

# ENDOCRINOLOGICAL AND AUXOLOGICAL ABNORMALITIES IN YOUNG CHILDREN WITH OPTIC NERVE HYPOPLASIA: A PROSPECTIVE STUDY

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**Objective** To determine the prevalence of endocrinopathies, neuroradiographical findings, and growth derangements in young children with optic nerve hypoplasia (ONH).

**Study design** A prospective observational study examined the prevalence of endocrinopathies at study enrollment and growth patterns in children with ONH. Subjects ( $n = 47$ , mean  $\pm$  SD  $15.2 \pm 10.6$  months) were followed until  $59.0 \pm 6.2$  months of age.

**Results** The prevalence of endocrinopathies was 71.7%: 64.1% of subjects had growth hormone (GH) axis abnormalities, 48.5% hyperprolactinemia, 34.9% hypothyroidism, 17.1% adrenal insufficiency, and 4.3% diabetes insipidus (DI). Endocrinopathies were not associated with ONH laterality, absence of the septum pellucidum, or pituitary abnormalities on neuroimaging. End height standard deviation score (SDS) was similar to start length SDS independent of GH surrogate status. A significant increase in end weight SDS was found for the cohort ( $p < .001$ ). A body mass index (BMI)  $>85^{\text{th}}$  percentile was noted in 44.4% of the cohort and in 52.1% of subjects with GH axis abnormalities. Initial hyperprolactinemia was positively associated with increased end BMI SDS ( $p = .004$ ).

**Conclusions** These prospective findings confirm the high prevalence of pituitary endocrinopathies in children with ONH reported in previous retrospective studies. Our data reveal that some of these children maintain normal height velocity despite GH axis abnormalities, and, as a group, they are at high risk for increased BMI. (*J Pediatr* 2006;148:78-84)

**D**e Morsier described an association between optic nerve hypoplasia (ONH) and an absent septum pellucidum in 1956, termed *septo-optic dysplasia*.<sup>1</sup> The significance of septo-optic dysplasia as a medical entity gained momentum when an association with pituitary dwarfism was noted in 1970 in three cases by Hoyt et al<sup>2</sup> and in a single case by Ellenberger and Runyan.<sup>3</sup> A series of 25 cases of ONH reported by Edwards and Layden the same year failed to note any endocrinological defects, despite numerous cases with neurological impairments.<sup>4</sup> Because this report preceded the era of computerized tomography scans, the prevalence of mid-line brain defects in these cases was unknown. Nonetheless, in a subsequent large series of cases, hypopituitarism occurred at a high frequency and was felt to be present almost exclusively in bilateral severe cases, with or without agenesis of the septum pellucidum.<sup>5</sup> Other studies have disputed whether or not laterality of ONH or radiological evidence of mid-line brain abnormalities affects the risk for hypopituitarism.<sup>6-9</sup> All of these and subsequent series have suffered from ascertainment bias, incomplete clinical documentation, and/or limitations of retrospective chart reviews. There have been no prospective studies to date analyzing the clinical outcomes of children with ONH.

ONH is the most common congenital optic disc anomaly and the leading single cause of blindness in infants and toddlers, with a current prevalence of 6.3/100,000 children.<sup>10</sup> Since its first description, it has become apparent that ONH can occur in association

See related article, p 85.

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BMI	Body mass index	IGF-I	Insulin-like growth factor-I
DI	Diabetes insipidus	ONH	Optic nerve hypoplasia
GH	Growth hormone	PWS	Prader-Willi syndrome
GHD	Growth hormone deficiency	SDS	Standard deviation scores
IGFBP-3	Insulin-like growth factor binding protein-3		

with pituitary endocrinopathies, with or without mid-line defects of the central nervous system.<sup>11</sup> The most prevalent of these endocrinopathies is thought to be growth hormone (GH) deficiency (GHD).<sup>12,13</sup> Interestingly, several patients with ONH and GHD have been described with normal growth during infancy and early childhood.<sup>14</sup> Although various hypotheses have been proposed to explain this phenomenon, including increased serum levels of insulin or an unrecognized circulating growth-promoting factor, the exact mechanism remains unknown.<sup>15</sup> The implications of normal growth in the endocrine evaluation of patients with ONH remain unclear. The purpose of this study was to determine the prevalence of endocrine dysfunction and growth outcomes in a prospective observational investigation of a large cohort of young children with ONH.

## METHODS

The pediatric ophthalmology clinic at Childrens Hospital Los Angeles serves as a referral center for patients with ONH from all over the United States. This prospective study was designed to evaluate the clinical risk factors for adverse endocrine, growth, visual, neurological, and neuropsychological outcomes. Subjects with a diagnosis of ONH were offered enrollment into the study if they were <36 months of age. After collecting baseline endocrinological, electrophysiological, and neuroradiological findings, subjects were followed annually until 5 years of age for visual, growth, and neurodevelopmental outcomes. One hundred and seventy subjects have been enrolled since 1992. Herein, we report the endocrinological and growth outcomes of the first 47 subjects to complete the study. Results of visual, neuroradiological, neurological, and neuropsychological outcomes will be reported elsewhere.

### Subjects

Characteristics of the cohort are reported in Table I. A diagnosis of ONH and laterality of disease were determined by a single pediatric neuroophthalmologist (MB). In all cases the diagnosis was confirmed by ocular fundus photography.<sup>16,17</sup> In eyes with ONH, the ratio of disc diameter to the disc-macula distance was 0.35 or below, whereas in eyes without ONH the ratio was above 0.35. A single neuroradiologist, who was masked to each subject's clinical characteristics and outcomes, determined neuroradiological abnormalities. Thirty-nine subjects had neuroimaging performed (25 magnetic resonance imaging and 14 computed tomography).

Informed consent was obtained from the parents of all subjects. The study was approved by the Committee on Clinical Investigations (Institutional Review Board) at Childrens Hospital Los Angeles.

### Endocrine Investigations

Assessment of endocrine dysfunction was based on treatment for hormone deficiencies and/or laboratory testing for GH axis abnormalities, hyperprolactinemia, hypothyroidism, adrenal insufficiency, and diabetes insipidus (DI) obtained at or before enrollment. Abnormalities of the GH axis were based

**Table I. Characteristics of Cohort**

	% (#/47)
Gender	
Male	61.7 (29)
Female	38.3 (18)
Referral Source	
Ophthalmologist	34.0 (16)
Pediatrician	12.8 (6)
Self	14.9 (7)
Neurologist	6.4 (3)
Visually Handicapped Service Provider	6.4 (3)
Endocrinologist	4.3 (2)
Optometrist	4.3 (2)
Unknown	17.0 (8)
Race/Ethnicity	
Hispanic	44.7 (21)
White	34.0 (16)
Asian-Pacific Islander	6.4 (3)
Other	14.9 (7)
Laterality of ONH	
Unilateral	19.1 (9)
Bilateral	80.9 (38)
Endocrinopathies <sup>†</sup>	
GH axis abnormality <sup>a</sup>	64.1 (25/39)
Hyperprolactinemia	48.5 (16/33)
Hypothyroidism	34.9 (15/43)
Adrenal insufficiency	17.1 (7/41)
Diabetes insipidus	4.3 (2/47)

<sup>†</sup>Total number of subjects varies based on available laboratory test results.  
<sup>a</sup>GH axis abnormality is defined as subnormal GH stimulation test and/or subnormal age-appropriate GH surrogate levels. Four subjects were deemed to have a GH axis abnormality based on outside initiation of GH treatment prior to enrollment.

on either decreased serum concentrations of GH surrogates (insulin-like growth factor-1 [IGF-1] and/or IGF binding protein-3 [IGFBP-3]) or subnormal serum GH responses to glucagon stimulation (GH peak <10 ng/mL). Four subjects were placed on GH replacement therapy by their treating physician before their enrollment in the study and were deemed to have an abnormality of their GH axis, but they were excluded from the auxological statistical analyses (described below) because serum GH surrogate studies were unavailable. Hyperprolactinemia was defined as a serum prolactin level  $\geq 18$  ng/mL for males and  $\geq 20$  ng/mL for females (the youngest subject in our cohort who underwent measurement of a serum prolactin level was 2.5 months of age).<sup>18</sup> We accepted criteria for central hypothyroidism, central hypoadrenalism, and central DI as determined by the treating pediatric endocrinologist. Acquisition of baseline laboratory data was at the discretion of the treating endocrinologist and may have been limited by managed care organizations. As a result, prevalence of endocrinopathies was restricted to those with available laboratory data at the time of study enrollment.

**Table II. The Distribution of Endocrinopathies for Subjects With and Without Abnormalities of the Septum Pellucidum and Pituitary Gland (#, %)**

	Septum Pellucidum (n = 39)		Pituitary Gland (n = 37)			Imaging Data
	Absent (n = 11)	Present (n = 28)	Abnormal (n = 2)	Normal (n = 35)	Unknown (n = 2)	Unknown (n = 8)
Any Endocrinopathy	7 (63.6)	21 (75)	2 (100)	25 (71.4)	1 (50)	5 (62.5) <sup>†</sup>
GH Axis Abnormalities	5 (45.5)	16 (57.1)	2 (100)	18 (51.4)	1 (50)	4 (50)
Hyperprolactinemia	4 (36.4)	10 (35.7)	1 (50)	12 (34.3)	1 (50)	2 (25)
Hypothyroidism	2 (18.2)	11 (39.3)	2 (100)	11 (31.4)	0 (0)	2 (25)
Adrenal Insufficiency	1 (9.1)	5 (17.9)	2 (100)	4 (11.4)	0 (0)	1 (12.5)
Diabetes Insipidus	1 (9.1)	1 (3.6)	0 (0)	2 (5.7)	0 (0)	0 (0)

†There was no difference in the prevalence of “any endocrinopathy” for subjects with or without neuroradiographic data ( $p = 0.669$ ).

### Auxological Data

Growth measurements (performed prospectively in our institution) included length/height (recumbent length was used until 3 years of age) and weight. For the sake of brevity, hereafter length/height will be referred to as height. Body mass index (BMI) was calculated at the end of the study because measurements of BMI have only been validated in children >2 years of age.<sup>19</sup> Absolute height, weight, and BMI measurements were normalized for age and sex by conversion to standard deviation scores (SDS) using Epi Info Version 3.2.2 (a nutrition anthropometry program that calculates percentiles and SDS using the 2000 Centers for Disease Control growth references).<sup>20</sup> BMI categories (based on 2000 Centers for Disease Control guidelines) were as follows: underweight (<5<sup>th</sup> percentile), at risk for being underweight (5<sup>th</sup>-15<sup>th</sup> percentile), normal (15<sup>th</sup>-85<sup>th</sup> percentile), at risk for being overweight (85<sup>th</sup>-95<sup>th</sup> percentile), and overweight (>95<sup>th</sup> percentile).<sup>21</sup>

To analyze the influence of GH surrogate status on growth outcomes, subjects who had both surrogates assessed were dichotomized as “both normal” or “at least one abnormal.” Auxological data were then analyzed by GH surrogate status to detect differences in median height SDS change, median weight SDS change, and median end BMI SDS. To eliminate potential treatment bias, all subjects on GH replacement therapy were removed and only the untreated subjects were evaluated for differences according to GH surrogate status. An additional analysis was conducted to examine the effect of GH replacement therapy versus untreated on auxological outcomes of subjects with at least one abnormal GH surrogate.

### Statistical Methods

Data analysis was performed with Statistical Analysis Systems version 9.0 to evaluate endocrine and growth outcomes in the cohort. The data were examined for associations between endocrine findings, ONH laterality, neuroradiological abnormalities, and growth outcomes. Continuous auxological variables were not normally distributed and, thus, the data are presented as median SDS with the 5<sup>th</sup> and 95<sup>th</sup> percentiles, and are analyzed with the appropriate nonparametric method. Data on weight were adjusted for height using regression analysis. Comparisons of unadjusted and adjusted results are

provided when there is a difference between them. The statistical significance level was defined as  $\alpha = .05$ , with two-sided alternative hypotheses.

Analyses evaluating associations between the presence of a pituitary endocrinopathy and either ONH laterality, a neuroradiological abnormality, or absence of the septum pellucidum were performed with Fisher’s exact test of association.

Analyses evaluating associations between unilateral versus bilateral ONH, hyperprolactinemia, and short stature (defined as height <-1 SDS) versus elevated BMI (defined as >85<sup>th</sup> percentile)<sup>21</sup> were performed with Fisher’s exact test. Spearman’s correlation test was used to evaluate the association between initial serum prolactin levels and both end BMI SDS and end height SDS.

## RESULTS

### Prevalence of Endocrinological Abnormalities

The distribution of specific endocrinopathies is listed in Table I. Hormonal dysfunction was present in 71.7% of subjects ( $n = 33/46$ ).

There was no association between endocrine abnormalities and unilateral versus bilateral ONH ( $p = .698$ ). Among those with neuroradiographical data, two subjects could not be assessed for pituitary gland abnormalities because of poor scan quality. Overall, 11 subjects had an absent septum pellucidum and two had abnormalities of the pituitary gland with an intact septum pellucidum (one had an ectopic neurohypophysis and absent infundibulum, and one had isolated ectopic neurohypophysis). The presence of endocrinopathies based on absence of the septum pellucidum or pituitary abnormalities on neuroimaging is presented in Table II. Of the 25 children with a normal pituitary gland on neuroimaging and an associated endocrinopathy, 18 had an intact septum pellucidum. Neither the presence of a radiological abnormality of the pituitary gland ( $p = 1.00$ ) nor the absence of the septum pellucidum ( $p = 1.00$ ) was associated with endocrinological dysfunction. There was no statistical difference in the presence of “any endocrinopathy” for those subjects with neuroradiographical data compared with those without data ( $p = .669$ ).

**Table III. Auxological Outcomes (SDS) for the Study Cohort**

n = 36 <sup>†</sup>	Start		End		Change <sup>‡</sup>	
	Median	5% & 95%ile	Median	5% & 95%ile	Median	5% & 95%ile
Height <sup>a</sup>	+0.17	-3.23, +1.96	-0.34	-2.00, +2.29	+0.53	-2.85, +2.22
Weight <sup>b</sup>	-0.24	-2.62, +3.04	+0.33	-1.80, +3.13	+0.89	-1.61, +2.43
BMI	-	-	+0.84	-0.94, +3.30	-	-

<sup>†</sup>Complete auxological data were not available for 11 subjects.

<sup>‡</sup>Change was calculated as the median of all individual differences between end and start values.

<sup>a</sup>There was no significant difference between start and end height SDS ( $p = 0.56$ ).

<sup>b</sup>There was a significant difference between start and end weight SDS ( $p < 0.001$ ).

**Table IV. Auxological Outcomes (SDS) stratified by GH surrogate\* status after separating by GH replacement therapy**

	# <sup>†</sup>	Change in Height SDS		Change in Weight SDS <sup>a</sup>		End BMI SDS	
		Median (5%, 95%)	p-value	Median (5%, 95%)	p-value	Median (5%, 95%)	p-value
<b>GH Replacement Therapy</b>							
Normal IGF-I & IGFBP-3	0	-		-		-	
Abnormal IGF-I or IGFBP-3	8	+1.84 (-1.33, +4.87)	0.019 <sup>b</sup>	+1.26 (+0.16, +3.09)	0.622 <sup>b</sup>	+0.93 (-0.90, +4.47)	0.965 <sup>b</sup>
<b>No GH Replacement Therapy</b>							
Normal IGF-I & IGFBP-3	9	+0.08 (-2.68, +1.68)	0.348 <sup>c</sup>	-0.19 (-1.36, +2.43)	0.967 <sup>c</sup>	+0.68 (-0.30, +3.01)	0.624 <sup>c</sup>
Abnormal IGF-I or IGFBP-3	10	-1.39 (-3.94, +1.94)		+0.60 (-2.20, +1.69)		+1.22 (-1.16, +2.75)	

\*IGF-I = insulin-like growth factor-I; IGFBP-3 = insulin-like growth factor binding protein-3.

<sup>†</sup>Auxological and GH surrogate data were available for 27 subjects.

<sup>a</sup>Adjusted for change in height.

<sup>b</sup>GH replacement *vs.* no GH replacement therapy for subjects with at least one abnormal GH surrogate (weight: unadjusted  $p$ -value = 0.069).

<sup>c</sup>Normal *vs.* at least one abnormal GH surrogate for subjects not receiving GH replacement therapy.

## Auxological Data

Changes in height, weight, and end BMI SDS were available for 36 (77%) subjects with an interval period of observation ranging between 10 and 63 months (mean  $45.1 \pm 12.2$  months) and are reported in Table III. In this cohort, there was no statistically significant difference in the median start *versus* end height SDS ( $p = .56$ ), but a significant increase was noted for median end weight SDS ( $p < .001$ ). A calculation of the end BMI SDS revealed that 44.4% of the cohort was  $>85^{\text{th}}$  percentile.

## Auxological Data, GH Surrogate Status, and GH Replacement Therapy

Among the subjects with complete data, 27 (75%) had both GH surrogates assessed. For this subset (data not shown), the observed median changes in height and weight SDS were +0.08 (-2.85, +2.22) and +0.46 (-1.61, +2.43), respectively. End BMI SDS was +1.13 (-0.94, +3.30). The data, dichotomized as “both normal” or “at least one abnormal” GH surrogate, did not indicate a statistically significant difference in the median change in height ( $p = .817$ ), weight

( $p = .357$ , adjusted for height), or end BMI ( $p = .572$ ) SDS based on GH surrogate status.

The growth outcomes for this group, stratified by GH replacement therapy and GH surrogate status, are presented in Table IV. Each of the eight subjects receiving GH replacement therapy had at least one abnormal GH surrogate. Of the 19 subjects not on GH replacement therapy, 10 had at least one abnormal surrogate.

Among subjects with at least one abnormal GH surrogate, auxological data were examined for differences based on GH replacement therapy. As expected, the change in height was statistically significantly greater for children receiving GH replacement therapy ( $p = .019$ ). After adjustment for change in height, there was no statistically significant difference in the change in weight ( $p_{\text{adjusted}} = .622$ ,  $p_{\text{unadjusted}} = .069$ ). There was a slight difference in the BMI outcome, but it was not statistically significant ( $p = .965$ ).

Among subjects without GH replacement therapy ( $n = 19$ , Table IV), an apparent decrease in height and an increase in weight SDS was noted for subjects with at least one abnormal GH surrogate compared with those with normal levels, although it did not reach statistical significance ( $p = .348$  and



**Table V. Comparison of body mass index (BMI) outcomes for subjects with GH axis abnormalities compared to the cohort**

	BMI Percentiles			
	<15 <sup>th</sup> %ile <sup>‡</sup>	15 <sup>th</sup> –85 <sup>th</sup> %ile <sup>‡</sup>	85 <sup>th</sup> –95 <sup>th</sup> %ile <sup>‡</sup>	>95 <sup>th</sup> %ile <sup>‡</sup>
	n (%)	n (%)	n (%)	n (%)
Cohort (N = 36 <sup>†</sup> )	1 (2.8)	19 (52.8)	7 (19.4)	9 (25.0)
Subjects with abnormal GH axis (N = 23 <sup>†</sup> )	1 (4.4)	10 (43.5)	5 (21.7)	7 (30.4)

<sup>†</sup>Final BMI data unavailable for 11 subjects in the cohort (n = 36/47) and 2 subjects with GH axis abnormalities (n = 23/25).

<sup>‡</sup><15<sup>th</sup> %ile = below normal; 15<sup>th</sup>–85<sup>th</sup> %ile = normal; 85<sup>th</sup>–95<sup>th</sup> %ile = at risk for being overweight; >95<sup>th</sup> %ile = overweight.

.967, respectively). Moreover, the median end BMI SDS was nearly double for subjects with at least one abnormal GH surrogate. However, this finding also did not reach statistical significance ( $p = .624$ ).

### Body Mass Index and its Associations

BMI outcomes were available for 77% of the cohort and 92% of subjects with an abnormal GH axis (Table V). For the latter subgroup, BMI >85<sup>th</sup> percentile was present in 52.1% and 30.4% were >95<sup>th</sup> percentile. There were no subjects with an end BMI below the 5<sup>th</sup> percentile.

BMI was not found to be associated with a GH axis abnormality or ONH laterality,  $p = 1.0$  and  $.238$ , respectively. A statistically significant correlation, albeit a weak one, was detected for initial serum prolactin levels and end BMI SDS ( $r_s = 0.556$ ,  $p = .004$ ). To further illustrate the significant association of initial hyperprolactinemia and obesity, a cross-tabulation revealed that 66.7% (10/15) of those with increased initial serum prolactin had an end BMI >85<sup>th</sup> percentile, whereas 10.0% (1/10) with a normal initial prolactin level had an end BMI >85<sup>th</sup> percentile ( $p = .005$ ). There was no association between hyperprolactinemia and short stature ( $p = 0.691$ ) or between initial serum prolactin levels and end height SDS ( $r_s = -0.062$ ,  $p = .770$ ).

## DISCUSSION

Since de Morsier's description in 1956, it has become clear that multiple factors are involved in the development of ONH and its associated pathologies, including various pituitary endocrinopathies and their sequelae. Although the pathogenesis of this entity is still not understood, it is plausible that a defect or insult at a vulnerable time in gestation would lead to both visual and hypothalamic-pituitary disturbances because both systems form at approximately the same time.<sup>22</sup> Possible mechanisms include a disorder of neuronal migration, axonal development, or dysregulation of developmental neuronal apoptosis.<sup>23</sup> Although the pathogenesis remains unclear,

it is evident that the growth patterns of these children are unlike those of other children with congenital GHD.

We recognize that the diagnosis of GHD is becoming increasingly more difficult in general<sup>24,25</sup> and, in the face of obesity, is even more problematic. Several studies have found obesity to blunt GH release following administration of almost all GH secretagogues.<sup>26,27</sup> It has been suggested that low serum levels of IGF-1 and IGFBP-3 are more reliable indicators of GHD than are low stimulated GH levels in diagnosing GHD in obese adults and in obese children with Prader-Willi syndrome (PWS) because the levels of GH surrogates are typically normal in the setting of simple exogenous obesity.<sup>28–30</sup> However, some studies found decreased serum IGF-1 and others found elevated serum IGF-1 in obese children.<sup>31,32</sup> The optimal test for determining GHD in ONH has not been determined, but GH surrogates may be more useful than GH stimulation because of the heightened prevalence of increased BMI in this population. Although either reduced serum levels of GH surrogates and/or subnormal GH stimulation was used to infer a GH axis abnormality in our cohort, these results were obtained at study initiation, usually before the development of increased BMI. Thus, GH axis status was unlikely to be affected by any pre-existing obesity.

In this study, we attempted to elucidate prevalence rates of endocrinopathies in this particular population of young children with ONH and prospectively characterize their growth patterns over a period of time. Because of the nature of the data accrual, not all subjects could be assessed for all hormonal deficiencies at the time of enrollment or during the observational period. Despite these limitations, a number of interesting conclusions can be made.

Previously reported prevalence rates of endocrinopathies associated with ONH in retrospective studies have ranged between 27 and 81%.<sup>11,15,33–35</sup> Potential explanations for the varying ranges include small sample sizes in previous studies, diagnostic bias from subspecialty source (ophthalmologists and endocrinologists reported 27% and 81%, respectively), or hypothalamic-pituitary disease that had not fully manifested at the initial evaluation. Our prospective study confirmed a high prevalence of endocrinopathies and, in fact, may be an underestimation, as it did not consider the possibility of developing endocrinopathies in the future. Consistent with other studies, abnormalities of the GH axis were the most common endocrinopathy found in our cohort.<sup>14</sup>

Our cohort revealed no association between ONH laterality and an endocrinopathy. Although subjects with a pituitary abnormality on neuroimaging had an endocrinopathy, approximately 71% of those with a normal pituitary gland also had an endocrinopathy. Thus, the presence of an endocrinopathy was independent of laterality of ONH or neuroradiological findings (including pituitary abnormalities or absence of the septum pellucidum), illustrating the importance that all children with ONH should be considered at risk for endocrine dysfunction regardless of radiographical documentation of septo-optic dysplasia. The absence of an association of endocrinopathy with radiographical abnormalities contrasts with some previous reports.<sup>11,35</sup> These retrospective reports were

subject to ascertainment bias and misclassification of endocrine dysfunction because endocrine assessment was more likely for symptomatic patients or for those with radiographical abnormalities. The results from this study are unlikely to be subject to detection or ascertainment bias because all subjects had similar baseline neuroradiographical and endocrinological studies, regardless of symptoms or signs.

Auxological data at the start of the study revealed that the initial median height and weight SDS were within 1 SDS of the mean for age and gender. Although the median SDS for height and the range did not change at the end of the study for the entire cohort, the end weight revealed a greater median SDS with a range that was skewed toward the heavier side, which highlights two important observations. First, comparison of the start length and end height SDS for the cohort failed to show any significant evidence of worsening short stature and, surprisingly, revealed several cases of relatively tall stature. Second, although the height SDS did not change, the median weight SDS increased and the group as a whole became overweight.

As expected, children with GH axis abnormalities receiving GH treatment had a significant increase in height compared with those not receiving treatment, but those untreated subjects with GH axis abnormalities had no significant difference in the change in height, change in weight, or end BMI SDS compared with those with normal GH surrogates. This may represent the syndrome of paradoxical "growth without GH" that has been noted previously in children with ONH without a clear explanation.<sup>36,37</sup> In one such child, Geffner et al were able to provide evidence that insulin (which had been hypothesized as a growth-promoting factor in some cases of hypothalamic obesity) was not the causative agent and showed the presence of an unidentified circulating growth-promoting factor from studies performed *in vitro*.<sup>36</sup> Costin and Murphree also provided data to exclude insulin as a causative agent for normal growth in children with ONH and GHD.<sup>15</sup> Another possible hormone that has been shown to have growth-promoting activity in animal models is prolactin.<sup>38</sup> In our subjects who underwent prolactin measurement, hyperprolactinemia, generally of a mild degree, was noted in half of them at study enrollment. Although there was no association detected with height, increased end BMI SDS was significantly associated with increased initial serum prolactin. An association between excess weight and elevated serum prolactin has previously been noted in exogenously obese adults<sup>39</sup> and is thought to be related to prolactin causing insulin resistance.<sup>40</sup> In ONH, patients may have decreased dopaminergic tone from a hypothalamic-pituitary axis abnormality that may contribute to both hyperprolactinemia and to increased BMI, as has been suggested by Wang and colleagues.<sup>41</sup> Serum leptin levels, which are increased in obese children, have also been proposed as a possible growth-promoting factor,<sup>42</sup> but they were not measured in this study.

Although there did not appear to be any significant height deceleration in our subjects with ONH and GHD, their degree of excessive weight gain, regardless of GH surrogate status or GH treatment, was striking and atypical of other

conditions associated with GHD, except for PWS<sup>43,44</sup> and other forms of hypothalamic obesity.<sup>45</sup> The observed weight gain is unlikely to be attributed to the degree of vision loss in our patients, as previous studies have shown that blindness is associated with less food intake and normal satiety.<sup>46</sup> One possible explanation for the weight gain could be decreased lipolytic activity resulting from the absence of GH,<sup>47</sup> as suggested in patients with PWS.<sup>48</sup> Another consideration is the presence of a structural or functional defect of the hypothalamus, as suggested by the frequent presence of hyperprolactinemia in our children with ONH. This may affect satiety and/or appetite regulation as has been proposed to occur in patients with hypothalamic obesity secondary to craniopharyngioma resection.<sup>49</sup> Further investigation is required to determine if GH therapy might improve weight excess/abnormal body composition in children with ONH and GHD, with or without linear growth failure, as has been noted to occur in children and adults with classic GHD and in adolescents and adults with exogenous obesity.<sup>50,51</sup>

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