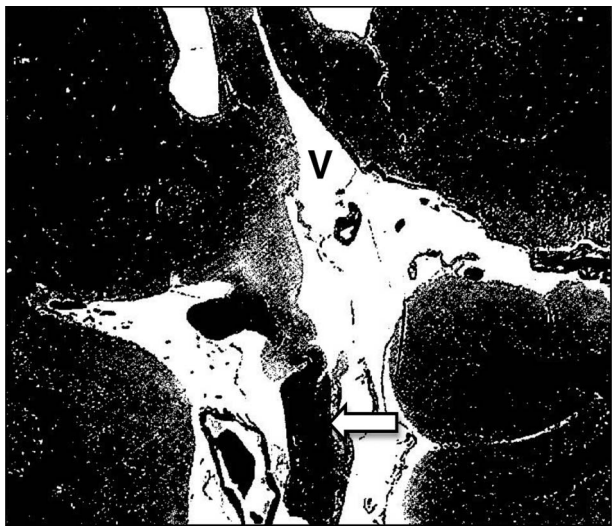

FIG. 4. Histologic coronal section through the posterior optic chiasm demonstrates downward displacement and vertical rotation of the left optic tract (*arrow*) and cystic opening in floor of the third ventricle (V3). This is from the case that de Morsier called "septo-optic dysplasia." Reproduced with permission from de Morsier (5).

identified 12 cases of partial or complete corpus callosum agenesis. Two of these had microphthalmos with bilateral optic atrophy and 1 had unilateral ONH.

Thus, prior to 1970, only 2 cases of ONH associated with absence of the septum pellucidum had been described in the medical literature, and neither of these had been identified by de Morsier.

In 1970, Ellenberger and Runyan (8) described a 23-year-old woman with unilateral ONH, absent septum pellucidum, and dwarfism. In the same year, Dr William Hoyt wrote the landmark article recognizing the association of ONH with growth hormone (GH) deficiency and predicted the absent septum pellucidum in the case reported by Ellenberger and Runyan. Hoyt et al (9) described 9 patients with ONH and pituitary dwarfism, 4 of whom were missing the septum pellucidum. They generously, but erroneously, attributed recognition of the association of ONH with agenesis of the septum pellucidum to de Morsier and resurrected the term "septo-optic dysplasia," which is now commonly referred to as de Morsier syndrome. "Hoyt syndrome" would be a more appropriate eponym, particularly since the association of ONH with hypopituitarism, not septum pellucidum agenesis, is the clinically important observation.

De Morsier would scarcely have recognized the attribution to himself. Trained as a psychiatrist under de Clérambault, he spent his career at the University of Geneva. Lacking a suitable neuropathologist replacement after the death of Edouard Long, de Morsier was enjoined to lecture in neuropathology for 1 h/wk starting in 1933, during which time he attempted to catalog the various craniodysraphisms. Ultimately, he was appointed as head of neurology in 1960, a position that he held until his retirement in 1964. Arguably, de Morsier's greatest contribution to medicine was his description of the Charles Bonnet syndrome, which he named after the 19th century naturalist, who in 1760 had documented the visual hallucinations of his grandfather (10). There is no record of de Morsier ever identifying a case of ONH.

PREVALENCE

ONH has been recognized as an increasingly frequent cause of congenital blindness affecting one or both eyes. In 1997, bilateral ONH surpassed retinopathy of prematurity as the single leading cause of infant blindness in Sweden (11). Only cortical visual impairment of multiple etiologies was more common than ONH in blind children. The prevalence of ONH in Sweden quadrupled between 1980 and 1999 to 7.1 per 100,000, while all other causes of childhood blindness declined as diagnosed by the same major ophthalmic center (12). In 2006, the prevalence of ONH in England had risen to 10.9 per 100,000 children (13).

Owing to incomplete registries of blindness, the prevalence of ONH in North America is unknown. Prior to 1970, it was considered rare. In fact, prior to 1962, only 1 case had been diagnosed in British Columbia, Canada, but 20 cases were subsequently diagnosed by 1974, for an estimated prevalence of 1.8 per 100,000 (14). Acers noted a similar increase in the incidence of reported cases in the 1970s (15). ONH was identified in 12% of blind infants in Harris County in Texas in the early 1980s (16). Surveys of schools for the blind in the United States in 1999 revealed that ONH accounted for 5.7% to 12.9% of blind students (17,18). Such surveys underestimate the actual prevalence because cognitive or behavioral impairments exclude most children with ONH from schools for the blind. In 2007, the Babies Count registry reported ONH as the third most prevalent cause (behind cortical vision impairment and retinopathy of prematurity) of any vision impairment in children aged 3 years or younger in the United States (19). Of all conditions, ONH was the most likely to cause legal blindness.

NEUROIMAGING

Septum Pellucidum

Following the resurrection of "SOD" by Hoyt et al, absence of the septum pellucidum garnered inappropriate dogmatic significance. Its association with pituitary dysfunction was documented in retrospective studies hampered by ascertainment bias (20,21). Other studies refuted the association, even to the point of showing no association of any adverse outcome with agenesis of the septum pellucidum (22–24). Indeed, as with de Morsier's experience, most cases of agenesis of the septum pellucidum are detected accidentally and not associated with optic nerve or hormone problems. The prevalence of absent septum pellucidum in the general population is unknown. In the only prospective study of ONH, absence of the septum pellucidum was not associated with laterality of ONH, vision, pituitary dysfunction, or developmental outcome (25,26).

Nonetheless, the term "septo-optic dysplasia" has persisted and its definition has evolved to include midline brain abnormalities, such as hypoplasia of the corpus callosum or pituitary anomalies on MRI, in addition to absent septum pellucidum. This definition has served to focus investigators on morphogenetic mechanisms. It disregards the fact that a small corpus callosum frequently denotes hemispheric disease and that most neuroradiographic abnormalities associated with ONH are not midline (26). These include hydrocephalus, white matter hypoplasia, cortical heterotopia, pachygyria, polymicrogyria, schizencephaly, and arachnoid cysts. Rather than reassessing the appropriateness of the nomenclature, investigators recognizing these nonmidline findings simply expanded the terminology to include "SOD plus" as a more severe expression on the spectrum of ONH (27).

Corpus Callosum

Corpus callosum hypoplasia is the most prevalent neuroimaging abnormality associated with ONH (Fig. 5). It is

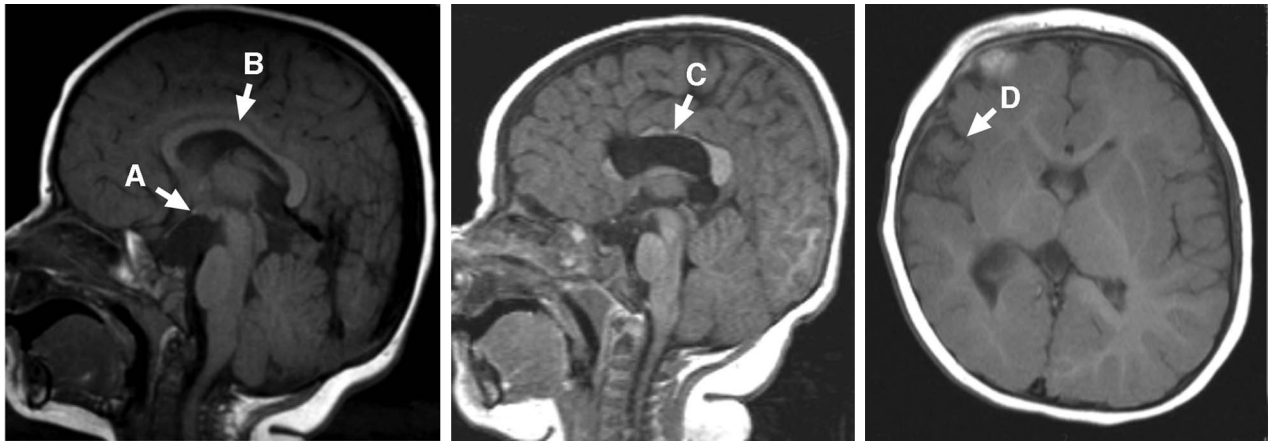

FIG. 5. ONH is commonly associated with ectopic posterior pituitary (A) or other pituitary abnormalities. The corpus callosum may be normal (B) or hypoplastic (C). Hypoplastic corpus callosum is frequently associated with cortical dysgenesis, such as polymicrogyria (D).

commonly associated with absence of the septum pellucidum; however, absence of the septum pellucidum cannot serve as a surrogate for corpus callosum hypoplasia, as partial agenesis of the corpus callosum may not be associated with absence of the septum pellucidum. Corpus callosum hypoplasia has been associated with developmental delay but not with hypopituitarism in children with ONH (26).

Corpus callosum hypoplasia is detected in 1.8 to 2.05 per 10,000 live births and in 2.3% of developmentally disabled individuals (28,29). Forty-nine percent of patients with corpus callosum hypoplasia have other central nervous system abnormalities, including nonmidline defects typically associated with ONH (cortical heterotopias, schizencephaly, white matter hypoplasia, polymicrogyria) (28). However, ONH occurs in less than 10% of children with corpus callosum hypoplasia (29). Corpus callosum hypoplasia is associated with a myriad of syndromic conditions and chromosomal abnormalities, but pituitary dysfunction in those without ONH is uncommon (30). Although both ONH and corpus callosum hypoplasia may be the consequence of more generalized problems with CNS development, the presence of ONH appears to be uniquely associated with hypothalamic dysfunction.

Pituitary Gland

Pituitary abnormalities on neuroimaging include empty sella, ectopic posterior pituitary, nonvisualized infundibulum and posterior pituitary. These findings occur in 13%–34% of children with ONH, and nearly all of those have hypopituitarism (26,31). However, hypopituitarism occurs in 75% of patients with ONH, the majority of whom have no pituitary abnormalities on neuroimaging. It is also interesting that absence of the posterior pituitary bright signal on T1 MRI has been associated with anterior pituitary function (31). However, most of these patients do not have diabetes insipidus, as would be expected if vasopressin granules are the cause of the bright signal (32).

Optic Nerve

Attempts to diagnose ONH based on neuroimaging measurements of the optic nerve or chiasm have been promising (33,34). Such studies have been retrospective, lacked controls with normal and atrophic optic nerves, or failed to adjust for age in young patients. With continued improvement, it seems likely that high-resolution MRI could be used to distinguish ONH from optic atrophy. Assessment of the intracranial portion of the optic nerves is more reliable for detecting ONH than assessment of the orbital component (35).

CLINICAL DIAGNOSIS

The diagnosis of ONH is made by ophthalmoscopic confirmation of a small optic disc. This may be difficult with the binocular indirect ophthalmoscope due to limited magnification. With inadequate resolution, small pale optic discs may be difficult to distinguish from the surrounding hypopigmented scleral canal and therefore misdiagnosed as normal-sized discs with optic atrophy. The optimal method for diagnosing ONH in a young child is with direct ophthalmoscopy. This is usually not difficult in visually impaired children who have minimal objection to the light or the proximity of the examiner, as long as the examiner does not touch the child's face. There are several funduscopic findings that assist the clinician in establishing the diagnosis of ONH. First, and most important, is an assessment of the area of the disc relative to the size of the central retinal vessels overlying it.

Second, tortuous retinal arterioles, venules, or both may accompany ONH (Fig. 6). Alternatively, the vessels may be uncommonly straight with decreased branching (Fig. 7). Such a nonbranching vascular pattern has also been recognized in children with primary GH deficiency (36). It is not known if these vascular patterns in ONH correlate with endocrine dysfunction.

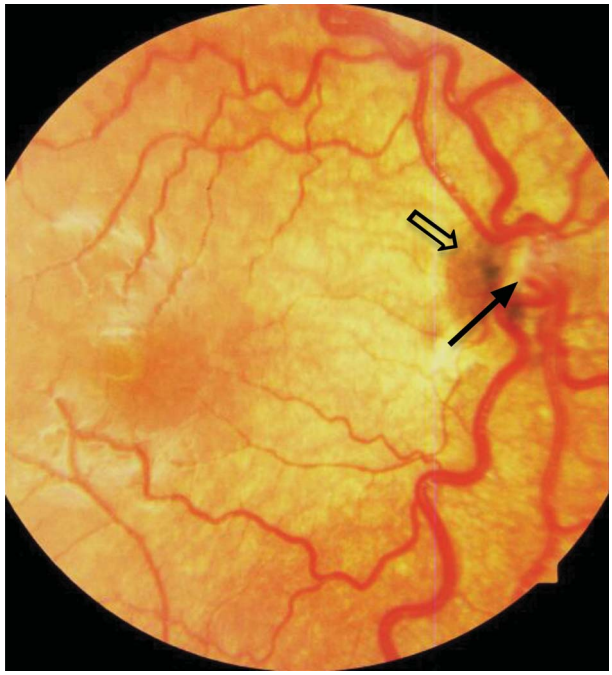

FIG. 6. Photograph of severe ONH (*filled arrow*) with a partially pigmented double ring (*unfilled arrow*) and tortuous vessels.

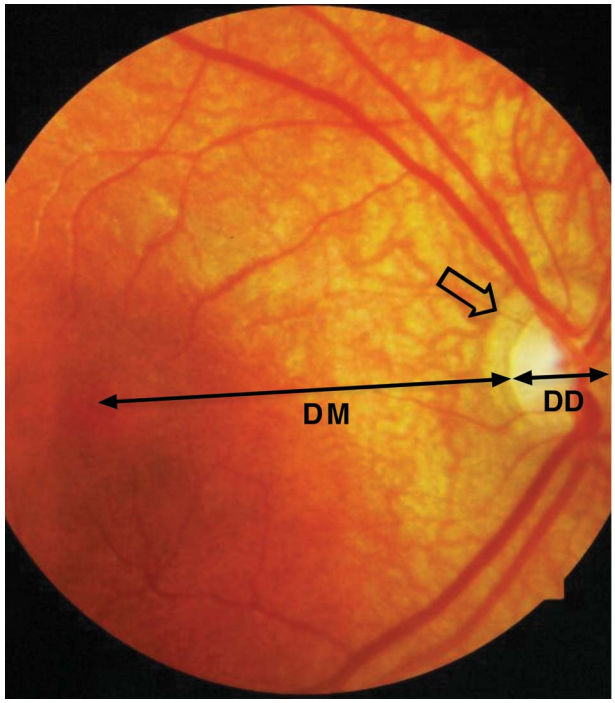

FIG. 7. Photograph of mild ONH with DD/DM ratio of 0.23; hypopigmented double ring (*unfilled arrow*); straight vessels.

Finally, in patients with ONH, a ring of hypopigmentation or hyperpigmentation often, but not always, surrounds the disc defining the area of the putative scleral canal (Figs. 6, 7). This is presumably caused by migration of sensory retina and/or pigment epithelium from their original margin at the edge of the optic canal to a new position at the border of the hypoplastic optic disc (37). This "double ring" sign does not define ONH as a similar appearance may be present in other conditions, such as myopia.

Although generally impractical, many authors have suggested that ONH can be confirmed with measurements of the optic disc from fundus photographs, particularly disc diameter (DD) or area relative to various retinal landmarks. In normal children, the ratio of the horizontal DD to the distance between the macula and the temporal edge of the disc (DM) is greater than 0.35 (25,38,39) (Fig. 7). DD/DM ratios less than 0.35 somewhat correlate with vision outcomes (40). Although most patients with DD/DM ratios less than 0.35 have generally been described as having ONH, some with DD/DM ratios of 0.30–0.35 have normal vision. Some overlap in optic disc size between normal and ONH is not surprising. The precise risk for systemic complications in these borderline cases has not been determined.

De Silva et al (41) found that the average DD/DM ratio at birth of preterm, but otherwise normal, infants was 0.26. Compared with measurements from adults made by other investigators, they estimated that the DD increases 44% in a lifetime compared with increases in DM of only 11%. This results in increased DD/DM ratio with age. Therefore, the age of the patient may need to be considered when measuring DD/DM ratios.

Attempts to diagnose ONH or predict vision from other imaging modalities, such as optical coherence tomography (OCT), have not been reported. Eyes with ONH may have a poorly developed foveal umbo on OCT in spite of a normal foveal appearance on ophthalmoscopic examination (42). The foveolar thickness is normal, but absence of the ganglion cell and nerve fiber layers results in a retina of uniform thickness, in which the umbo cannot be distinguished with OCT.

Some authors have broadly defined ONH to include any optic disc with congenitally decreased neuronal area (43). As such, those eyes with a normal-sized optic discs, but with enlarged cups, would qualify as having ONH. This appearance typically occurs in premature infants with periventricular leukomalacia (44). Although such optic nerves have fewer than the normal number of axons and may be technically hypoplastic, these children are not at risk for the same developmental and endocrinologic complications as children with small discs of typical ONH. They should, therefore, not be considered in the same diagnostic category. A similar argument can be made for eyes with major congenital malformations, such as microphthalmos, large colobomas, or persistent hyperplastic primary vitreous, which may consequently have small optic nerves.

VISION

Poor visual behavior is usually the first sign of ONH. Nystagmus usually develops at 1–3 months of age followed

by strabismus, typically esotropia, in the first year of life. Children with markedly asymmetric or unilateral ONH may present primarily with strabismus rather than nystagmus. Patients with relatively symmetric hypoplasia may have asymmetric vision from superimposed amblyopia due to strabismus or anisometropia.

Approximately 80% of children with ONH are bilaterally affected and two thirds of those are asymmetrically affected (26). The unilateral cases are usually detected at a later age than those with bilateral involvement. Children with unilateral ONH are at risk for hypothalamic/pituitary dysfunction (69%) and developmental delay (39%), although that risk is significantly lower than patients with bilateral ONH (81% and 78%, respectively) (25,26).

Visual acuity ranges from no light perception to near normal. More than 80% of bilateral cases are legally blind (45). Most children experience some improvement in their vision in the first few years of life. This may be due to optic nerve myelination that occurs in the first 4 years of life, leading to improved axonal conduction (46).

HYPOTHALAMIC DYSFUNCTION

Hypothalamic dysfunction is the most common nonvisual problem in patients with ONH and results in loss of regulation of homeostatic mechanisms controlling behavior and pituitary gland function.

Hypopituitarism

In most cases of ONH, hypopituitarism is believed to be due to hypothalamic dysfunction rather than pituitary dysgenesis. Children with ONH and hypopituitarism usually have moderately elevated serum prolactin levels, as this hormone is normally suppressed by the hypothalamus. In a prospective study, hypopituitarism was not correlated with laterality of ONH (25). GH deficiency was the most common endocrinopathy (70%), followed by hypothyroidism (43%), adrenocorticotropic hormone deficiency (27%), and diabetes insipidus (5%). This high prevalence of endocrinopathy is consistent with previous retrospective studies (47,48). Delayed or precocious puberty is common, but the incidence is unknown.

Evolving pituitary dysfunction in children with ONH is poorly understood, but cases of acquired hypopituitarism have been reported (48,49). Normal pituitary function at the time of initial evaluation does not preclude development of endocrinopathy in the future.

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 (50). Children with ONH frequently exhibit hyperphagia with obesity or hypophagia, with or without wasting. Some children also have an aversion to certain textures of food. Water-seeking behavior (and consequent enuresis) is also common and may be mistakenly attributed to diabetes insipidus.

Sleep

The biological clock is generated within the suprachiasmatic nuclei of the anterior hypothalamus above the optic chiasm. These nuclei receive photic information via the optic nerves to synchronize the clock to the 24-hour light–dark cycle. The circadian pacemaker is reset each day with visual stimulation (51–53). Disturbance of the circadian system can have significant pernicious effects on physiology and behavior (54,55). Many children with ONH have sleep or wakefulness disturbances over the 24-hour day (56,57). Alternatively, they may have inadequate retinohypothalamic input to daily entrain the circadian clock, resulting in free-running sleep–wake cycles asynchronous with other family members. In either case, such sleep irregularities commonly result in behavioral difficulties and disruption of family life.

Temperature Regulation

The medial preoptic region of the hypothalamus is involved in body temperature regulation and, through communication with the paraventricular nucleus, regulates fever response (58). It is not surprising that many infants and children with ONH have problems with body temperature regulation and may be frequently hospitalized to rule out sepsis (59).

DEVELOPMENTAL OUTCOMES

In 1984 Margalith et al (60) were the first to report developmental delays in ONH, estimating neuropsychological handicaps in nearly three fourths of cases of ONH. Burke et al (61) estimated delayed development, based on neurologic examination, at a similar frequency. Observations of developmental delay in association with ONH range from isolated focal defects to global delay (62,63). Garcia-Filion et al (26) found developmental delays in 71% of ONH patients using standardized neuropsychological instruments in a prospective study. Motor delays were the most common (75%) and communication delays were the least common (44%). Independent risk factors for significantly delayed cognitive and overall development included hypoplasia of the corpus callosum and hypothyroidism but not absence of the septum pellucidum. Developmental delay occurred in unilateral (39%) and bilateral (78%) cases of ONH.

Autism spectrum disorders are overrepresented in the visually impaired population, with prevalence estimates up to 25% in children (64). The prevalence of autism appears even higher in children with ONH. In a group of 13 Swedish children with ONH and blindness, 6 had autism and 3 had an "autistic-like" condition (65). Parr et al (66) reported that, in a sample of 83 children with ONH and moderate to severe vision impairment (worse than 6/30), 37% (31 of 83) had social, communicative, and repetitive or restricted

behavioral difficulties and the majority of those (26 of 31) had a clinical diagnosis of autism spectrum disorder. Precise prevalence estimates of autism require modifications of the autism diagnostic instruments for visually impaired subjects. Such modifications have not yet been validated.

PATHOGENESIS AND GENETICS

The presumed association of midline cerebral defects with ONH has led to a focus on the genetic mechanisms involved in division of the prosencephalon into cerebral hemispheres and formation of the pituitary gland. Several candidate genes have been identified as responsible for cases of septo-otpic dysplasia. These include mutations of HESX1 associated with holoprosencephaly and SOX2 associated with anterior pituitary hypoplasia and hypogonadism. Only 5 cases of ONH in humans have been associated with the HESX1 mutation (67,68). Some of these were in cases of severe forebrain malformation, such as alobar holoprosencephaly (69). Such major malformations would be expected to impact the development of subsequent structures, such as the optic nerves, corpus callosum, and septum pellucidum. The vast majority of cases of ONH cannot be attributed to specific mutations. In fact, less than 1% of cases of ONH in large series were found to have an HESX1 mutation, and none were found to have SOX2 mutations (70,71).

The dearth of families with more than 1 affected child and the lack of substantiated reports of transgenerational transmission argue against a hereditable cause for most cases of ONH. Fundus photographs from the only multigenerational report are not convincingly representative of ONH (72). There have been no reports of affected identical twins.

PRENATAL RISK FACTORS

Lack of definitive genetic associations has led to a search for prenatal environmental or biological risk factors for the development of ONH. Nearly all prenatal associations with ONH originate from retrospective review of records or anecdotal reports. The most commonly reported associations include young maternal age and/or primiparity (60,68,70,73,74), maternal use of recreational drugs (8 total cases) (13,45,60,75,76), anticonvulsants (9 total cases) (59,75,77), antidepressants (3 total cases) (20,73,78), and viral infections during pregnancy (4 total cases) (60,61,79). In small case series, ONH has been reported in 25%–48% of children with fetal alcohol syndrome (80,81), but in large series of near-consecutive cases of ONH, any prenatal alcohol exposure was reported in 6%–33%, and there were no reports of excessive prenatal alcohol consumption (82,83).

Two studies have systematically and sequentially investigated prenatal correlates in large cohorts of patients with ONH. The first was a case–control study of 100 severe bilateral cases in Sweden, and data were obtained from interviews conducted in the first trimester of pregnancy by a variety of midwives (73). Those data have the advantage of being relatively unbiased by recall or pregnancy outcomes but have the disadvantage of not capturing associations that may have occurred after the interview. That study found increased risk with young maternal age, primiparity, and early prenatal smoking exposure but not with drug or alcohol exposure.

The second study used a postnatal questionnaire and compared exposures with national registry data from pregnant women during the same period (83). This study confirmed that young maternal age and primiparity were independent risk factors but refuted an association with tobacco, alcohol, or drug exposure. In addition, it suggested prenatal maternal weight loss or poor weight gain and premature labor (without premature birth) as additional risk factors.

MANAGEMENT

Since ONH is particularly associated with abnormal hypothalamic function, physicians should be vigilant for signs of hypothalamic dysfunction along with any vision problems in children and vice versa. All neonates with jaundice and recurrent hypoglycemia should have ophthalmoscopic evaluation, especially if associated with temperature instability. Similarly, all infants with poor visual behavior, strabismus, or nystagmus by 3 months of age should have an ophthalmoscopic examination to rule out ONH.

Once ONH is confirmed ophthalmoscopically, MRI of the brain 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. Findings of schizencephaly or polymicrogyria should prompt neurologic examination in anticipation of focal deficits or seizures. In the past, MRI of the brain was used to identify absence of the septum pellucidum in order to determine the need for endocrinologic evaluation. This feature can now be disregarded, as all children with ONH regardless of the septum pellucidum status need pituitary function evaluated.

Endocrinologic workup should include fasting morning cortisol and glucose, thyroid-stimulating hormone, free T4, and the GH surrogates—insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP-3). If the child is less than 6 months of age, luteinizing hormone, follicle-stimulating hormone, and/or testosterone levels should be checked in order to anticipate delayed sexual development. Beyond 6 months of age, sex hormones are not normally produced until puberty, and thus cannot be tested. Micropenis, also a harbinger of delayed puberty, can be treated with testosterone during infancy.

Children should be monitored at least semi-annually for growth. With growth deceleration, thyroid function tests should be repeated and provocative GH testing should be performed. These should also be done if IGF-1 or IGFBP-3 is low, even if the child is growing normally. Free T4 should be rechecked at least semi-annually until 2 years of age and annually thereafter until at least 4 years of age.

If fasting morning cortisol is low, it should be repeated or provocative testing for cortisol should be done. This can often be done simultaneously with GH testing, using glucagon as the provocative agent. Children with inadequate cortisol response to provocative tests should be given both oral and injectable forms of glucocorticoids 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 dialogue into song can sometimes ameliorate delayed verbal communication.

Children with autistic behaviors should be evaluated by a neuropsychologist skilled in autism assessment as well as experienced in dealing with visually impaired children. Lacking such experience, the autism expert should enlist assistance from a teacher for the visually impaired to appropriately modify the testing instruments. 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 (56).

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. Children with unilateral or markedly asymmetric ONH should not be treated with patching.

Early surgical correction of strabismus should be reserved 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

ONH is an increasingly prevalent, probably nonhereditary, cause of congenital blindness that is the unifying feature of a syndrome that usually includes developmental, hypothalamic, and/or neuroanatomical abnormalities. The first recognized association was with absence of the septum pellucidum, yet it has now been shown that this is the least significant, and least prognostic, of the associated abnormalities. The presence of ONH imparts risk for serious systemic and neurologic problems that need to be carefully monitored. Focus on the septum pellucidum has distracted physicians from the serious and complicated nature of the syndrome. "Septo-optic dysplasia" and "de Morsier syndrome" are inappropriate and historically inaccurate terms that should be abandoned.

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