HORMONE
RESEARCH IN
PÆDIATRICS

Brain Malformations Do Not Predict Hypopituitarism in Young Children with Optic Nerve Hypoplasia

Pamela Garcia-Filion[a]   Hashem Almarzouki[e]   Cassandra Fink[a, c]
Mitchell Geffner[c, d]   Marvin Nelson[b, d]   Mark Borchert[a, d]

[a]The Vision Center, Children's Hospital Los Angeles, Los Angeles, CA, USA; [b]Department of Radiology, Children's Hospital Los Angeles, Los Angeles, CA, USA; [c]Department of Endocrinology, Diabetes, and Metabolism, Children's Hospital Los Angeles, Los Angeles, CA, USA; [d]The Saban Research Institute, Children's Hospital Los Angeles, Los Angeles, CA, USA; [e]Department of Ophthalmology, King Saud bin Abdulaziz University for Health Sciences, Jeddah, Kingdom of Saudi Arabia

Abstract

Background: Optic nerve hypoplasia (ONH), a leading cause of pediatric blindness, is associated with brain malformations and hypopituitarism in the constellation known as septo-optic dysplasia. Neuroimaging is used to anticipate hypopituitarism, but with unconfirmed reliability. We report prospective findings on the association of hypopituitarism with brain malformations. ***Methods:*** Children (<24 months) with ONH ($n = 146$; 87% bilateral) underwent baseline MRI and annual examinations and hormonal testing. Hypopituitarism status at age 5 years was classified. ***Results:*** A total of 74% had brain malformation(s). Hypopituitarism (69%) was not associated with brain malformations ($p = 0.351$); this persisted after adjusting for the laterality of ONH and the timing of MRI ($p_{adj} = 0.869$). No association was noted for absent septum pellucidum (38%; $p = 0.073$), corpus callosum abnormality (51%; $p = 0.625$), and major malformations (22%; $p = 0.407$). A malformation conferred a positive predictive value of 71% (95% CI: 62%, 80%), and a negative predictive value of 37% (95% CI: 22%, 54%). Overall, 10% ($n = 15$) of the cohort presented with a triad of absent septum pellucidum, corpus callosum abnormality, and other major malformation; only half ($n = 8$) of these had hypopituitarism. All 13 subjects with pituitary malformations manifested hypopituitarism, conferring predictive values of 100% (positive) and 34% (negative). ***Conclusions:*** Hypopituitarism and brain malformations are highly prevalent, but have unrelated associations with ONH. Brain MRI in infants and toddlers with ONH is an unreliable screen for hypopituitarism risk.

© 2017 S. Karger AG, Basel

Introduction

Optic nerve hypoplasia (ONH), a congenital cause of visual impairment, is recognized as a spectrum disease of the central nervous system that manifests with brain malformations, neurological deficits, and endocrinopathy [1]. Over the past 40 years, the population prevalence has increased 9-fold, affecting as many as 17.3 per 100,000 children younger than 18 years of age [2].

Mark Borchert, MD
Children's Hospital Los Angeles, The Vision Center
4650 Sunset Blvd., MS #88
Los Angeles, CA 90027 (USA)
E-Mail mborchert @ chla.usc.edu

The phenotypical heterogeneity of ONH has led to diagnostic terms that center on the presence of brain malformations with a purported association for disparate outcomes [3–14]. Septo-optic dysplasia (SOD), the most prevalent term, originated from a 1956 postmortem case report of an asymptomatic patient with an absent septum pellucidum ("septo-+") and a unilaterally rotated optic tract ("-optic") [15]. In 1970, Hoyt et al. [16] first described the association between ONH and hypopituitarism, using the term SOD to ascribe clinical significance to the absent septum pellucidum. This report triggered research in risk associations of brain malformations with hypopituitarism under the assumption that midline brain and pituitary malformations share common embryogenesis [8, 10–13, 16–18]. As reports emerged [4, 10, 11, 13, 14, 19–22], the definition of SOD expanded to encompass ONH and any malformation in the midline (involving the septum pellucidum, corpus callosum, or pituitary gland), nonmidline (holoprosencephaly, schizencephaly, hydrocephalus, etc.), and/or hypopituitarism. The association of hypopituitarism with brain malformations remains a topic of debate.

Despite improvements in neuroimaging techniques, there has been little progress in understanding the likelihood and clinical significance of brain malformations in ONH, or their association with hypopituitarism risk. There has been wide variability in the prevalence estimates of both brain malformations (26–90%) and hypopituitarism (10–100%) [3, 6–12, 22–33], making association rates difficult to estimate. As some pituitary hormone deficiencies develop over time [34], association rates may be underestimated in cross-sectional studies of children done at a young age. Further, the differences between selective versus broad inclusion criteria, imaging modality, and ad hoc versus systematic testing of hypopituitarism complicate the reconciliation between studies and generalization to children with ONH. These inconsistencies have resulted in variability in recommendations for the clinical management of these children [9, 11, 12, 17, 22, 25–28, 30, 31]. This is particularly problematic in young children, for whom the risk of undiagnosed pituitary dysfunction confers serious developmental or even life-threatening consequences.

We sought to fill this gap by leveraging an observational registry of infants and toddlers diagnosed with ONH who underwent annual clinical visits until the age of 5 years. Toward this end, we analyzed our prospective data to determine the prevalence and association of brain malformations at baseline with hypopituitarism at age 5 years.

Materials and Methods

Participants
Since 1992, the Children's Hospital Los Angeles is the site of a multidisciplinary observational registry on ONH to centralize systematically collected data about the disease status at the time of presentation (baseline) and annually until the age of 5 years. Children with suspected ONH are referred from a broad range of sources, including pediatricians, endocrinologists, neurologists, and vision specialists [29]. Participation in the registry requires a presentation prior to age 24 months and diagnosis of ONH confirmed by ophthalmoscopy (M.B.). Methodology for the diagnosis of ONH, clinical protocols, and the standardized data collection have been extensively published [29].

The evaluation of pituitary function includes comprehensive endocrine testing at baseline (TSH, free T4, fasting AM cortisol, growth hormone [GH] surrogates [IGF-1 and IGFBP-3], LH, FSH and/or testosterone in infants <6 months of age, and prolactin) and additional test results from the treating endocrinologist of the subjects. Since 2002, all subjects without known hormonal problems had annual repeat free T4, morning cortisol, and at least 1 provocative GH test over the course of the observation period. Auxological data are collected annually to monitor normal growth trajectory.

Consistent with previously reported definitions [29], a pediatric endocrinologist (M.G.) ascertained the subjects' pituitary function based on clinical evaluation, laboratory levels, and growth parameters [35–37]. More specifically, a subject was classified as having a hormone deficiency if he/she were being treated with hormone replacement for GH, levothyroxine, hydrocortisone, and/or desmopressin (at the time of enrollment), had subnormal laboratory hormone levels for free T4, or had subnormal stimulated peak serum GH or cortisol level after glucagon provocation. The criteria for GH deficiency were defined as being treated with GH replacement at the time of enrollment as a consequence of neonatal panhypopituitarism, a stimulated peak serum GH level (<10 ng/mL after glucagon), or height deceleration in the presence of subnormal levels of GH surrogates. Diabetes insipidus (DI) was diagnosed on the basis of failure to concentrate urine in the face of clinical hypernatremia or with water deprivation testing.

Participants underwent baseline neuroradiology examination of the brain, if this had not already been performed (noncontrast MRI with either 1.5 or 3 T has been used exclusively since 2002). These all included T1 and T2 axial scans and T1 sagittal scans of the brain. Specific scans with pituitary imaging protocols were not routinely obtained. Of the 255 registry subjects enrolled as of May 2014, those that reached the age of 5 years by the time of this study with baseline MRI were included.

The Institutional Review Board at the Children's Hospital Los Angeles approved the registry, and informed consent was obtained from a parent or guardian of all patients.

Malformations on MRI
A neuroradiologist (M.N.), who was masked to the subjects' clinical characteristics and to the original MRI interpretation, reviewed the MRIs of the brain. The images were specifically reviewed for the presence of malformations involving the septum pellucidum, corpus callosum, pituitary gland, and/or other parts of the brain (major and minor). A corpus callosum abnormality was ascertained as either corpus callosum hypoplasia or agenesis.

Garcia-Filion/Almarzouki/Fink/Geffner/
Nelson/Borchert

Pituitary gland malformations were subdivided into absent adeno-hypophysis and ectopic neurohypophysis. The absence of the neurohypophysis (posterior pituitary bright spot) constituted an abnormality only if the infundibulum was also absent. Other major malformations that were recorded included cortical heterotopia, schizencephaly, gyral malformations, cerebellar hypoplasia, white matter hypoplasia, ventriculomegaly, hydrocephalus, and hypothalamic dysgenesis. Minor (or incidental) findings were also documented.

Statistical Analysis

Descriptive statistics summarize the clinical characteristics of the registry cohort. Frequency (%) distributions of categorical data were compared between groups by χ^2 (or Fisher exact) test. Between-group differences of continuous data, expressed as median values (with interquartile range) regardless of distribution, were assessed using the Student t test or nonparametric analog in the absence of normal distribution. The relative risk (RR) for brain malformations or hypopituitarism between groups was computed by binomial log-linear regression [38]. The RR estimates were adjusted for laterality of ONH and the timing of MRI (prior to or after registry enrollment). The probability that a brain malformation can accurately predict and/or detect hypopituitarism was also estimated (sensitivity, prediction positive, prediction negative). The statistical estimates are presented with the corresponding 95% confidence intervals (95% CI). Statistical significance was defined as an alpha of 0.05, using 2-sided alternative hypotheses. Data were analyzed using Stata SE 11.0 (College Station, TX, USA).

Results

During the study period, 178 participants were eligible (i.e., at the age of 5 years); 32 were excluded due to CT imaging only, which left a study cohort of 146 participants (49% male) with MRI findings. The median age at the time of MRI was 8.3 months (interquartile range 5.3–16.3), and 63% ($n = 92$) had MRI before enrolling in the registry. A total of 74% ($n = 108$) of subjects had a brain malformation. The prevalence was similar regardless of the timing of MRI (before vs. after enrollment) ($p = 0.650$).

Table 1 lists the various brain malformation findings stratified on laterality of ONH (13% unilateral). Compared to those with bilateral ONH, subjects with unilateral ONH were 61% less likely to have a brain malformation (95% CI: 0.37, 0.98). Individually, an absent septum pellucidum was equally prevalent between laterality groups ($p = 0.516$).

Hypopituitarism by the age of 5 years manifested in 69% of the cohort ($n = 101$); of these, deficiency was isolated to GH in 33 subjects. A brain malformation did not correlate with having hypopituitarism ($p = 0.351$). The lack of association persisted after adjusting for laterality

Table 1. Characteristics of the patient cohort ($n = 146$)

	n	%
Gender		
Male	72	49
Age at consent, months[a]	8.3 (5.3–16.3)	
Laterality		
Unilateral	19	13
Hypopituitarism[b]	101	69
Growth hormone deficiency[c]	99	68
Hypothyroidism	64	44
Cortisol deficiency	44	31
Diabetes insipidus	15	11
Age at MRI, months[a]	12.4 (7.5–19.8)	
Brain malformation	108	74
Absent septum pellucidum	56	38
Corpus callosum abnormality[d]	75	51
Pituitary gland malformation[e]	13	9
Absent pituitary gland	1	1
Ectopic neurohypophysis	9	6
Absent neurohypophysis[f]	5	4
Major malformation[b]	32	22
Cortical heterotopia	10	7
Ventriculomegaly	7	5
White matter hypoplasia	7	5
Schizencephaly	6	4
Gyral abnormality	5	3
Cerebellar hypoplasia	4	3
Hydrocephalus[g]	3	2
Hypothalamic dysgenesis	1	1

[a] Data are presented as the median (interquartile range). [b] Frequency counts are not mutually exclusive; multiple pituitary hormone deficiency occurred in 66 subjects. [c] Growth hormone sufficiency in 7 subjects could not be confirmed with a stimulation test. [d] Corpus callosum abnormality includes 5 subjects with agenesis. [e] Pituitary gland status could not be determined in 1 subject. [f] Absent neurohypophysis was defined as a nonvisualized bright spot and absent infundibulum. [g] Includes 1 subject with Dyke's diverticulum.

of ONH and timing of MRI ($p_{adj} = 0.869$). A brain malformation conferred a positive predictive value of 71% (95% CI: 62%, 80%) and a negative predictive value of 37% (95% CI: 22%, 54%) for hypopituitarism.

Specific Brain Malformations

Hypopituitarism did not correlate (Table 2) with findings of absent septum pellucidum ($p_{unadj} = 0.188$), abnormal corpus callosum ($p_{unadj} = 0.268$), or other major malformations ($p_{unadj} = 0.636$). The lack of associations persisted after adjustment for laterality of ONH and timing of MRI ($p_{adj} = 0.073$, $p_{adj} = 0.625$, and $p_{adj} = 0.407$, respectively).

Table 2. Risk of hypopituitarism at age 5 years associated with specific brain malformations

	Hypopituitarism, n (%)[a]		Unadjusted		Adjusted[b]	
	no (n = 45)	yes (n = 101)	risk ratio[c]	95% CI	risk ratio[c]	95% CI
Any brain malformation	31 (29)	77 (71)	1.13	0.86, 1.48	1.01	0.79, 1.28
Absent septum pellucidum	21 (47)	35 (35)	0.85	0.67, 1.08	0.82	0.66, 1.02
Corpus callosum abnormality	20 (44)	55 (55)	1.13	0.91, 1.41	0.95	0.80, 1.16
Major malformation	11 (24)	21 (21)	0.94	0.71, 1.23	0.90	0.70, 1.16
Combination[d] of malformations	7 (16)	8 (8)	0.75	0.46, 1.22	0.70	0.43, 1.12
Pituitary gland malformation[e]	0 (0)	13 (13)	–	–	–	–

[a] The hormone status is presented as "yes" for hypopituitarism and "no" for normal hormone levels. [b] Adjusted for laterality and the timing of MRI (prior to vs. after enrollment). [c] No abnormality is the referent. [d] Combination denotes an absent septum pellucidum, corpus callosum abnormality, and a major malformation. [e] Pituitary gland status could not be determined in 1 subject.

Table 3. Absence of the septum pellucidum and the risk of additional brain malformations

	Septum pellucidum, n (%)		Unadjusted[a]		Adjusted[a]	
	intact (n = 90)	absent (n = 56)	risk ratio	95% CI	risk ratio[b]	95% CI
Corpus callosum abnormality	38 (42)	37 (66)	1.56	1.15, 2.13	1.53	1.45, 2.03
Major malformation	14 (16)	18 (32)	2.07	1.12, 3.82	2.06	1.13, 3.76
Pituitary gland malformation	8 (9)	5 (9)	0.99	0.34, 2.88	1.02	0.36, 2.90

[a] Intact septum pellucidum is the referent. [b] Adjusted for laterality and the timing of MRI (prior to vs. after enrollment).

A pituitary gland malformation was present in 13 subjects, all of whom manifested hypopituitarism (Table 2), including 2 with DI. The positive and negative predictive values of a pituitary gland malformation for hypopituitarism were 100 and 34% (95% CI: 0.26, 0.43), respectively. Among those with an ectopic neurohypophysis (n = 8), the infundibulum was absent in all but 1 subject in whom the neurohypophysis was partially descended.

Among 133 subjects with an intact pituitary gland, 66% (n = 87) had hypopituitarism, including 12 with DI. There were 4 patients in whom the bright spot of the neurohypophysis was not visualized despite a visible infundibulum: 3 had hypopituitarism, including 1 with DI.

Concomitance of Brain Malformations
Table 3 describes the association of brain malformations with the absence of the septum pellucidum. The greatest association was with major malformations (RR$_{adj}$ = 2.06) followed by corpus callosum abnormality (RR$_{adj}$ = 1.53), but not pituitary gland malformation (RR$_{ajd}$ = 1.02). There were 15 subjects with the malformation triad historically linked with SOD (absent septum pellucidum, corpus callosum abnormality, and other major malformations); of these, only half (n = 8) manifested hypopituitarism (Table 2).

Discussion

The concurrence of brain malformations and ONH has been extensively reported, albeit with significant variability in rates and association with hypopituitarism. In young patients with ONH, findings of brain malformations have been ascribed prognostic values to determine the need for endocrinological evaluation [9, 11, 12, 17, 22, 25–28, 30, 31]. The speculated significance of brain malformations for hypopituitarism stems from the notion that SOD is a distinct entity that bestows high risk for hormone deficiencies. Using the only existing prospective registry of young children with ONH, we demonstrate that brain malformations are pervasive in young children with ONH and are an unreliable screen for hypopituitarism risk. The corresponding type I and II error

rates of brain malformations for the detection of hypopituitarism are 69 and 24%, respectively.

Our cohort of ONH had a predominance of bilaterally affected cases, similar to previous reports [6, 10, 17, 22, 26, 29, 31]. A diagnosis of ONH in one or both eyes was not associated with increased prevalence of absent septum pellucidum, but bilateral disease was associated with a higher risk of other brain malformations. Unilateral cases were not protected from brain malformations, and in fact, nearly 50% of the unilateral cases in our cohort had at least 1 identified brain malformation. This refutes previous reports that brain malformations are exclusive to bilateral ONH [9, 12, 26, 28, 31].

Corpus callosum abnormalities, not absence of the septum pellucidum, were the most common brain malformations in these children with ONH. Notwithstanding the prefix of "septo-" in "SOD," an absent septum pellucidum remains inconsequential to morbidity. An absent septum pellucidum in isolation, or coupled with a corpus callosum abnormality and/or major malformations, did not confer risk of hypopituitarism (Table 2), nor did any combination of structural abnormalities with the exception to the pituitary gland. Our findings add to the mounting evidence refuting the clinical significance of the (absent) septum pellucidum in ONH [10, 12, 24, 30–32].

Absence of the septum pellucidum has been ascribed clinical significance in ONH, due in part to its association with other malformations such as corpus callosum hypoplasia [8, 12, 31, 39]. The septum pellucidum forms by the fusion of leaflets stretching between the developing corpus callosum and hippocampal commissure, beginning at around 12 weeks of gestation [40]. Corpus callosum growth continues following birth, and may thus be hypoplastic without affecting the septum pellucidum. Agenesis of the septum pellucidum is thus a corollary of aplasia, but not hypoplasia, of the corpus callosum. Several homeobox genes influence this process, the dysregulation of which also leads to holoprosencephaly, anophthalmos, and pituitary aplasia [41]. Because of this, the constellation of findings historically called SOD [16] has been presumed to implicate this genetically controlled sequence [17, 18]. However, absence of the septum pellucidum is commonly seen in cases of ONH when the corpus callosum is normal or merely hypoplastic (26 and 46%, respectively, in our cohort), and in otherwise neurologically normal individuals [39, 42]. In such cases, absence of the septum pellucidum more likely indicates a separation from the developing corpus callosum due to factors not necessarily under genetic control.

Our study identified pituitary malformation in 9% of subjects, within the large prevalence range of 6–64% reported in the literature [6, 9, 12, 17, 27–29, 31, 32]. Specific pituitary imaging protocols were not utilized in this study. Thus, quantification of adenohypophyseal mass could not be performed, and it was not possible to determine whether the anterior pituitary gland was small, although it was present in all subjects. On the other hand, the neurohypophyseal bright spot was clearly visible in 95% of subjects. Since this is not likely to be a false-positive finding, it is also unlikely that imaging protocols caused a spuriously low prevalence of neurohypophyseal abnormalities.

While a pituitary malformation was highly predictive of hypopituitarism, the converse cannot be said for a structurally intact pituitary gland. Our reported specificity of a pituitary gland malformation for hypopituitarism (34%) is lower than some earlier reports. In previous studies of various brain abnormalities, sampling patients that underwent neuroimaging and clinically selective, or one-time, endocrinological testing may help explain discrepant rates [3, 8–12, 14, 16, 22–28, 30–32]. For example, patients with identified hypopituitarism may be more likely to get pituitary imaging, while patients with identified pituitary malformation are more likely to get frequent hormonal testing. Most reports used broad criteria for a malformation and have considered absence of the neurohypophyseal bright spot in isolation as sufficient [8, 12, 13, 17, 27, 28, 30–32]. Since visualization of the posterior pituitary bright spot on MRI may be influenced by secondary factors, such as hydration status and plasma glucose levels [43], the lack of a bright spot in isolation will artificially inflate the rate of pituitary gland malformations. Even so, broadening our definition to include all subjects with a nonvisualized bright spot increased the prevalence of a pituitary gland malformation to only 12%. It seems incongruous that an absent neurohypophysis would predict adenohypophyseal dysfunction instead of DI [8, 12, 27], which only occurred in 10% of the cases reported by Ramakrishnaiah et al. [30] and in 11% of this cohort. Furthermore, the prevalence of hypopituitarism (75%) and DI (25%) in our subjects with a nonvisualized bright spot is consistent with the prevalence in the overall subject population and argues against a true association. In contradistinction to previous reports [12, 27, 44], 13 (out of 15) of our subjects with DI had a visible posterior pituitary bright spot, validating the structure-function mismatch noted by others [31, 32, 45]. The high prevalence of hypopituitarism (66%) with an intact pituitary gland on MRI reinforces the importance of monitoring

hormone levels, despite normal neuroimaging, until normal endocrinological status can be concluded with confidence.

Many strengths of this registry endorse the generalizability of our findings to the management of young children with ONH. The main strength over previous reports is the use of prospective, systematically collected data in subjects enrolled near-sequentially prior to age 24 months from a broad referral base [29]. The prevalence of brain malformations and hypopituitarism in our cohort was higher than that in most other reports on ONH, with only 12% of our subjects not having a brain malformation or hypopituitarism. Ahmad et al. [46] reported similar findings in a cohort of patients with ONH, and in that study CT was the predominant imaging modality. The lack of association of brain malformations at baseline with hypopituitarism by the age of 5 years, despite the high prevalence of both, is not likely the result of ascertainment bias, detection, or low statistical power. Differences from previous reports include the exclusive use of MRI techniques for the diagnosis of brain malformations, standardized serial endocrine testing [1] to overcome limitations of point prevalence estimates [17, 26, 31], and focus on cases diagnosed early in life which are more likely to have more severe findings [6, 12, 14, 19, 26, 27, 31]. One limitation of our study is that we may have slightly underestimated the prevalence of GH deficiency and hypothyroidism since evolving hypopituitarism has been reported in children with ONH [34]. For our reported prevalence of GH deficiency, we are somewhat reassured that our capture rate was high based on data from the GENESIS GH registry in which the mean age of initiation of GH treatment in 165 subjects with SOD was 3 years, with a range of 0.9–5.4 years [47].

Several limitations are worth noting. Our study findings are restricted to patients with ONH and cannot be generalized to hypopituitarism risk in patients with congenital brain malformations without ONH. We also included MRI scans that were obtained prior to enrollment – a source of potential bias. The rate of hypopituitarism was slightly, but significantly, higher in those subjects that had MRI scans performed prior to enrollment, suggesting that early clinical manifestations of hypopituitarism may have contributed to early suspicion of the diagnosis. Nonetheless, absence of association of brain malformations with hypopituitarism was independent of MRI status at the time of enrollment. Lastly, exclusion of cases from our registry that presented after the age of 2 years limits generalizability to very young children with ONH. Nevertheless, these findings reduce the complexity of clinical decision making in patients with ONH diagnosed in early life. In clinical practice, we generally see patients every 4–6 months (more frequently in younger children), which would allow earlier detection of a reduced growth rate and the initiation of a laboratory evaluation.

While we conclude that brain malformations are not predictive of hypopituitarism in this population, they are a known risk factor for seizures and developmental delay in this condition [11, 12, 29, 31], and their early identification may be important for predicting and/or preventing adverse outcomes. For example, corpus callosum hypoplasia is associated with a 3-fold increased risk of cognitive deficits [29].

Since 1970, investigations of ONH have used brain malformations and laterality as the criteria for diagnostic subtype and risk of hypopituitarism [6, 7, 10, 12, 13, 18, 28]. This study demonstrates that infants with unilateral ONH also have high risk for hypopituitarism, albeit less than bilaterally affected infants. Brain malformations are common in children with ONH and are unrelated to hypopituitarism; both manifest independently in the ONH disease spectrum. All infants and toddlers with ONH should be considered at high risk for hypopituitarism regardless of findings on neuroimaging.

Acknowledgments

Disclosure Statement

The authors have no conflicts of interest to report.

References

1 Garcia-Filion P, Borchert M: Optic nerve hypoplasia syndrome: a review of the epidemiology and clinical associations. Curr Treat Options Neurol 2013;15:78–89.

2 Tear Fahnehjelm K, Dahl S, Martin L, Ek U: Optic nerve hypoplasia in children and adolescents; prevalence, ocular characteristics and behavioural problems. Acta Ophthalmol 2014;92:563–570.

3 Morishima A, Aranoff GS: Syndrome of septo-optic-pituitary dysplasia: the clinical spectrum. Brain Dev 1986;8:233–239.

4 Kuban KC, Teele RL, Wallman J: Septo-optic-dysplasia-schizencephaly. Radiographic and clinical features. Pediatr Radiol 1989;19:145–150.

5 Miller SP, Shevell MI, Patenaude Y, Poulin C, O'Gorman AM: Septo-optic dysplasia plus: a spectrum of malformations of cortical development. Neurology 2000;54:1701–1703.

6 Reidl S, Mullner-Eidenbock A, Prayer D, Bernert G, Frisch H: Auxological, ophthalmological, neurological and MRI findings in 25 Austrian patients with septo-optic dysplasia (SOD). Horm Res 2002;58:16–19.

7 Polizzi A, Pavone P, Iannetti P, Manfre L, Ruggieri M: Septo-optic dysplasia complex: a heterogeneous malformation syndrome. Pediatr Neurol 2006;34:66–71.

8 Traggiai C, Stanhope R: Endocrinopathies associated with midline cerebral and cranial malformations. J Pediatr 2002;140:252–255.

9 Zeki SM, Hollman AS, Dutton GN: Neuroradiological features of patients with optic nerve hypoplasia. J Pediatr Ophthalmol Strabismus 1992;29:107–112.

10 Acers TE: Optic nerve hypoplasia: septo-optic-pituitary dysplasia syndrome. Trans Am Ophthalmol Soc 1981;79:425–457.

11 Barkovich AJ, Fram EK, Norman D: Septo-optic dysplasia: MR imaging. Radiology 1989;171:189–192.

12 Brodsky MC, Glasier CM: Optic nerve hypoplasia. Clinical significance of associated central nervous system abnormalities on magnetic resonance imaging. Arch Ophthalmol 1993;111:66–74.

13 Kaufman LM, Miller MT, Mafee MF: Magnetic resonance imaging of pituitary stalk hypoplasia. A discrete midline anomaly associated with endocrine abnormalities in septo-optic dysplasia. Arch Ophthalmol 1989;107:1485–1489.

14 Margalith D, Tze WJ, Jan JE: Congenital optic nerve hypoplasia with hypothalamic-pituitary dysplasia. A review of 16 cases. Am J Dis Child 1985;139:361–366.

15 De Morsier G: Etudes sur les dysraphies cranio-encephaliques. III. Agenesis du septum lucidum avec malformation du tractus optique. La dysplasie septo-optique. Schweiz Arch Neurol Psychiatr 1956;77:267–292.

16 Hoyt WF, Kaplan SL, Grumbach MM, Glaser JS: Septo-optic dysplasia and pituitary dwarfism. Lancet 1970;1:893–894.

17 Mehta A, Hindmarsh PC, Mehta H, Turton JP, Russell-Eggitt I, Taylor D, Chong WK, Dattani MT: Congenital hypopituitarism: clinical, molecular and neuroradiological correlates. Clin Endocrinol (Oxf) 2009;71:376–382.

18 Webb EA, Dattani MT: Septo-optic dysplasia. Eur J Hum Genet 2010;18:393–397.

19 Patel H, Tze WJ, Crichton JU, McCormick AQ, Robinson GC, Dolman CL: Optic nerve hypoplasia with hypopituitarism. Septo-optic dysplasia with hypopituitarism. Am J Dis Child 1975;129:175–180.

20 Mosier MA, Lieberman MF, Green WR, Knox DL: Hypoplasia of the optic nerve. Arch Ophthalmol 1978;96:1437–1442.

21 Menezes L, Aicardi J, Goutieres F: Absence of the septum pellucidum with porencephalia. A neuroradiologic syndrome with variable clinical expression. Arch Neurol 1988;45:542–545.

22 Roberts-Harry J, Green S, Willshaw H: Optic nerve hypoplasia: associations and management. Arch Dis Child 1990;65:103–106.

23 Masera N, Grant DB, Stanhope R, Preece MA: Diabetes insipidus with impaired osmotic regulation in septo-optic dysplasia and agenesis of the corpus callosum. Arch Dis Child 1994;70:51–53.

24 Costin G, Murphree AL: Hypothalamic-pituitary function in children with optic nerve hypoplasia. Am J Dis Child 1985;139:249–254.

25 Siatkowski R, Sanchez J, Andrade R, Alvarez A: The clinical, neuroradiographic, and endocrinologic profile of patients with bilateral optic nerve hypoplasia. Ophthalmology 1997;104:493–496.

26 Skarf B, Hoyt C: Optic nerve hypoplasia in children: association with anomalies of the endocrine and CNS. Arch Ophthalmol 1984;102:62–67.

27 Phillips PH, Spear C, Brodsky MC: Magnetic resonance diagnosis of congenital hypopituitarism in children with optic nerve hypoplasia. J AAPOS 2001;5:275–280.

28 Signorini SG, Decio A, Fedeli C, Luparia A, Antonini M, Bertone C, Misefari W, Ruberto G, Bianchi PE, Balottin U: Septo-optic dysplasia in childhood: the neurological, cognitive and neuro-ophthalmological perspective. Dev Med Child Neurol 2012;54:1018–1024.

29 Garcia-Filion P, Epport K, Nelson M, Azen C, Geffner ME, Fink C, Borchert M: Neuroradiographic, endocrinologic, and ophthalmic correlates of adverse developmental outcomes in children with optic nerve hypoplasia: a prospective study. Pediatrics 2008;121:e653–e659.

30 Ramakrishnaiah RH, Shelton JB, Glasier CM, Phillips PH: Reliability of magnetic resonance imaging for the detection of hypopituitarism in children with optic nerve hypoplasia. Ophthalmology 2014;121:387–391.

31 Birkebaek NH, Patel L, Wright NB, Grigg JR, Sinha S, Hall CM, Price DA, Lloyd IC, Clayton PE: Endocrine status in patients with optic nerve hypoplasia: relationship to midline central nervous system abnormalities and appearance of the hypothalamic-pituitary axis on magnetic resonance imaging. J Clin Endocrinol Metab 2003;88:5281–5286.

32 Haddad NG, Eugster EA: Hypopituitarism and neurodevelopmental abnormalities in relation to central nervous system structural defects in children with optic nerve hypoplasia. J Pediatr Endocrinol Metab 2005;18:853–858.

33 Atapattu N, Ainsworth J, Willshaw H, Parulekar M, MacPherson L, Miller C, Davies P, Kirk JM: Septo-optic dysplasia: antenatal risk factors and clinical features in a regional study. Horm Res Paediatr 2012;78:81–87.

34 Ma NS, Fink C, Geffner ME, Borchert M: Evolving central hypothyroidism in children with optic nerve hypoplasia. J Pediatr Endocrinol Metab 2010;23:53–58.

35 Ahmad T, Borchert M, Geffner M: Optic nerve hypoplasia and hypopituitarism. Pediatr Endocrinol Rev 2008;5:772–777.

36 Fink C, Vedin AM, Garcia-Filion P, Ma NS, Geffner ME, Borchert M: Newborn thyroid-stimulating hormone in children with optic nerve hypoplasia: associations with hypothyroidism and vision. J AAPOS 2012;16:418–423.

37 Vedin AM, Garcia-Filion P, Fink C, Borchert M, Geffner M: Serum prolactin concentrations in relation to hypopituitarism and obesity in children with optic nerve hypoplasia. Horm Res 2012;77:277–280.

38 Greenland S: Model-based estimation of relative risks and other epidemiologic measures in studies of common outcomes and in case-control studies. Am J Epidemiol 2004;160:301–305.

39 Schaefer GB, Bodensteiner JB, Thompson JN Jr: Subtle anomalies of the septum pellucidum and neurodevelopmental deficits. Dev Med Child Neurol 1994;36:554–559.

40 Rakic P, Yakovlev PI: Development of the corpus callosum and cavum septi in man. J Comp Neurol 1968;132:45–72.

41 Garcia-Filion P, Borchert M: Prenatal determinants of optic nerve hypoplasia: review of suggested correlates and future focus. Surv Ophthalmol 2013;58:610–619.

42 Scoffings DJ, Kurian KM: Congenital and acquired lesions of the septum pellucidum. Clin Radiol 2008;63:210–219.

43 Fujisawa I: Magnetic resonance imaging of the hypothalamic-neurohypophyseal system. J Neuroendocrinol 2004;16:297–302.

44 Sorkin JA, Davis PC, Meacham LR, Parks JS, Drack AV, Lambert SR: Optic nerve hypoplasia: absence of posterior pituitary bright signal on magnetic resonance imaging correlates with diabetes insipidus. Am J Ophthalmol 1996;122:717–723.

45 Karthikeyan A, Abid N, Sundaram PC, Shaw NJ, Barrett TG, Hogler W, Kirk JM: Clinical characteristics and management of cranial diabetes insipidus in infants. J Pediatr Endocrinol Metab 2013;26:1041–1046.

46 Ahmad T, Garcia-Filion P, Borchert M, Kaufman F, Burkett L, Geffner M: Endocrinological and auxological abnormalities in young children with optic nerve hypoplasia: a prospective study. J Pediatr 2006;148:78–84.

47 Deal C, Hasselmann C, Pfaffle RW, Zimmermann AG, Quigley CA, Child CJ, Shavrikova EP, Cutler GB Jr, Blum WF: Associations between pituitary imaging abnormalities and clinical and biochemical phenotypes in children with congenital growth hormone deficiency: data from an international observational study. Horm Res Paediatr 2013;79:283–292.