Published in final edited form as:

J AAPOS. 2012 October ; 16(5): 418–423. doi:10.1016/j.jaapos.2012.05.012.

Newborn TSH in children with optic nerve hypoplasia: Associations with hypothyroidism and vision

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Abstract

Purpose—To assess in children with optic nerve hypoplasia (ONH) whether newborn screening (NBS) thyroid-stimulating hormone (TSH) measurements can detect central hypothyroidism and whether newborn TSH or subsequent thyroidal status is associated with visual function.

Methods—A subset of patients in the registry of children with ONH at Children's Hospital Los Angeles who were born in California was used to make a retrospective comparison of NBS TSH levels and subsequent postnatal thyroid status. Another subset of registry subjects with vision and thyroid status data at age 5 years was assessed for the relationship of vision to NBS TSH levels and ultimate thyroidal status.

Results—A total of 135 subjects from the ONH registry were included in this study. Approximately 50% of subjects in each analysis were hypothyroid. Those diagnosed with hypothyroidism had lower median NBS TSH levels than did euthyroid subjects (3.2 vs 4.5 μ IU/mL; $P = 0.006$) and significantly worse quantitative vision outcomes (median visual acuity, logMAR 3.0 vs 1.0; $P = 0.039$). Receiver operating characteristic analysis suggested an optimal NBS TSH cut-point of 3.3 μ IU/mL. Serum TSH over this level (30/43) was associated with relatively better vision outcomes (median visual acuity, logMAR 1.2 vs 3.3; $P = 0.04$).

Conclusions—Children with ONH and lower NBS TSH levels are more likely to have central hypothyroidism and less likely to experience good vision than those with higher NBS TSH levels.

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Study conducted at Children's Hospital Los Angeles.

Preliminary data presented at the 17th Annual Meeting of the International Neuro-Ophthalmology Society (INOS), Napa, California, June 7–12, 2008.

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Optic nerve hypoplasia (ONH) is a leading cause of vision impairment in children. Characterized by nonprogressive dysgenesis of one or both optic nerves, ONH is frequently associated with pituitary hormone deficiencies.¹⁻⁴ Central hypothyroidism in these children is of particular importance because of the developmental delays that may result from delayed diagnosis. Our previous studies of children in the ONH research registry of Children's Hospital Los Angeles showed that 43% had central hypothyroidism, and that this was associated with a 12.5-fold increased risk for cognitive delay.⁵

Thyroid hormone (TH) is crucial for brain development during the first few months to years of life.⁶⁻⁸ TH influences neuronal migration, axonal outgrowth, and myelination within the central nervous system.⁹⁻¹³ To help reduce mental retardation, all states in the US have mandated newborn screening (NBS) programs for congenital primary hypothyroidism.^{14,15} In 18 states, including California, NBS involves initial measurement of thyroid-stimulating hormone (TSH), elevations of which prompt confirmatory evaluation of thyroid function.¹⁵ Low TSH levels are not reported; however, children with central hypothyroidism can have low, normal, or mildly elevated TSH levels.¹⁶ Thus they are not identified with TSH-based NBS methods and may not be diagnosed until a later age, when symptoms become apparent.^{17,18} The first aim of the present study was to assess whether NBS TSH levels are predictive of subsequent diagnosis of central hypothyroidism in children with ONH. The second was to assess whether indices of thyroid status (either the NBS TSH or the subsequent thyroid status) correlates with visual function or visual development in children with ONH. While clinically apparent visual dysfunction is not a classic feature of congenital primary hypothyroidism, transiently low TH levels in preterm infants have been associated with visual deficits at 6 months of (corrected) age.¹⁹ Furthermore, hypothyroidism may affect vision more in the setting of coexisting optic nerve disease than it does in isolation. For example, our clinical registry study of subjects with ONH demonstrates that most children with ONH experience some degree of spontaneous improvement in vision during the first few years of life^{4,20}; we hypothesize that low circulating TH levels may preclude vision improvement in previously compromised optic nerves that are already at risk for reduced vision.

Methods

In 1992 Children's Hospital Los Angeles established an ONH registry to collect ophthalmological, endocrinological, and neuropsychological data from subjects with a diagnosis of ONH in at least one eye. As of November 2007, this registry had clinical data for 214 subjects diagnosed with ONH at <36 months of age by a single neuro-ophthalmologist. Children in the registry are followed annually through 5 years of age. Clinical data collected include initial and annual visual acuity, optic nerve size measured from fundus photographs using the ratio of horizontal disk diameter to the disk-macula distance (DD/DM),²⁰ and comprehensive endocrine testing, including both free thyroxine (T4) and TSH measurements to evaluate thyroidal status. Endocrine data are collected from the treating endocrinologist, and repeat thyroid function testing is performed at least once for the study. The study samples for this report were drawn from this ONH registry. The details of this study's methodology are described elsewhere.^{3,5} The registry was approved by the Children's Hospital Los Angeles Committee on Clinical Investigations and the State of California Committee for the Protection of Human Subjects and conforms to the requirements of the United States Health Insurance Portability and Accountability Act. Informed consent was obtained from the subjects' mothers at the time of study enrollment.

Newborn Screening

NBS TSH results were retrospectively acquired from the Genetic Disease Branch of the Department of Health Services for those subjects born in California. Subjects who were

adopted were not included because identifying birth information was not available to acquire their data. Subjects without available NBS results were excluded from analyses that required this information.

Thyroidal Status

All subjects had thyroid function tests performed at the time of study enrollment and subsequently as clinically indicated. Pediatric endocrinologists who were masked from the NBS and vision data independently reviewed the thyroid function test results and treatment history, and assigned thyroidal status. The reference ranges reported by the various laboratories defined abnormal results. Subjects were categorized as hypothyroid if there was evidence of low TH levels or if they were started on TH replacement by their treating providers. Subjects were categorized as euthyroid if their last available measurements of thyroid function were normal without treatment.

Vision

The neuro-ophthalmologist investigator (MB) measured best-corrected visual acuity at the final study visit (5 years of age) using Snellen eye charts or linear “E” or Allen figures for illiterate subjects. Those with visual acuity <20/200 were assessed with a “tumbling E” from a distance of <20 feet. The worst Snellen-equivalent visual acuity that could be thus measured was 20/8000. Snellen visual acuity from 20/20 to 20/8000 was converted to the negative log of the minimum angle of resolution (logMAR), yielding values that ranged from 0.0 to 2.6, respectively. Motion perception was rated as comparable to logMAR 3.0,²¹ light perception as 3.3, and no light perception as 4.0. The appropriate logMAR values for light perception and no light perception are disputed because these vision categories are not considered visual acuities²¹; however, assignment of values for use in research is acceptable as long as nonparametric (eg, rank order) statistical tests are used.²²

The subjects’ initial visual acuity was categorized qualitatively because age precluded quantitative measurement. Qualitative vision descriptions (based on fixation and pursuit behavior) were grouped into six categories (Table 1). Final quantitative vision measures were also assigned to corresponding categorical variables to enable comparison with initial assessment (Table 1).

In order to eliminate the confounding effect of amblyopia, the eye with better final vision was used. Consequently, vision analysis included only subjects with vision outcome data and bilateral ONH, because children with unilateral ONH were not expected to show effects of hypothyroidism on vision in the normal eye.

Statistical Analysis

Data analysis was performed using Stata 8.0 (College Station, TX). Data were not normally distributed and thus are presented as median values with 5th and 95th percentiles. Nonparametric statistical tests were employed.

The distributions of NBS TSH levels were compared between euthyroid and hypothyroid subjects using receiver operating characteristic (ROC) curve analysis. An appropriate cut-point was established to estimate predictive values for detection of central hypothyroidism and to stratify and compare subjects with final quantitative vision. The optimal threshold was identified by examining the sensitivity and specificity of the NBS TSH levels for hypothyroid status.

A separate analysis of all subjects with final quantitative vision stratified by thyroidal status was performed to detect differences in vision outcomes. Final quantitative vision on the

logMAR scale was analyzed by nonparametric methods (Mann-Whitney-Wilcoxon test), enabling inclusion of subjects with motion perception or worse by assignment of higher ordinal logMAR values (Table 1). Subjects with nonquantitative final vision (based only on fixation and pursuit behavior) were excluded from analysis.

Analysis of vision improvement was performed by comparing initial to final vision categories among those with final quantitative vision. Vision improvement was classified dichotomously using various thresholds to define improvement (eg, improvement by two or more categories, or improvement by three or more categories). Each such analysis excluded those subjects whose vision was too good to allow for the threshold level of improvement (eg, only those with initial vision equal to, or worse than, category 3 could potentially improve by two categories or more).

The Mann-Whitney-Wilcoxon test was applied to detect differences in continuous variables between groups and the Wilcoxon signed-rank test was used for comparisons between paired measurements. Categorical variables were analyzed with the χ^2 or the Fisher exact test. Statistical significance was set at $\alpha < 0.05$ with two-sided alternative hypotheses.

Results

A total of 135 subjects in the ONH registry database had the requisite clinical data to be included in one or more analysis (Table 2).

NBS data were available for 94 subjects in the registry (Figure 1), 78 of whom had subsequent thyroidal function determined. The NBS TSH levels in subjects with central hypothyroidism were significantly lower (median, 3.2 μ IU/mL; 5th and 95th percentiles, 1.7 and 7.1) than in euthyroid subjects (median, 4.5 μ IU/mL; 5th and 95th percentiles, 1.0 and 13.8; $P = 0.006$). A TSH threshold of 3.3 μ IU/mL provided the optimal cut-point in the ROC analysis [0.70 (95% CI, 0.59–0.82)]. For a NBS TSH level ≤ 3.3 μ IU/mL, the positive predictive value for central hypothyroidism was 69%; the negative predictive value, 63%. The specificity and sensitivity were 56% and 74%, respectively.

Of those with NBS data, 43 subjects had bilateral ONH and final quantitative vision measurements at age 61.7 ± 4.4 months (Figure 2). There was no statistically significant difference in NBS TSH levels between those with and without final quantitative vision measurement ($P = 0.16$). The initial vision categories between those with NBS TSH ≤ 3.3 μ IU/mL and those with NBS TSH > 3.3 μ IU/mL were not significantly different ($P = 0.18$). Final quantitative vision was better in those with a NBS TSH level > 3.3 μ IU/mL (median, logMAR 1.2; 5th and 95th percentiles, logMAR 0.40 and 3.3 vs median logMAR 3.3; 5th and 95th percentiles, logMAR 0.13 and 4; $P = 0.040$). Compared to subjects with a NBS TSH ≤ 3.3 μ IU/mL, a greater number of cases with NBS TSH > 3.3 μ IU/mL experienced vision improvement by at least one category (79% vs 42%; $P = 0.020$) and by at least two categories (44% vs 17%; $P = 0.110$). Indisputable improvement in categorical vision (ie, from only light perception behavior or worse [categories 5 and 6] to quantifiable vision [categories 1–3]) occurred in 2 of 11 subjects with NBS TSH ≤ 3.3 μ IU/mL and in 7 of 19 subjects with NBS TSH > 3.3 μ IU/mL. This difference was not statistically significant ($P = 0.419$). Subjects with NBS TSH > 3.3 μ IU/mL also tended to have a larger relative optic disk size than those with a NBS TSH ≤ 3.3 μ IU/mL (DD/DM 0.20 ± 0.08 vs 0.16 ± 0.06 ; $P = .058$) in the better eye.

Final vision measurements at age 60.2 ± 6.3 months and current thyroidal status determined by serum TH levels and treatment history were available for 117 subjects in the registry, with or without known NBS TSH levels (Figure 2), of whom 97 had bilateral ONH and were included in this analysis. Of the 97 subjects with bilateral ONH, central hypothyroidism was

diagnosed in 52 (54%); of the 20 subjects with unilateral ONH, only 3 (15%) had hypothyroidism ($P = 0.002$).

Presenting vision at the time of study enrollment did not differ between euthyroid and hypothyroid subjects (Fisher exact test; $P = 0.136$), although vision status of category 1 was more common among euthyroid than hypothyroid subjects ($P = 0.040$). Initial categorical vision status could not be confidently determined in 1 of the 97 bilaterally affected subjects. Differences in the age at time of initial vision assessment were not significant between subjects with (12.7 ± 12.9 months) and without (14.6 ± 22.5 months) hypothyroidism ($P = 0.46$).

Final quantitative vision was available in 82 of 97 bilateral cases (85%), of whom 43 (52%) were categorized as hypothyroid. There was no difference in the frequency of hypothyroidism ($P = 0.78$) between those with and without final quantitative vision. The severity of ONH was marginally greater in those without final quantitative vision compared to those with final vision (DD/DM 0.16 ± 0.07 vs 0.23 ± 0.13 , $P = 0.043$). Overall, final logMAR visual acuity in euthyroid subjects (median, 1.0; 5th and 95th percentiles, 0.14 and 4) was better than in subjects with hypothyroidism (median, 3.0; 5th and 95th percentiles, 0.3 and 4.0; $P = 0.039$). Euthyroid subjects were also more likely to have categorical improvement in vision by at least one category (81% vs 66%) and by at least two categories (54% vs 31%), although these differences did not reach statistical significance. Euthyroid subjects had significantly larger relative optic disk size in the better eye compared to hypothyroid subjects (DD/DM, 0.26 ± 0.13 vs 0.18 ± 0.10 ; $P = 0.001$).

Discussion

ONH is a major risk factor for central hypothyroidism, which is itself a cause of developmental delay; 93% of children with ONH and hypothyroidism have developmental delay.⁵ Diagnosis of hypothyroidism in ONH is often delayed. In a large study of children with ONH, Garcia-Filion and colleagues⁵ reported that 52% of children with hypothyroidism were not diagnosed prior to the time of study enrollment (mean age, 15.7 months). Since the first few years of life represent a critical treatment window, significant and irreversible brain damage may have already occurred by the time hypothyroidism is diagnosed in most children with ONH.

More comprehensive newborn screening for central hypothyroidism could result in earlier diagnosis and treatment of affected children.^{16–18,23} However, there is some controversy regarding the best screening strategy (TSH and/or T4 level). In the current study of subjects with ONH, those with central hypothyroidism had lower NBS TSH levels than did those with normal thyroidal function. However, the NBS TSH cut-point identified in this study ($3.3 \mu\text{IU/mL}$) generated a suboptimal sensitivity (74%) and specificity (56%) for an eventual diagnosis of central hypothyroidism. Low sensitivity could be due in part to the fact that children with ONH are at risk for late-onset central hypothyroidism²⁴ and children with a later onset would have normal NBS TSH levels. Due to the range of enrollment ages in this analysis, we were unable to differentiate between those children with early-onset central hypothyroidism and those with evolving central hypothyroidism. Additionally, subjects were determined to be euthyroid at a relatively young age (median age, 16 months; 5th and 95th percentiles, 3.4 and 56.3); we do not know whether any of these subjects may have developed central hypothyroidism at a later age. This may have contributed to low specificity of NBS TSH.

Based on these results, it may be possible to detect central hypothyroidism in newborns by modifying the reportable NBS TSH levels to include low results. Further prospective studies

are necessary to define the appropriate NBS TSH cut-off and the cost-effectiveness of such an approach compared to alternative screening methods.

Several prior studies have shown an association between visual deficits in children and insufficient TH in the prenatal and/or neonatal period.^{6,19,25} These studies have mostly noted deficits in visual processing (such as contrast sensitivity, color vision, and visual-motor skills) and not in visual acuity; however, they included relatively small cohorts and reported vision outcomes only after a short period of time, and quantifying differences in visual acuity may not have been possible.

The present study demonstrates the association between thyroid function and vision at age 5 years in children with ONH. The initial categorical vision was not different between groups with NBS TSH ≤ 3.3 $\mu\text{IU/mL}$ and >3.3 $\mu\text{IU/mL}$ or between the hypothyroid and euthyroid groups. However, subjects with NBS TSH levels ≤ 3.3 $\mu\text{IU/mL}$ and those with hypothyroidism were more likely to have worse vision by age 5 years. In addition, longitudinal vision improvement was more common in children with higher NBS TSH levels. Indisputable improvement in categorical vision (ie, from only light perception behavior, or worse, to quantifiable vision) occurred in 37% of subjects with NBS TSH >3.3 $\mu\text{IU/mL}$ and in only 18% of subjects with NBS TSH ≤ 3.3 $\mu\text{IU/mL}$. Although this difference was not statistically significant, more modest categorical vision improvement was significantly associated with NBS TSH >3.3 $\mu\text{IU/mL}$. A similar but not statistically significant pattern was detected in the comparison between thyroidal statuses, with improvement in categorical vision more likely in the euthyroid group.

That vision was similar at enrollment but differed significantly at age 5 years in euthyroid children and in those with higher NBS TSH levels and that the latter group shows more longitudinal improvement over time suggest that thyroid status might influence postnatal vision improvements in children with ONH. There are two important caveats to this conclusion. First, hypothyroidism in this analysis was also associated with the severity of ONH, based on relative optic disk size, which may limit the potential for vision improvement. Second, hypothyroidism is associated with developmental delays that may affect visual acuity test performance. It should also be noted that the vision improvement estimated in this study suffers from lack of precision and from lack of validation of the method for comparing categories of visual behavior with quantifiable visual acuity. Finally, we have insufficient data to evaluate the effect that either evolving hypothyroidism or early treatment may have had on the vision outcome in this study.

In conclusion, although neonatal TSH levels are associated with subsequent thyroid status in children with ONH, the best method for detecting central hypothyroidism in neonates remains unclear. Central hypothyroidism appears to be associated with worse vision outcomes in children with ONH, in addition to developmental delay, but further studies are needed to determine whether early detection and treatment of hypothyroidism in children with ONH may improve neurological development or vision outcomes. Until this is known, clinicians should evaluate thyroidal status promptly following the diagnosis of ONH.

Acknowledgments

Supported in part by the One Small Voice Foundation and Grant Number 1UL1RR031986, Children's Hospital Los Angeles Clinical Translational Science Institute, with funds provided by the National Center for Research Resources (NCRR), NIH.

The authors thank Steven Mittelman, MD, PhD, and Kristina Tarczy-Hornoch, MD, DPhil, for critically reviewing the manuscript.

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FIG 1. NBS TSH as a predictor of thyroidal status. **Difference is statistically significant ($P < 0.05$).

FIG 2.

NBS TSH and thyroidal status: Relationships to vision outcomes. *Initial vision was not determinable in 1 subject. **Difference is statistically significant ($P < 0.05$).

Table 1

Categories of visual acuity

Category	Qualitative description	Quantitative logMAR VA ^a
1	Fixation and pursuit of a 1-inch toy at 1 foot	1.0 (20/200)
2	Fixation and pursuit of a 6-inch toy at 1 foot	>1.0–1.6 (<20/200–20/800)
3	Poor fixation and ability to follow a face or large toy	>1.6–2.6 (<20/800–20/8000)
4	Behavioral response to motion	3.0
5	Behavioral response to light	3.3
6	No visual behavior	4.0

VA, visual acuity.

^aSnellen equivalent.

Table 2

Demographics and clinical characteristics

Characteristics	Percent ^a	n/N
Sex		
Male	53	71/135
Ethnicity		
Caucasian	38	51/135
Hispanic	44	59/135
African American	3	4/135
Asian/Pacific Islander	2	3/135
Other	8	11/135
Mixed	5	7/135
Endocrinopathies ^b		
GH deficiency	70	82/118
Hypothyroidism	43	54/127
Adrenal insufficiency	30	38/126
Neuroradiographic abnormalities ^b		
Corpus callosum hypoplasia	48	61/128
Absent septum pellucidum	41	52/128
Laterality		
Bilateral	82	111/135

^aPercentages are rounded up to the nearest integer and may not total 100.

^bPercentages are not mutually exclusive. The total number of subjects varies depending on available laboratory tests and imaging results.