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Neuroradiographic, Endocrinologic, and Ophthalmic Correlates of Adverse Developmental Outcomes in Children With Optic Nerve Hypoplasia: A Prospective Study

Pamela Garcia-Filion, MPH[a,b], Karen Epport, PhD[c], Marvin Nelson, MD[d,e], Colleen Azen, MS[c], Mitchell E. Geffner, MD[f,g], Cassandra Fink, MPH[a], Mark Borchert, MD[a,g]

[a]Division of Pediatric Ophthalmology, Department of Ophthalmology, and [f]Division of Pediatric Endocrinology, Diabetes, and Metabolism, Department of Pediatrics, University of Southern California Keck School of Medicine and Childrens Hospital Los Angeles, Los Angeles, California; [b]Division of Biostatistics, Department of Preventive Medicine, and [e]Department of Radiology, University of Southern California Keck School of Medicine, Los Angeles, California; [c]General Clinical Research Center, [d]Department of Imaging Services, and [g]Saban Research Institute, Childrens Hospital Los Angeles, Los Angeles, California

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ABSTRACT

BACKGROUND. Developmental delay has been reported to occur with optic nerve hypoplasia, a leading cause of pediatric blindness, but has not been systematically examined for its prevalence and correlation with associated pathologies of optic nerve hypoplasia.

OBJECTIVE. The purpose of this study was to determine the developmental outcomes of children with optic nerve hypoplasia and the correlation of development with neuroradiographic, endocrinologic, and ophthalmic findings.

METHODS. We conducted a prospective analysis of 73 subjects diagnosed with optic nerve hypoplasia at <36 months of age for developmental outcomes at 5 years of age. Subjects underwent neuroradiographic imaging, endocrinologic testing and examination, and ophthalmologic examination; developmental outcomes were assessed by using the Battelle Developmental Inventory.

RESULTS. At 5 years of age, developmental delay was present in 71% of subjects with optic nerve hypoplasia. Of patients with unilateral (18%) and bilateral optic nerve hypoplasia, 39% and 78%, respectively, experienced developmental delay. Corpus callosum hypoplasia and hypothyroidism were significantly associated with poor outcome in all of the developmental domains and an increased risk of delay. Absence of the septum pellucidum was not associated with adverse development. Six subjects had neither a neuroradiographic nor an endocrinologic abnormality, and of those, 4 were developmentally delayed.

CONCLUSIONS. These prospective data confirm the significant association of developmental delay with optic nerve hypoplasia and identify corpus callosum hypoplasia and hypothyroidism as strong correlates. A diagnosis of optic nerve hypoplasia warrants neuroradiographic and endocrinologic testing for risk factors of delay and developmental assessments for early intervention planning.

OPTIC NERVE HYPOPLASIA (ONH) is a congenital abnormality characterized by an underdeveloped optic nerve in 1 or both eyes.[1] Considered a leading cause of vision loss in young children,[2] the incidence of ONH was recently estimated at 10.9 per 100 000,[3] a sixfold increase over the estimate of 1.8 per 100 000 in 1977.[4] Although the etiology of ONH is still not understood, a variety of risk factors have been suggested, including young maternal age, prima gravida, smoking, and fertility or antidepressant medications.[5]

Endocrinopathies, neuroradiographic abnormalities, and developmental delay are associated pathologies.[6–8] In a prospective study, endocrinopathies were present in 72% of young children with ONH.[6] Estimates of cerebral malformations have varied from 39% to 90% in retrospective studies.[7–11] The frequent association of ONH with absence of the septum pellucidum led to the historical attribution of significance to this finding and the designation of the syndrome of septo-optic dysplasia.[12,13] More recently, the clinical significance of an absent septum pellucidum or other neuroradiographic abnormalities in patients with ONH has been questioned.[6,14,15]

Limited data are available from retrospective studies on the prevalence of developmental delay in children with ONH. Margalith et al[7] first reported an association between ONH and neuropsychiatric disorders, estimating mental retardation in 71%. Burke[16] estimated a similar prevalence (70%) of delay from neurologic examination. Although most reports on ONH acknowledge the presence of handicaps,[7,10,17–21] no studies have systematically characterized or quantified delay in this population.

Little is known about the associations between neuroradiographic, endocrinological, or ophthalmic abnormalities and adverse developmental outcomes in children with ONH. Although central nervous system abnormalities have been documented in high prevalence in children with nonspecific forms of developmental delay, there have been no prospective studies on the association of central nervous system abnormalities with adverse developmental outcomes in children with ONH. Identification of clinical risk factors for delay in these children may lead to early detection and intervention strategies to obviate adverse outcomes.

The ophthalmology clinic at Childrens Hospital Los Angeles (CHLA), is a referral center for patients with ONH from across the United States. At CHLA, children <36 months of age with ONH have been prospectively followed to investigate the risk factors for adverse endocrinologic, visual, and developmental outcomes at age 5 years. Since 1992, 187 of 252 eligible subjects have been enrolled. Herein we report the developmental outcomes at age 5 years and associations with neuroradiographic, endocrine, and ophthalmic findings for the first 73 subjects to complete the study.

METHODS

Subjects

All of the subjects with a diagnosis of ONH made by a single neuro-ophthalmologist were offered enrollment if completion of baseline tests was anticipated before 36 months of age. Subjects were categorized on race or ethnicity using parent report.

Informed consent for participation was obtained from all of the subjects. The study was performed in accordance with protocols approved by the committee on clinical investigations (institutional review board) at CHLA.

Clinical Measures

The diagnosis of ONH was confirmed by fundus photography.[22,23] Optic nerves with a ratio of ≤0.35 for the horizontal disk diameter to the disk-macula distance (DD/DM) were classified as hypoplastic, whereas >0.35 was considered normal. Severity of ONH was estimated by taking the smaller value of the 2 eyes.

An MRI scan of the brain was requested for enrolled subjects. A computed tomography scan was accepted in lieu of an MRI scan in subjects for whom insurance approval was denied. A single neuroradiologist, masked to the subject's clinical characteristics, reviewed the neuroradiographic images for specific malformations: absence of the septum pellucidum; hypoplasia of the corpus callosum (CCH); abnormalities of the pituitary gland (absent infundibulum, ectopic, or absent neurohypophysis and/or absent adenohypophysis); and other major malformations (defined as hydrocephalus, schizencephaly, holoprosencephaly, pachygyria, and/or white matter hypoplasia). Lesser neuroradiographic abnormalities were incidentally noted. Measurements of the cross-sectional area of the CCH (CCA) were obtained for subjects who underwent MRI by projecting the midsagittal image to 3 times the actual size, tracing the edge of the CCH, and measuring the traced area (centimeters squared) with a planimeter while correcting for the magnification.

Pediatric endocrinologists, unaware of the developmental outcomes, determined the status of the hypothalamic-pituitary axes on the basis of treatment for hormone deficiencies and/or laboratory testing. Routine tests included fasting AM glucose, free T4, thyrotropin, cortisol, insulin-like growth factor-1, insulin-like growth factor–binding protein 3, and prolactin. A glucagon-stimulation test for growth hormone (GH) and cortisol was performed at age 4 years (sooner if the patient was eligible for GH treatment on the basis of growth deceleration). Diabetes insipidus was assessed in subjects with clinical indication by obtaining serum osmolality after prolonged water deprivation; subjects were otherwise determined to have normal antidiuretic hormone levels. The number of subjects with complete laboratory testing varies because of refusal by the parents or denial by health insurers.

Final visual acuity was measured at 5 years of age by using the Snellen eye chart or with linear "E" or linear Allen figures for illiterate subjects. Subjects with visual acuity of <6/120 were assessed with a "tumbling E" at distances of <6 m. Visual acuity was converted to logMAR acuity,[24] with no light perception considered 4.0, light perception considered 3.3, and motion perception considered 3.0. Visual acuities that could not be quantified, but were qualitatively better than motion perception, were not included in analyses. The acuity of the better eye (smallest logMAR value) was used in the analyses.

Developmental Assessments

A single neuropsychologist, masked to the subjects' clinical characteristics, evaluated the developmental status

FIGURE 1
Distribution of developmental outcomes. PSD indicates personal-social; AD, adaptive; MD, motor; CD, communication; COG, cognition.
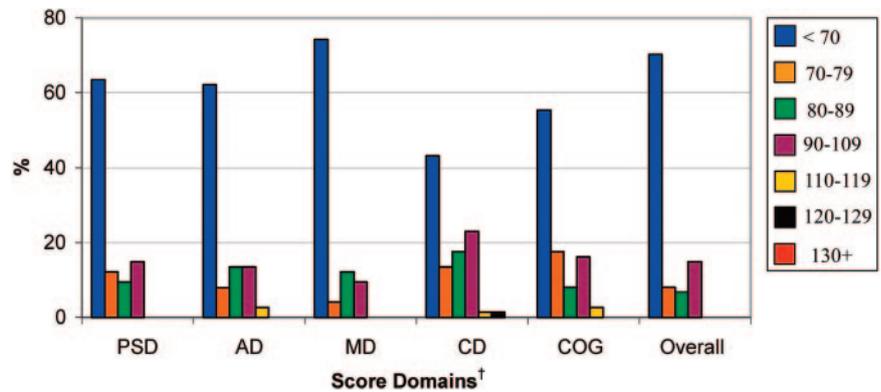
of subjects using the Battelle Developmental Inventory (BDI). This tool was selected on the basis of availability of normative data, targeted age range, and adaptations for and previous use with visually impaired populations.[25]

The BDI involves direct individual assessment and parental interview to measure key developmental skills in children from birth to 8 years. It assesses 6 developmental domains: personal-social, adaptive, motor, communication, cognition, and overall development. Overall development is a summary domain driven by performance in the individual domains. The BDI produces SD quotients (mean ± SD: 100 ± 15), derived from converting percentile ranks to standardized scores. The lowest possible score on the BDI is 65 (−2.3 SD). There are 7 score categories: developmental delay (65–69); borderline (70–79); low average (80–89); average (90–109); high average (110–119); superior (120–129); and very superior (≥130). Final BDI scores for the study sample were not normally distributed, and a large percentage received a score of <70 (Fig 1). Consequently, outcome data were dichotomized as delayed (65–69) and not delayed (≥70) for analyses.

Statistical Analysis

Analysis was performed with SAS (SAS Institute, Inc, Cary, NC) and NCSS (NCSS, Kaysville, UT). Developmental outcomes were examined for associations with neuroradiographic, endocrinologic, and ophthalmic findings.

Associations with dichotomous clinical findings were analyzed univariately by Fisher's exact test. CCA, best final visual acuity (logMAR), and severity of ONH (DD/DM) were analyzed univariately by logistic regression. LogMAR and DD/DM data were not normally distributed and, thus, transformed for analysis by taking the square root and natural log, respectively. Significant findings were further investigated to determine whether the associations were confounded by other factors. When necessary, Spearman's correlation test and Student's t test were used to assess the independence of explanatory variables. Categorical confounders were adjusted for by stratifying on the confounding variable to determine whether the association varied. Continuous confounders were adjusted for using multiple logistic

regression. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by logistic regression, using the profile likelihood method. If logistic regression was unable to calculate an OR because of 0 cell count, 0.5 was added to each cell for estimation of OR (95% CI).

The statistical significance level was defined as an α value of .05, with 2-sided alternative hypotheses. In the absence of an association between a clinical finding and all of the 6 BDI domains, the smallest P value (P_{all}) is reported.

RESULTS

Characteristics of the study cohort ($n = 73$) are presented in Table 1. Of the 187 subjects enrolled, 35 were lost to follow-up, 3 died, and 76 remain active but have not reached 5 years of age. Subjects lost to follow-up did not differ significantly from completed subjects with regard to gender ($P = .49$), race or ethnicity ($P = .38$), and laterality of ONH ($P = .19$).

The mean age at enrollment and final developmental assessment were 15.7 ± 9.2 months and 60 ± 5.2 months, respectively. Duration of gestation was known in 93% (68 of 73) of subjects, of which 18% (12 of 68) were preterm (<37 weeks). There was no significant difference in the frequency of delay observed in subjects born after 36 weeks (70%) versus preterm (75%; $P = 0.99$).

Neuroradiographic Associations

Neuroradiographic images were available for 89% (65 of 73) of subjects, of which 74% were MRIs. A neuroradiographic abnormality was present in 63% (41 of 65) of subjects. CCH was significantly associated with poor outcome in all of the developmental domains and an increased risk of delay (Table 2). Excluding subjects with other major malformations did not alter the association of CCH with development. Other major malformations were significantly associated with delay in personal-social ($P = .02$), adaptive ($P = .02$), communication ($P = .004$), and cognitive ($P = .008$) skills, as well as overall development ($P = .05$). However, all of the subjects with other major malformations had CCH, and, thus, these associations could not be evaluated for independence. An absent septum pellucidum was not associated with

TABLE 1 Characteristics of Cohort

Characteristic	%[a]	n/N
Gender		
Male	58	42/73
Female	42	31/73
Referral Source		
Ophthalmologist	26	19/73
Self	19	14/73
Pediatrician	14	10/73
Neurologist	7	5/73
Resource for visually impaired	7	5/73
Endocrinologist	7	5/73
Optometrist	4	3/73
Unknown	16	12/73
Race or ethnicity		
Hispanic white	49	36/73
White	34	25/73
Asian/Pacific Islander	3	2/73
Black	4	3/73
Other (mixed race)	10	7/73
Laterality of ONH		
Unilateral	18	13/73
Bilateral	82	60/73
Endocrinopathies[b]		
GH deficiency	70	46/66
Hypothyroidism	43	29/68
Adrenal insufficiency	27	18/67
Hyperprolactinemia	62	33/53
Diabetes insipidus	5	4/73
Neuroradiographic abnormalities[b]		
CCH	38	25/65
Absent septum pellucidum	38	25/65
Pituitary gland abnormality[c]	13	8/63
Other major malformation[d]	14	9/65
Hydrocephalus	6	4/9
Schizencephaly	2	1/9
Holoprosencephaly	2	1/9
Pachygyria	3	2/9
White matter hypoplasia	3	2/9

[a] Percentages are rounded up to the next integer and, thus, may not total 100.

[b] Frequency estimates are not mutually exclusive. The total number of subjects varies depending on available laboratory tests and imaging results.

[c] Two subjects could not be assessed because of inadequate imaging.

[d] One subject had 2 major malformations.

delay ($P_{all} \geq$ .20). A pituitary gland malformation was not associated with delay ($P_{all} \geq$ .10). Lesser malformations were noted in 20% (13 of 65): 2 subjects had

TABLE 2 CCH and Odds of Developmental Delay

BDI Domains (Delay)	Corpus Callosum (n = 65)		Fisher's Exact P	OR (95% CI)
	Hypoplastic (n = 25), n (%)	Normal (n = 40), n (%)		
Personal-social	24 (96)	19 (48)	<.001	26.53 (4.86–496.20)
Adaptive	24 (96)	17 (43)	<.001	32.47 (5.94–608.95)
Motor	25 (100)	25 (63)	<.001	31.00 (2.93–314.53)[a]
Communication	19 (76)	9 (23)	<.001	10.91 (3.54–38.31)
Cognition	24 (96)	13 (33)	<.001	49.85 (9.00–940.37)
Overall	24 (96)	23 (58)	<.001	17.74 (3.23–332.53)

[a] We added 0.5 to cells with 0 for OR estimation; CI was estimated by the score method.

TABLE 3 CCA Measurements and Developmental Outcome

BDI Domains	CCA, cm²[a]				OR (95% CI)[b]
	Delayed		Not Delayed		
	n	Mean ± SD	n	Mean ± SD	
Personal-social	26	2.12 ± 1.35	15	3.19 ± 0.93	2.10 (1.20–4.18)[c]
Adaptive	26	2.13 ± 1.35	15	3.18 ± 0.95	2.06 (1.18–4.07)[c]
Motor	33	2.41 ± 1.38	8	2.93 ± 0.94	1.39 (0.76–2.83)
Communication	18	1.92 ± 1.33	23	2.97 ± 1.12	2.01 (1.19–3.72)[d]
Cognition	25	2.00 ± 1.30	16	3.30 ± 0.87	2.68 (1.45–5.86)[d]
Overall	29	2.24 ± 1.35	12	3.17 ± 0.96	1.90 (1.06–3.85)[c]

[a] There was no difference between subjects with (n = 41) and without (n = 32) measurements of CCA ($P_{all} \geq$ .56).

[b] Data show the odds of delay for each unit decrease in CCA (cm²), adjusted for age at the time of neuroimaging.

[c] Data were significant at $P <$ .05.

[d] Data were significant at $P <$ .01.

ventriculomegaly (1 delayed), 1 had microcephaly (not delayed), 4 had arachnoid cysts (all delayed; all with hypothyroidism or CCH), and 6 had cortical heterotopia (4 delayed). These malformations were collapsed into 1 variable, which was not associated with delay ($P_{all} \geq$ .27). There was no difference in the developmental outcomes of subjects with and without neuroradiographic images ($P_{all} \geq$ .68).

Of the 48 subjects (50% boys) who underwent MRI scans, CCA measurements were available for 85% ($n =$ 41). There was no gender difference in CCA measurements ($t = 1.44$; $P =$ .16); the average age at the time of imaging was 11.4 ± 12.8 months.

Subjects classified by the neuroradiologist as having CCH (39%) had a mean CCA of 1.4 ± 1.0 cm² compared with 3.2 ± 0.97 cm² ($t = 5.61$; $P <$ .001) for corpus callosi classified as normal. The CCA, before and after adjusting for age at the time of neuroimaging, was significantly smaller for subjects with delayed personal-social (adjusted P [P_{adj}] = .02), adaptive ($P_{adj} =$ .03), communication ($P_{adj} =$ .009), and cognitive ($P_{adj} =$ .005) skills, and overall development ($P_{adj} =$ .04). Table 3 compares the CCAs for those with and without delay and provides the odds of delay for each unit decrease in area, adjusted for age.

Endocrinologic Associations

Hormonal dysfunction was present in 79% (57 of 72) of subjects. Hypothyroidism was significantly associated with delay in all of the domains of development, with the odds of delay ranging from 6.6 to 12.8 (Table 4). The associations between delay and hypothyroidism were independent of CCH status. GH deficiency was associated with delay in personal-social ($P =$ .03), motor ($P =$ .04), and cognitive ($P =$ .003) skills, as well as overall development ($P =$ .05). These associations were no longer significant after stratification for thyroid status ($P_{all} \geq$ .70). Adrenal insufficiency was associated with delay in personal-social ($P =$ .01), adaptive ($P =$ .005), communication ($P =$ .03), and cognitive ($P =$ .001) skills, as well as overall development ($P =$ .008). These associations were no longer significant after stratification for thyroid status ($P_{all} \geq$ .19). Although commonly ob-

TABLE 4 Hypothyroidism and Developmental Delay (#,%)

BDI Domains (Delay)	Thyroid Status ($n = 68$)		Fisher's Exact P	OR (95% CI)
	Hypothyroid ($n = 29$)	Euthyroid ($n = 39$)		
Personal-social	25 (86)	19 (49)	.001	6.58 (2.09–25.56)
Adaptive	25 (86)	17 (44)	<.001	8.09 (2.56–31.52)
Motor	27 (93)	23 (59)	.001	9.39 (2.35–63.45)
Communication	18 (62)	12 (31)	.01	3.68 (1.37–10.46)
Cognition	25 (86)	13 (33)	<.001	12.50 (3.90–49.58)
Overall development	27 (93)	20 (51)	<.001	12.83 (3.23–86.48)

served, hyperprolactinemia was not associated with developmental outcomes ($P_{all} \geq .38$). All 4 of the subjects with diabetes insipidus were delayed in each domain.

Ophthalmic Associations

Best final logMAR visual acuity (median [fifth percentile, 95th percentile]) in bilateral ($n = 54$) and unilateral ($n = 13$) patients with ONH was 1.33 (0.30, 4.0) and 0.08 (0, 0.40), respectively ($t = 4.85$; $P < .001$). Final visual acuity could not be quantified in 6 bilateral cases. Of these, 3 could fixate and follow a 1-in toy at $^1/_3$ m, 1 could fixate and follow a face at $^1/_3$ m, and 2 were able to follow a face with poor fixation. The median (fifth percentile, 95th percentile) DD/DM ratio for eyes with ONH ($n = 125$) was 0.15 (0.08, 0.32); optic disk size could not be measured in 4 bilateral cases.

The worse final visual acuity in the better eye was associated with delay in all 6 of the domains ($P < .01$) and also with CCH ($t = -4.79$; $P < .001$). After adjusting for CCH, the associations remained significant for adaptive ($P = .003$) and cognitive ($P = .03$) skills, became marginally significant for communication skills ($P = .06$), and approached significance for overall development ($P = .08$).

Among patients with bilateral ONH, 78% experienced overall delay compared with 39% of patients with unilateral ONH ($P = .007$). Laterality, confounded by visual acuity and CCH, was associated with delayed adaptive ($P < .001$) and communication ($P = .004$) skills, cognition ($P = .002$), and overall development ($P = .007$); was marginally associated with personal-social skills ($P = .053$); and approached significance for delayed motor skills ($P = .073$). These associations could not be adjusted because of small sample size.

On the basis of the size of the smaller optic disk (estimator of severity), 58% (40 of 69) of subjects had severe (DD/DM: ≤0.15), 35% (24 of 69) had moderate (DD/DM: 0.16–0.30), and 7% (5 of 69) had mild ONH (DD/DM: 0.31–0.35).[22] Severity of ONH was associated with adaptive skills ($P = .01$) and overall development ($P = .02$) and approached significance for personal-social skills ($P = .06$). These associations did not remain significant after adjusting for laterality ($P_{all} \geq .14$).

DISCUSSION

Various developmental handicaps have been reported among patients with ONH, ranging from an isolated report of deficits in spatial recognition to global devel-

opmental delay.[26–29] Overall delay occurred in 71% of our subjects, with motor delays being the most common (75%) and communication delays the least common (44%). Brodsky and Glasier[8] previously reported a positive association between delay and any neuroradiographic abnormality in a retrospective study of patients with severe cases of ONH. In our prospective study, the prevalence of delay did not differ between those with (78%) and without (63%) any neuroradiographic abnormality ($P = .25$). CCH and CCA, however, were strong predictors of developmental delay. Only 1 subject with CCH did not have delay compared with 17 of those with a normal CCH, 14 of whom had low average or better developmental outcomes. CCA was highly correlated with all of the domains except motor skills; the most significant association occurred with cognition, conferring a near threefold increase in risk for delay with each unit (centimeters squared) decrement in CCA. These results are not surprising, because abnormalities in interhemispheric communication have been associated with neuropsychiatric disorders in children,[30] and previous reports have found a high prevalence of CCH in subjects with nonspecific developmental delay and/or autism.[31–33] Although our analysis of CCA did not involve a control group, there was a strong correlation between CCA and CCH, as determined by a masked neuroradiologist.

CCH was positively associated with an absent septum pellucidum and the presence of other major malformations. Among those with CCH, 60% had an absent septum pellucidum ($P = .008$), and 36% had other major malformations ($P < .001$). The absence of the septum pellucidum, per se, was unrelated to development and confirms previous retrospective reports.[8,10,19,34] All of the subjects with other major malformations had CCH. Thus, the association between major malformations and developmental outcomes could not be distinguished from that of CCH in this sample.

The reported prevalence of radiographic pituitary abnormalities varies from 6% to 64%.[6,19] Pituitary gland malformations were found in 13% of our subjects, all of whom had overall delay and were proportionately distributed on the status of the CCH. The prevalence of delay in subjects with a pituitary malformation, although not statistically significant, is higher than the estimate of Brodsky and Glasier (66%).[8]

This prospective study revealed a significant association between hypothyroidism and developmental delay. In cases of hypothyroidism, 93% had overall delay at the age of 5 years. Although an association between congenital primary hypothyroidism and delay has been well established,[35] this is the first reported association between a specific endocrinopathy and developmental outcomes in children with ONH. Previous studies have commented on a possible association but were unable to substantiate their observations.[7,8,21] Margalith et al[7] noted growth retardation in many of their subjects with developmental handicaps and suggested that these likely represented undetected cases of hypopituitarism. In our subjects, there was no correlation between developmental delay and the presence of any endocrinopathy ($P =$

.35). Although other individual forms of hypopituitarism were associated to some extent with delay in our subjects, these associations disappeared after stratifying for hypothyroidism. Thus, hypothyroidism stands out as a significant risk factor for delay independent of CCH or more generalized pituitary dysfunction.

Hypothyroidism in our subjects was rarely detected in early infancy, and 52% of our subjects with hypothyroidism were undiagnosed before study enrollment. Thus, the potential benefit of early thyroid hormone replacement on development could not be assessed. In addition, this suggests that neonatal screening for hypothyroidism in the United States, designed for primary disease, cannot be relied on and may need modification to allow for detection of central hypothyroidism, as occurs in children with ONH.

Worse visual acuity of the better eye, after accounting for CCH, was associated with delayed adaptive and cognitive skills and may reflect an inability to fully adjust for the influence of CCH on development by using a categorical measure. The analyses could not be adjusted for CCA because of small sample size and the need to account for the subject's age at the time of neuroimaging. This finding also suggests that the adaptive and cognitive skills tested by the BDI may be partially vision dependent. However, a wide range of visual acuities was observed across all of the developmental strata, demonstrating that good vision does not preclude delay. It was not possible to distinguish the amount of vision loss because of cortical impairment from that because of optic nerve dysfunction in these subjects.

Only 6 (10%) of our subjects had no neuroradiographic or endocrine abnormalities, yet 4 had overall developmental delay. Thus, the risk for delay is high even in the absence of neuroradiographic or endocrine abnormalities. Similarly, patients with unilateral or mild cases of ONH are not protected from developmental delay, although patients with bilateral cases are at increased risk.

This study is the first known prospective investigation of young children with ONH. Using a prospective design and consecutively enrolling subjects from a variety of sources helped minimize bias. The true demographic characteristics for the population of children with ONH are unknown. On the basis of the nature of subject accrual, the demographics observed in this sample may provide the best estimate of the disease's gender and racial or ethnic distribution in the United States. Subjects originated from a variety of referral sources, reducing the likelihood of selecting for subjects more or less likely to have or not have a particular pathology. Nineteen percent of enrolled subjects were lost to follow-up; this is not a likely source of bias, because they did not significantly differ from the completed subjects on gender, race or ethnicity, and laterality. The study experienced a 26% nonparticipation rate; thus, selection bias cannot be ruled out. Detection bias was limited by the application of a standard protocol for neuroradiographic, endocrinologic, and ophthalmic assessment. Although there were subjects missing neuroradiographic and endocrinologic data, their clinical characteristics were similar to the remaining subjects and, thus, their exclusion was unlikely to inject bias.

The results of this study are limited by the high frequency of developmental delay across all of the domains. The BDI bottoms out with a score of 65; 68% (50 of 73) of all of the subjects and 96% (50 of 52) of subjects classified as having overall delay received the lowest possible score. Without qualitative measurements, we were unable to tease out the varying degrees of delay for correlation with clinical characteristics. In addition, subjects categorized as "not delayed" for purposes of this study actually represent a broad spectrum of development, including 17% to 41% who were borderline delayed in the various domains. Adjustment for confounders was impeded by the risk of statistical breakdown from small or 0 cell counts. As more subjects complete the study, an increase in statistical power will improve adjustment for confounders and estimation of associations with development.

CONCLUSIONS

The high prevalence of hypopituitarism, cerebral abnormalities, and developmental delay found in this prospective study highlights the importance of thorough evaluation for all patients with ONH regardless of optic nerve size, visual acuity, or laterality. Additional studies are needed to determine the effectiveness of earlier diagnosis or intervention, particularly for hypothyroidism, on developmental outcomes in patients with ONH.

REFERENCES

1. Hoyt CS, Billson FA. Optic nerve hypoplasia: changing perspectives. *Aust NS J Ophthalmol.* 1986;14(4):325–331
2. Steinkuller PG, Du L, Gilbert C, Foster A, Collins ML, Coats DK. Childhood blindness. *J AAPOS.* 1999;3(1):26–32
3. Patel L, McNally RJQ, Harrison E, Lloyd IC, Clayton PE. Geographical distribution of optic nerve hypoplasia and septo-optic dysplasia in northwest England. *J Pediatr.* 2006;148(1):85–88
4. Jan JE, Robinson GC, Kinnis C, MacLeod PJM. Blindness due to optic-nerve atrophy and hypoplasia in children: an epidemiological study. *Dev Med Child Neurol.* 1977;19(3):353–363
5. Tornqvist K, Ericsson A, Källén B. Optic nerve hypoplasia: risk factors and epidemiology. *Acta Ophthalmol Scand.* 2002;80(3):300–304
6. Ahmad TQ, 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(1):78–84

7. Margalith D, Jan JE, McCormich AQ, Tze WJ, Lapointe J. Clinical spectrum of congenital optic nerve hypoplasia: review of 51 patients. *Dev Med Child Neurol.* 1984;26(3):311–322

8. Brodsky MC, Glasier CM. Optic nerve hypoplasia. Clinical significance of associated central nervous system abnormalities on magnetic resonance imaging. *Arch Ophthalmol.* 1993;111(1):66–74

9. Skarf B, Hoyt CS. Optic nerve hypoplasia: association with anomalies of the endocrine and CNS. *Arch Ophthalmol.* 1984;102(1):62–67

10. Roberts-Harry J, Green SH, Willshaw HE. Optic nerve hypoplasia: associations and management. *Arch Dis Child.* 1990;65(1):103–106

11. Zeki SM, Hollman AS, Dutton GN. Neuroradiological features of patients with optic nerve hypoplasia. *J Pediatr Ophthalmol Strabismus.* 1992;29(2):107–112

12. De Morsier G. Studies on malformation of cranioencephalic sutures. III. Agenesis of the septum lucidum with malformation of the optic tract [in French]. *Schweiz Arch Neurol Psychiatr.* 1956;77(1–2):267–292

13. Hoyt WF Kaplan SL, Grumbach MM, Glaser JS. Septo-optic dysplasia and pituitary dwarfism. *Lancet.* 1970;1(7652):893–894

14. Wilson DM, Enzmann DR, Hintz RL, Rosenfeld. Computed tomographic findings in septo-optic dysplasia: Discordance between clinical and radiological findings. *Neuroradiology.* 1984;26(4):279–283

15. Williams J, Brodsky MC, Griebel M, et al. Septo-optic dysplasia: the clinical insignificance of an absent septum pellucidum. *Dev Med Child Neurol.* 1993;35(6):490–501

16. Burke JP. Optic nerve hypoplasia, encephalopathy, and neurodevelopmental handicap. *Br J Ophthalmol.* 1991;75(4):236–239

17. Hellström A, Wiklund LM, Svensson E. The clinical and morphologic spectrum of optic nerve hypoplasia. *J AAPOS.* 1999;3(4):212–220

18. Teär Fahnehjelm K, Wide K, Flodmark, Ek U, Hellström A. Posterior ocular malformations in children: somatic, neuroradiological and cognitive aspects. *Acta Pædiatr.* 2003;92(3):301–308

19. Birkabaek NH, Patel L, Wright NB, et al. 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(11):5281–5286

20. Singh J, Ghose S, Vashisht S, Goulatia RK. Optic nerve hypoplasia; clinical and ultrasonographic study. *Can J Ophthalmol.* 1985;20(6):205–210

21. Ek U, Fernell E, Jacobson L. Cognitive and behavioural characteristics in blind children with bilateral optic nerve hypoplasia. *Acta Paediatr.* 2005;94(10):1421–1426

22. Borchert M, McCulloch D, Rother C, Stout AU. Clincal assessment, optic disk measurements, and visual-evoked potential in optic nerve hypoplasia. *Am J Ophthalmol.* 1995;120(5):605–612

23. Zeki SM, Dudgeon J, Dutton GN. Reappraisal of the ratio of disc to macula/disc diameter in optic nerve hypoplasia. *Br J Ophthalmol.* 1991;75(9):538–541

24. Holladay J. Proper method for calculating average visual acuity. *J Refract Surg.* 1997;13(4):388–391

25. Newborg J, Stock J, Wnek L. *The Battelle Developmental Inventory.* Allen, TX: DLM Teaching Resources; 1988

26. Reidl SW, Müllner-Eidenböck 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(suppl 3):16–19

27. Griffiths P, Hunt S. Specific spatial defect in a child with septo-optic dysplasia. *Dev Med Child Neurol.* 1984;26(3):391–400

28. Miller SP, Shevell MI, Patenaude Y, Poulin C, O'Gorman AM. Septo-optic dysplasia plus: a spectrum of malformation of cortical development. *Neurology.* 2000;54(8):1701–1703

29. Garcia ML, Ty EB, Taban M, David Rothner A, Rogers D, Traboulsi EI. Systemic and ocular findings of 100 patients with optic nerve hypoplasia. *J Child Neurol.* 2006;21(11):949–956

30. Giedd JN, Blumenthal J, Jeffries NO, et al. Development of the human corpus callosum during childhood and adolescence: a longitudinal MRI study. *Prog Neuropsychopharmacol Biol Psychiatry.* 1999;23(4):571–588

31. Cascio C, Styner M, Smith RG, et al. Reduced relationship to cortical white matter volume revealed by tractography-based segmentation of the corpus callosum in young children with developmental delay. *Am J Psychiatry.* 2006;163(12):2157–2163

32. Boger-Megiddo I, Shaw DWW, Friedman SD, et al. Corpus callosum morphometrics in young children with autism spectrum disorder. *J Autism Dev Disord.* 2006;36(6):733–739

33. Soto-Ares G, Joyes B, Laemaître MP, Vallée L, Pruvo JP. MRI in children with mental retardation. *Pediatr Radiol.* 2003;33(5):334–345

34. Barkovich AJ, Kuzniecky RI, Dobyns WB, Jackson GD, Becker LE, Evrard P. A classification scheme for malformations of cortical development. *Neuropediatrics.* 1996;27(2):59–63

35. Derksen-Lubsen G, Verkerk PH. Neuropsychologic development in early treated congenital hypothyroidism: analysis of literature data. *Pediatr Res.* 1996;39(3):561–566