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Optic Nerve Hypoplasia Syndrome: A Review of the Epidemiology and Clinical Associations

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Opinion statement

Background: Optic nerve hypoplasia (ONH) has developed into a leading cause of congenital blindness. The frequently associated features of hypopituitarism and absent septum pellucidum were felt to have embryonic linkage as "septo-optic dysplasia" or "de Morsier's syndrome." More recent studies have suggested these associations are independent of one another. This review provides an assessment of the historical and recent evidence linking neuroradiologic, endocrinologic and developmental morbidity in patients with ONH. The prenatal risk factors, heritability, and genetic mutations associated with ONH are described. Results: Recognition of the critical association of ONH with hypopituitarism should be attributed to William Hoyt, not Georges de Morsier. De Morsier never described a case of ONH or recognized its association with hypopituitarism or missing septum pellucidum. Hypopituitarism is caused by hypothalamic dysfunction. This, and other more recently identified associations with ONH, such as developmental delay 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. The predominant prenatal risk factors for ONH are primiparity and young maternal age. Presumed risk factors such as prenatal exposure to drugs and alcohol are not supported by scrutiny of the literature. Heritability and identified gene mutations in cases of ONH are rare. Conclusion: Children with ONH require monitoring for many systemic, developmental, and even life-threatening problems independent of the severity of ONH and presence of brain malformations including abnormalities of the septum pellucidum. "Septo-optic dysplasia" and "de Morsier's syndrome" are historically inaccurate and clinically misleading terms.

Introduction

The birth defect known as optic nerve hypoplasia (ONH) has emerged as a leading cause of childhood blindness and visual impairment. ONH as a diagnosis has been misunderstood for decades owing to its association with "septo-optic dysplasia". Since the first description of ONH, research has made tremendous progress in understanding the clinical significance of ONH. It is now clear that ONH is a pervasive disease of child neurodevelopment associated with anatomic abnormalities and overall miswiring of the brain that results in visual impairment and profound systemic and functional morbidity. This review will summarize the state of knowledge on the epidemiology of ONH and its clinical associations with neuro-anatomical, hypothalamic and/or developmental abnormalities. A review of the historical literature that led to the incorrect linkage of ONH with de Morsier's "septo-optic dysplasia" is provided. The case will be made for abandonment of this term in favor of nomenclature that is inclusive of ONH and the spectrum of systemic involvement.

History

The first description and illustration of the optic disc appearance of ONH was by Schwarz in 1915 [1]. In 1941, David Reeves reported the youngest patient (4 months old) with agenesis of the septum pellucidum identified by air encephalogram that coincidentally was blind [2]. The diagnosis was described as "bilateral primary optic atrophy of undetermined origin, probably; however, on the basis of a congenital aplasia" and was deemed to be ONH.

ONH as a diagnosis has long been associated with "septo-optic dysplasia", albeit erroneously. A detailed history of the origin of this term has been previously described to clarify the inappropriate link between ONH and septo-optic dysplasia [3••]. Georges de Morsier described the absence of the septum pellucidum identified incidentally in a series of post-mortem brains. The report noted that one of the specimens was from a female patient with a unilateral vertically rotated optic tract that died of pyelonephritis at 84 years of age without a history of vision problems. This single case led to the term "la dysplasia septo-optique" (septo-optic dysplasia) [4]. In the same report, de Morsier also described a living 44 year-old alcoholic male patient with enlargement of the blind spot on visual field testing that was incidentally noted to have an absent septum pellucidum on air encephalogram. From a literature review, these two cases were supplemented with 34 other documented cases (11 autopsy cases and 23 radiographic cases) of agenesis of the septum pellucidum. Eight of the additional cases had an eye or optic nerve problem: one with bilateral anophthalmia; three with bilateral optic atrophy; and three with unilateral optic atrophy. Of the cases cited by de Morsier, the only case with definite ONH was that previously described by Reeves [2]. It was from this compilation of disparate cases that an association of eye problems with agenesis of the septum pellucidum (i.e. septo-optic dysplasia) originated. There is no evidence that de Morsier ever described a case of ONH or intended for "septo-optic dysplasia" to apply to ONH exclusive of other ocular problems. Nevertheless, subsequent reports credited de Morsier with the association of absence of the septum pellucidum and ONH.

Subsequently, Gross and Hoff [5] reported autopsy findings from 465 brains from severely neurologically impaired patients. Thirteen brains were missing the septum pellucidum, of which, one had bilateral ONH, and seven had optic atrophy. Twelve brains exhibited partial or complete agenesis of the corpus callosum and coexistent microphthalmous with atrophy in two cases and unilateral ONH in one case.

In 1970, Hoyt et al. published a case series report of nine patients with ONH and pituitary dwarfism, four of whom were missing the septum pellucidum [6]. This landmark article on the association of ONH with hypopituitarism generously, but erroneously, attributed recognition of the association of ONH with agenesis of the septum pellucidum to de Morsier. The resurrected term "septo-optic dysplasia" was also referred to as de Morsier Syndrome. Prospective cohort research has demonstrated that agenesis of the septum pellucidum is independent of hypopituitarism, and that hypopituitarism may be the major manifestation of hypothalamic dysfunction [7, 8, 9•].

Prevalence

ONH is recognized as a common cause of congenital blindness. In 1997, bilateral ONH surpassed retinopathy

of prematurity as the single leading cause of infant blindness in Sweden [10]. Only cortical visual impairment from multiple causes was more prevalent 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 [11]. In 2006, a report from England described the prevalence of ONH as 10.9 per 100,000 children [12].

The prevalence of ONH in North America is unknown. Prior to 1962, only one 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 [13]. ONH was identified in 12 % of blind infants in Harris County in Texas in the early 1980s [14]. ONH accounted for 5.7 % to 12.9 % students from schools for the blind in the United States in 1999 [15, 16]. Such surveys underestimate the actual prevalence, because cognitive or behavioral impairments preclude most children with ONH from attending 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 and the most likely to cause legal blindness in children age three years or younger in the United States [17].

Etiologic correlates

Maternal factors

The most prominent and consistently reported prenatal features of ONH are young maternal age and primiparity [18–22]. Many reports speculate that the association of young maternal age reflects an increased risk of unhealthy behavior and poor preconceptual health. Generally based on anecdotal reports, there is underwhelming evidence for this hypothesis owing to a dearth of findings of risky behavior in cohort studies employing standardized methods. Maternal age and primiparity may be surrogate factors for multiple underlying health and demographic factors that drive prenatal risk for ONH but are unexplored as of yet. Of interest is the finding of a high prevalence of prenatal maternal weight loss or poor weight gain, and premature labor (without premature birth) in a cohort study of near-consecutive cases of ONH [23••]. The former suggests a potential role for prenatal weight and nutrition in the occurrence of ONH. This hypothesis is supported by a report on the geographic clustering of cases of ONH with population factors of deprivation [12].

Prenatal exposures

ONH has long been linked to recreational (e.g., LSD) or prescription (e.g., anticonvulsants, quinine, antidepressants) drugs [12, 18, 21, 24–30], viral infection [18, 31, 32], maternal diabetes [33], and alcohol use [34, 35] during pregnancy. Nearly all of these suggested etiologic correlates arose primarily from isolated exposures or case reports, providing the lowest level of evidence. In two small case series reports of fetal alcohol syndrome (FAS), ONH was reported in 25 – 48 % [34, 35]. The generalizability of these findings is undermined by the highly selective patient inclusion. If ONH is frequently caused by alcohol exposure, then the prevalence of ONH should far exceed the current prevalence estimate of 10.9 per 100,000. Moreover, the suggested risk conferred by excessive alcohol use during pregnancy is refuted by an absence of exposures in a population study [21] and a cohort study of near-consecutive cases of ONH [23••].

Two studies have systematically and sequentially investigated prenatal correlates in large cohorts of patients with ONH. The first was a population-based case–control study of 100 severe bilateral cases in Sweden in which data were obtained from interviews within the first trimester of pregnancy [21]. These data have the advantage of being relatively unbiased by recall or pregnancy outcomes, but the disadvantage of not capturing associations that may have occurred after the interview. The analysis found increased risk with young maternal age, primiparity, and early prenatal smoking exposure, but not with drug or alcohol exposure.

The second was a cohort study in which maternal data, systematically gathered by a post-natal questionnaire, were compared with national birth data from pregnant women during the same period of time [23••]. Although this methodology can have recall bias, the study confirmed that young maternal age and primiparity were independent risk factors. Commonly implicated exposures (e.g., tobacco, alcohol, drug, viral infection) were uncommon in this cohort and discounted these factors as unlikely to be major contributors of ONH.

Genetic factors

Numerous genes have been ascribed pathogenic linkage to ONH because of the phenotypic overlap of

the associated neuro-anatomical abnormalities of ONH with isolated abnormalities of the forebrain and/or hypothalamic-pituitary axis [36–41]. This has led to an investigative focus on the genetic mechanisms involved in division of the prosencephalon into cerebral hemispheres and formation of the pituitary gland. From murine model research, several candidate genes have been identified as potential genetic correlates of "septo-otpic dysplasia" [36–41]. The ocular abnormalities in these rarely survivable murine mutant phenotypes are distinct from ONH, including anophthalmous, microphthalmous and retinal dystrophy due to disturbed development of the optic vesicle and optic cup. The majority of translational research endeavors have involved human cases described as having "septo-optic dysplasia" with or without ONH in the phenotype. Nearly all of the identified mutations were detected in cases of isolated hypopituitarism and/or midline malformations without ONH. A thorough review of the genetic research literature on ONH uncovered four cases of suspected ONH (by MRI only) with gene mutations. These include mutations of HESX1 in two cases [42, 43], OTX2 in one case [44], and PROKR2 in one case [45]. Genetic mutations in cases of ONH are rare, and a specific genotype/phenotype linkage has yet to be found to explain the majority of cases [19, 46].

The paucity of families with more than one affected child and the lack of substantiated reports of trans-generational transmission argue against a hereditable cause for cases of ONH. Five reports of ONH in multiple family members exist in the literature, including one of monozygotic twins with mild unilateral ONH in opposite eyes and no other noted clinical abnormalities [47–51]. Fundus photographs from the only transgenerational report are not convincingly representative of ONH [49].

A lack of definitive genetic associations has led to a search for prenatal environmental or biological contributors. However, the etiology of ONH is likely multifactorial involving a gene-environment interaction, whereby gene variants modify susceptibility to a toxic or beneficial product that influences the biologic response. Attributing ONH to a single genetic mutation is unwise, but it remains possible. The pathogenesis of ONH more likely reflects a combination of factors that disrupt the temporally and spatially dependent cascade of genes required for early neuronal genesis during a gestational window of heightened vulnerability.

Clinical diagnosis

Diagnosis of ONH requires ophthalmoscopic confirmation of a small optic disc. In young children, the optimal method for diagnosing ONH is with direct ophthalmoscopy. Use of this method in blind children is eased by their minimal objection to the light or the proximity of the examiner, as long as the examiner does not touch the child's face. Diagnosis of ONH may be difficult with binocular indirect ophthalmoscopy due to limited magnification. Small pale optic discs may also make distinguishing the surrounding hypopigmented scleral canal difficult, contributing to misdiagnosis as normal sized discs with optic atrophy.

Establishing the diagnosis of ONH is facilitated by several funduscopic findings. The most important is an assessment of the area of the disc relative to the size of the overlying central retinal vessels. Another characteristic is tortuous retinal arterioles, venules, or both, that commonly accompany ONH (Fig. 1a). However, uncommonly straight vessels with decreased branching may also be present (Fig. 1b). Nonbranching vascular patterns have been recognized in children with primary growth hormone (GH) deficiency, although it is not known if these vascular patterns in ONH correlate with endocrine dysfunction [52].

Finally, a ring of hypo- or hyperpigmentation often surrounds the disc defining the area of the putative scleral canal in patients with ONH (Fig. 1a). Such a finding is presumed to reflect 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 rim of the hypoplastic optic disc [53]. This "double ring" sign, however, does not define ONH, as a similar appearance may be present in other conditions such as myopia.

ONH may be confirmed with measurements of the optic disc from fundus photographs using the relative distance of the disc diameter or area to various retinal landmarks. One method is the ratio of the horizontal disc diameter (DD) to the distance between the macular and the temporal edge of the disc (DM). The DD/DM ratio of optic nerves with normal vision is estimated to be greater than 0.35 [7, 54, 55]. DD/DM ratios less than 0.35 correlate, albeit imperfectly, with vision

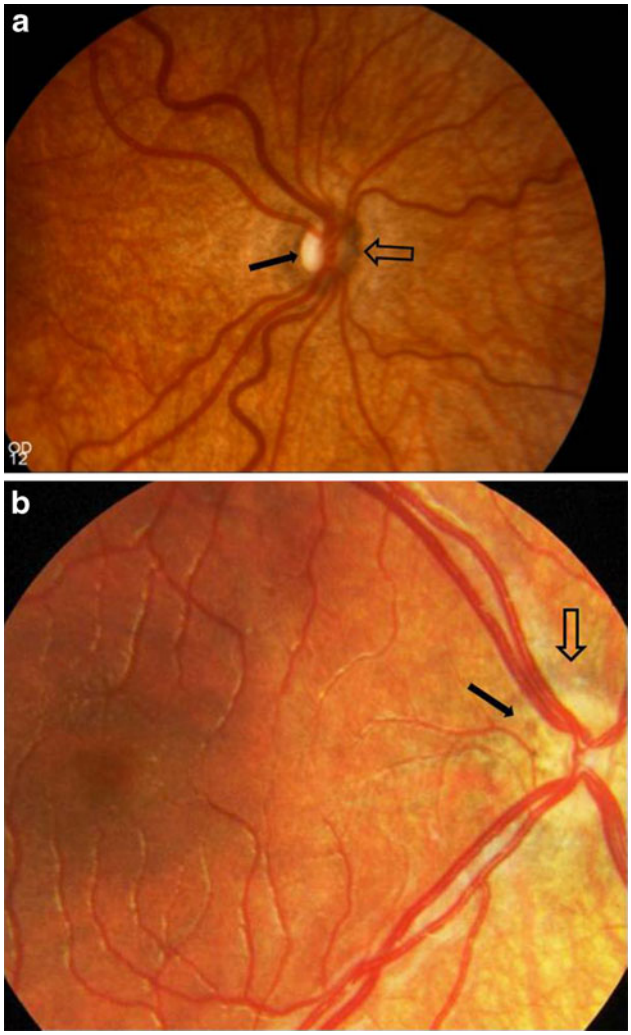

Figure 1. a) Photograph of ONH (filled arrow) with a pigmented double ring (unfilled arrow) and tortuous vessels. **b**) Photograph of ONH (filled arrow) with a hypopigmented double ring (unfilled arrow), which may be confused with optic atrophy, and straight vessels.

outcomes [56]. Most patients with DD/DM ratios less than 0.35 have generally been described as having ONH, although normal vision occurs in some with DD/DM ratios of 0.30 to 0.35. The overlap in optic disc size between normal and ONH is not surprising but the risk for systemic complications in these borderline cases is unknown.

Some physicians broadly define ONH to include any optic disc with a congenitally decreased neuronal area [57]. Such findings of normal sized optic discs and enlarged cups typically occur in premature infants with periventricular leukomalacia [58]. With fewer axons than normal, these optic nerves may be technically hypoplastic. However, these children are not at risk for the same developmental and endocrinological complications as children with small discs typical of ONH. These cases should, therefore, not be considered in the same diagnostic category. A similar argument can be made for eyes with major congenital ocular malformations such as microphthalmous, large colobomas, or persistent hyperplastic primary vitreous which may consequently have small optic nerves.

Clinical associations

Visual impairment

Visual impairment is the central feature of ONH. In fact, the first sign of ONH is typically poor visual behavior noted by parents or clinicians. Nystagmus usually develops at 1 to 3 months of age followed by strabismus, typically esotropia. Approximately 80 % of children with ONH are bilaterally affected with two-thirds asymmetrically affected [23••]. Bilateral cases with symmetric hypoplasia may have asymmetric vision from superimposed amblyopia due to strabismus or anisometropia.

Patients with unilateral ONH, usually diagnosed at a later age than bilateral cases, present primarily with strabismus rather than nystagmus. 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) [7, 23••].

Visual acuity ranges from no light perception to near normal. More than 80 % of bilateral cases are legally blind [29]. Most children experience some improvement in their vision in the first few years of life [59]. This may be due to improvement in superimposed cortical vision impairment, or due to optic nerve myelination that occurs in the first 4 years of life leading to improved axonal conduction [60]. Recent research findings by Fink et al. suggest that the improvement in vision in ONH may also be related to thyroid status. In this study, vision improvement by age 5 years was less common in patients

with low thyroid levels, and in those with low newborn levels of thyroid stimulating hormone (TSH) [59].

Neuroradiographic abnormalities

Following the resurrection of "septo-optic dysplasia" by Hoyt and colleagues, absence of the septum pellucidum became associated with pituitary dysfunction in research reports hampered by ascertainment bias [24, 61]. Many studies challenged the association by reporting no adverse outcomes in those with agenesis of the septum pellucidum [62–64]. These findings confirmed the observations in de Morsier's report that most cases of agenesis of the septum pellucidum are incidentally detected and are independent of optic nerve or hormone problems. The prevalence of agenesis of the septum pellucidum in the general population is unknown. In the only prospective study of ONH, an absent septum pellucidum was not associated with laterality of ONH, vision status, endocrinopathy, or developmental delay [7, 23••].

Septo-optic dysplasia as a diagnosis has evolved to include midline brain abnormalities such as corpus callosum hypoplasia or pituitary abnormalities. The expanded definition has led many researchers to postulate morphogenetic mechanisms involving prosencephalic cleavage [19, 38, 65]. This disregards the fact that a small corpus callosum frequently denotes hemispheric disease. Most neuroradiographic abnormalities associated with ONH are not midline and include hydrocephalus, white matter hypoplasia, cortical heterotopia, pachygyria, polymicrogyria, schizencephaly and arachnoid cysts [7, 23••]. Rather than reassess the appropriateness of the term "septo-optic dysplasia", the diagnosis has been expanded to represent a spectrum disease for which the additional neuroanatomical pathology suggests a more severe expression of ONH [19, 38, 65, 66]. The validity of this is challenged by prospective research findings of systemic and functional morbidity in the majority of cases of ONH, even in the absence of neuroradiographic abnormalities.

Abnormalities of the corpus callosum are common neuroradiographic findings in children with ONH (Fig. 2a) and may include hypoplasia and partial or complete agenesis of the corpus callosum. Corpus callosum hypoplasia is the most prevalent [7, 8, 56].

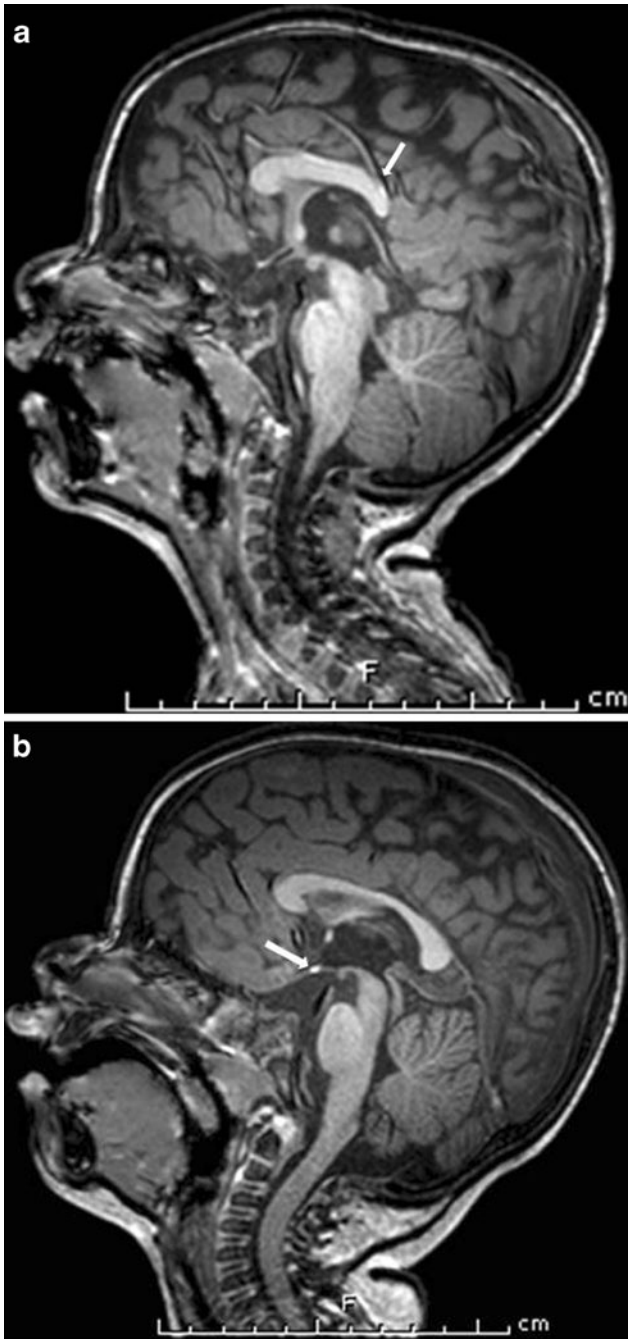

Figure 2. a) ONH is commonly associated with a hypoplastic or absent corpus callosum. In this case, the splenium is hypoplastic. **b**) Abnormalities of the pituitary gland include an ectopic posterior pituitary bright spot.

While corpus callosum hypoplasia is commonly associated with absence of the septum pellucidum, the latter cannot serve as a proxy for corpus callosum hypoplasia as partial agenesis of the corpus callosum may occur regardless of the septum pellucidum status. Corpus callosum hypoplasia has been associated with developmental delay, but not with hypopituitarism in children with ONH [8].

The population prevalence of corpus callosum hypoplasia is estimated to be 1.8-2.1/10,000 live births and affects 2.3 % of developmentally disabled individuals [67, 68]. Among patients with corpus callosum hypoplasia, nearly half have other central nervous system abnormalities including non-midline defects also associated with ONH (cortical heterotopias, schizencephaly, white matter hypoplasia, polymicrogyria) [67]. However, ONH occurs in less than 10 % of children with corpus callosum hypoplasia [68]. Pituitary dysfunction, a common finding in children with ONH, is uncommon in children with corpus callosum hypoplasia and no ONH [69].

Neuroradiographic abnormalities of the pituitary gland may include an empty sella, ectopic posterior pituitary and non-visualized infundibulum and posterior pituitary. Such findings occur in 13 – 34 % of children with ONH (Fig. 2b), which is highly predictive of hypopituitarism [23••, 70]. However, an intact pituitary gland on neuroimaging does not preclude hypopituitarism as the majority of children with ONH and hypopituitarism do not have visible pituitary abnormalities [7]. Absence of the posterior pituitary bright signal on T1 MRI has been associated with abnormal anterior pituitary function [70], but not diabetes insipidus (from posterior pituitary dysfunction), as would be expected if vasopressin granules are the cause of the bright signal [71].

Optic nerve

The potential utility of neuroradiographic measurement of the optic nerve or chiasm to diagnose ONH has been promising [72, 73]. Research studies have been retrospective, lacked a control group of normal and atrophic optic nerves or failed to adjust for age in young patients. As technology improves, it seems likely that high-resolution MRI could be used to distinguish ONH and optic atrophy. To this end, assessment of the intracranial portion of the optic nerves may be more reliable for detecting ONH than assessment of the orbital component [74].

Hypothalamic dysfunction

Hypothalamic dysfunction is the most common non-visual source of morbidity in children with ONH. The resulting disruption in homeostatic mechanisms impacts pituitary gland function, temperature regulation, and behavior involving hunger, thirst and sleep.

Endocrinopathy

Endocrinopathy affects the majority of children with ONH regardless of laterality of ONH or neuroradiographic abnormalities of the septum pellucidum or corpus callosum [7, 8]. Hormonal abnormalities are believed to be due to hypothalamic dysfunction rather than pituitary dysgenesis in the majority of cases. Prospective research identified hypopituitarism in 75 % of children with ONH, a finding that is consistent with previous retrospective studies [75, 76]. Growth hormone (GH) deficiency was the most common deficiency (70 %), followed by hypothyroidism (43 %), adrenocorticotropic hormone (ACTH) deficiency (27 %), and diabetes insipidus (5 %). Pubertal development may be delayed or early, although the incidence in this population is unknown. Evolving pituitary dysfunction has been documented but is poorly understood in children with ONH [75, 77].

The presence of central hypothyroidism has been associated with low newborn screening (NBS) levels of TSH in children with ONH. In the same study, central hypothyroidism and low NBS TSH levels were correlated with low vision status at age 5 years [59]. The impact of early detection and treatment of hypothyroidism on neurologic and vision outcome in children with ONH is unknown.

Hypopituitarism in children with ONH is often accompanied by elevated serum prolactin levels, a hormone normally suppressed by the hypothalamus. Mild hyperprolactinemia, a marker of underlying hypothalamic dysfunction [78], affects over half of children with ONH [7, 8, 79]. In a prospective study of children with ONH, the presence of hyperprolactinemia in subjects less than 3 years of age

correlated with hypopituitarism and, in particular, growth hormone (GH) deficiency at age five years. Hyperprolactinemia may persist in up to one-third of affected cases of ONH, which increases the likelihood of hypopituitarism and GH deficiency [9•].

Other hypothalamic morbidity

Body temperature regulation, linked to the medial preoptic region of the hypothalamus [79], is commonly affected in children with ONH. This often results in hospitalization to rule out sepsis [28].

Hyperphagia with obesity or hypophagia (with or without wasting) affect many children with ONH, and may be accompanied by an aversion to certain textures of food. This is likely related to dysfunction of the hypothalamic ventromedial nuclei, which stimulate hunger in response to leptin, and the lateral nuclei, which stimulate feeding behavior and regulate metabolism [80]. Children may also exhibit water-seeking behavior (and consequent enuresis), which may be mistaken as diabetes insipidus.

Abnormal sleep/wake cycles are frequently reported in children with ONH [81, 82]. The biological clock, generated in the anterior hypothalamus, receives photic information via the optic nerves to synchronize a 24-hour light–dark cycle. Each day, the circadian pacemaker is reset with visual stimulation [83–85]. Regulation is also dependent on adequate retinohypothalamic input. It is therefore not surprising that children with ONH may experience disturbances in the sleep/wake cycle. A disrupted circadian system introduces an additional risk to physiologic and behavioral morbidity in this population [86, 87]. Such disturbances run asynchronous with other family members and present a major source of family stress. In both scenarios, sleep irregularities often lead to behavioral difficulties and disruption of family life.

Neuropsychological outcomes

Developmental delay

In 1984, Margalith et al. described developmental delays in a population based study of ONH [18]. Neuropsychological handicaps were described in nearly three-fourths of cases of ONH. Subsequent findings confirmed the high prevalence [31], including findings from a prospective study [8]. Developmental delay ranges from isolated focal defects to global delay [88, 89]. Using a standardized neuropsychological instrument and longitudinal follow-up until 5 years of age, developmental delays were identified in 71 % of children with ONH. The most common delay was in motor skills (75 %) while communication delays constituted the least common (44 %). Independent risk factors for delayed overall development and cognition included corpus callosum hypoplasia and hypothyroidism, but not absence of the septum pellucidum. Developmental delay occurred in unilateral (39 %) and bilateral (78 %) cases of ONH [8].

Autism spectrum disorder

Autism spectrum disorders are highly prevalent in the visually impaired population, with prevalence estimates up to 25 % [90]. Observational research suggests that the prevalence of autism is higher in children with ONH. In a case series report of thirteen children with ONH and blindness, investigators described autism in six and "autistic-like" conditions in three [91]. Parr et al. reported that, in a sample of 83 children with ONH and moderate to severe vision impairment, 37 % displayed social, communicative and repetitive or restricted behavioral difficulties and the majority of those had a clinical diagnosis of autism spectrum disorder [92]. A precise prevalence estimate of autism in visually impaired patients (including ONH) is difficult without appropriate and validated modifications to autism diagnostic instruments. In 2011, Fink and Borchert published pilot data from a validation study of a modified version of the Social Responsiveness Scale. In a sample of 46 patients with ONH greater than age 5 years, the modified instrument identified 46 % with deficits in reciprocal social behavioral [93].

Clinical management

ONH rarely occurs in isolation [8], and thus physicians should be aware of the risk for medical and developmental complications in this population. An ophthalmoscopic exam is warranted in all neonates with jaundice and recurrent hypoglycemia, especially if associated with temperature instability. All infants with poor visual behavior, strabismus, or nystagmus by 3 months of age should have an ophthalmoscopic examination to rule out ONH.

The vision status of children with ONH should be monitored at least annually, and any refractive errors should be treated when the visual acuity rea-

ches a functional level. Amblyopia therapy should be reserved for those cases in which the potential vision in each eye is felt to be fairly good. If the ONH is asymmetric, maintenance of improved vision would require prolonged patching which can further threaten development in a child with many other handicaps. Thus, children with unilateral or markedly asymmetric ONH should not be treated with patching. Additionally, surgical correction of strabismus should be reserved for patients with symmetrical functional vision in both eyes, and thus some potential for binocularity. Otherwise, surgery should be postponed until the strabismus is an impending psychosocial issue.

A MRI of the brain is necessary to rule out treatable conditions such as hydrocephalus. The MRI can also be used to anticipate developmental delay in those with corpus callosum hypoplasia or other major malformations. Findings of schizencephaly or polymicrogyria should prompt neurologic examination for risk of focal deficits or seizures. MRI identification of absence of the septum pellucidum confers no prognostic value. This feature can be disregarded, as all children with ONH require evaluation of pituitary function regardless of the presence or absence of the septum pellucidum.

Endocrinologic labs should include fasting morning cortisol and glucose, TSH, free T4, and the growth hormone surrogates - insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP-3). In patients less than 6 months of age, labs should include leuteinizing hormone, follicle-stimulating hormone, and/or testosterone levels to assess risk of delayed sexual development. Sex hormones are not normally produced beyond 6 months of age, and thus cannot be tested until puberty. Micropenis, a hallmark for delayed puberty, can be treated with testosterone during infancy.

Normal pituitary function at the time of initial evaluation does not preclude development of endocrinopathy in the future in children with ONH. Free T4 should be reassessed at least semi-annually until two years of age and annually thereafter until at least four years of age. Length or height should be monitored at least semi-annually. In patients with growth deceleration, thyroid function should be reassessed and provocative GH testing should be performed. Children with ONH may grow normally in spite of subnormal GH. Therefore, provocative GH testing should also be done if IGF-1 or IGFBP-3 is low.

Children with a low fasting morning cortisol should undergo a repeat cortisol measurement, or provocative testing for cortisol. This can often be done simultaneously with GH testing, using glucagon as the provocative agent. Children with inadequate cortisol levels require either daily oral glucocorticoids for maintenance or oral and injectable administration of glucocorticoids during illness or physical stress.

Physical, occupational and/or speech therapy are necessary in most children with ONH. Referral for early intervention is critical to address the developmental deficits associated with ONH. Therapists should give attention to early development of oral motor skills to overcome aversion to certain textures of food. Children exhibiting autistic behaviors should be evaluated by a neuropsychologist with expertise in autism assessment as well as assessment of visually impaired children. In the absence of such skills, the neuropsychologist should consult a teacher for the visually impaired to modify the assessment tool(s). Delayed verbal communication is often improved by incorporation of dialogue into song.

Children with disturbed sleep cycles can be treated with low doses (0.1 – 0.5 mg) of melatonin in the evening or, alternatively, with soporific doses (3–5 mg) at bedtimes [81]. This may facilitate entraining the circadian clock.

Conclusions

Optic nerve hypoplasia is the unifying feature of a syndrome that includes a combination of developmental, hypothalamic and/or neuro-anatomical abnormalities. Etiology of this apparently epidemic cause of blindness remains incomplete, with the only predominate risk factors being young maternal age and primiparity. Genetic causes are rare. Absence of the septum pellucidum, historically ascribed clinical significance, confers no prognostic value of the associated clinical abnormalities. The status of the septum pellucidum has historically misled physicians in the clinical management of children with ONH. It is the presence of ONH that signifies the need for careful, ongoing monitoring to anticipate the systemic and neurologic morbidity that affects this population. The terms “septo-optic dysplasia” and “de Morsier’s syndrome” are historically inaccurate and inappropriate for this condition.

Disclosure

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

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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This review article provides a critical discussion on the history and evolution of the term "septo-optic dysplasia" relative to optic nerve hypoplasia.

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