Published in final edited form as:

Horm Res Paediatr. 2012 ; 77(5): 277–280. doi:10.1159/000338330.

Serum Prolactin Concentrations in Relation to Hypopituitarism and Obesity in Children with Optic Nerve Hypoplasia

Amy M. Vedin, M.D.¹, Pamela Garcia-Filion, Ph.D.^{2,3}, Cassandra Fink, M.P.H.², Mark Borchert, M.D.^{2,4}, and Mitchell E. Geffner, M.D.^{1,4}

¹Center for Endocrinology, Diabetes, and Metabolism, Department of Pediatrics, Keck School of Medicine of USC and Children's Hospital Los Angeles

²The Vision Center, Department of Ophthalmology, Keck School of Medicine of USC and Children's Hospital Los Angeles

³Division of Biostatistics, Department of Preventive Medicine, Keck School of Medicine of USC

⁴Saban Research Institute of Children's Hospital Los Angeles

Abstract

Background/Aims—The majority of children with optic nerve hypoplasia (ONH) develop hypopituitarism and many also become obese. These associated conditions are a major cause of morbidity and are possibly due to hypothalamic dysfunction. Because mild hyperprolactinemia often occurs in subjects with disorders of the hypothalamus, we examined whether hyperprolactinemia was present in children with ONH during the first three years of life and whether it was a marker for hypopituitarism and/or obesity.

Methods—Data were retrospectively analyzed from a registry study of children with ONH. The initial serum prolactin was obtained prior to age 36 months (n=125) and compared with pituitary function and body mass index (BMI) at age 5.

Results—Seventy-two percent of subjects had an elevated initial serum prolactin and 60% had hypopituitarism. An elevated initial prolactin was associated with hypopituitarism (OR 2.58; 95% CI 1.16, 5.73), specifically with growth hormone deficiency (OR 2.77; 95% CI 1.21, 6.34). Thirty-one percent of subjects had a BMI 85th %ile, but this did not correlate with initial hyperprolactinemia.

Conclusions—Early hyperprolactinemia correlates with the presence of hypopituitarism in children with ONH, but it is not a reliable prognosticator of hypopituitarism. Additionally, hyperprolactinemia does not predict future weight excess.

Keywords

Optic nerve hypoplasia; prolactin; hypopituitarism; growth hormone; obesity

INTRODUCTION

Optic nerve hypoplasia (ONH), with a prevalence of 10.9 per 100,000, has been recognized over the past 30 years as a major cause of congenital blindness [1–3]. It rarely occurs in isolation, but more commonly presents with a number of systemic co-morbidities thought to

Corresponding author: Amy M. Vedin, M.D., Children's Hospital Los Angeles, 4650 Sunset Boulevard, MS 61, Los Angeles, CA 90027, Tel: 011 1 323 361 7695, Fax: 011 1 323 361 1350, avedin@chla.usc.edu.

Conflict of interest: The authors do not have any conflicts of interest to report.

be related to hypothalamic dysfunction [4–8]. The most common of these is hypopituitarism which may cause significant morbidity in this population. In our prior study of 47 consecutive subjects with ONH, the prevalence of endocrinopathies was 72%.

Currently there are no good clinical or biochemical markers that accurately predict which children will develop endocrinopathies in the backdrop of ONH. The presence of an endocrinopathy in our prior study was not associated with any radiological abnormalities and, thus, neuro-imaging cannot be used to predict hypopituitarism in children with ONH [4]. Hypopituitarism can develop at any time in the first years of life and is usually diagnosed by either the presence of symptoms (later in the disease course) or by screening tests done at the discretion of the treating physician. Thus, patients with ONH may experience the health consequences of a hormonal abnormality before it is diagnosed and treated, highlighting the need for a better prognostic strategy in these children.

Hypothalamic dysfunction may also manifest as obesity. In a prior study, 44% of subjects with ONH had a body mass index (BMI) $\geq$ 85th percentile at age 5 years [4]. Obesity may be attributed to hypothalamic dysfunction involving the appetite/satiety centers of the lateral hypothalamic and ventro-medial nuclei. In addition, the obesity has been ascribed to associated endocrinopathies such as growth hormone (GH) deficiency and/or hypothyroidism. Vision impairment and/or developmental delay may also contribute to the high prevalence of obesity in children with ONH [9,10]. It is not known if markers for hypothalamic dysfunction could serve as predictors of obesity in children with ONH.

Mild hyperprolactinemia can occur in subjects with hypothalamic and/or pituitary stalk dysfunction [11], and is often seen in subjects with ONH [4,6]. Markedly elevated prolactin levels, seen in patients with prolactinomas, have been associated with weight gain and obesity in both adults [12–14] and children [15,16]. There have been many proposed mechanisms to attempt to explain these findings, such as decreased dopaminergic tone and leptin resistance [13,17], but the pathophysiology remains unclear. There are no large studies investigating the relationship between mild hyperprolactinemia and either hypothalamic dysfunction and/or obesity in children with ONH.

The aims of this study were to examine whether elevated serum prolactin levels measured prior to age 3 years are a marker of hypopituitarism and/or obesity (BMI $\geq$ 85th percentile) in children with ONH using prospectively collected data.

METHODS

An ONH registry was established in 1992 to collect prospective ophthalmic, endocrinological, and neuropsychological data on subjects with ONH. Clinical data from 262 subjects comprise this ongoing database and include comprehensive endocrine testing at the time of study enrollment ($\geq$ 36 months) (including measurements of prolactin, IGF-I, IGFBP-3, cortisol, TSH, and free thyroxine); additional endocrine data collected from subjects' treating endocrinologists; and repeat thyroid function testing and glucagon GH stimulation testing. Subjects are followed in this registry until age 5 years. The details of the study methodology of this registry are described elsewhere [4,5]. The study was approved by the Children's Hospital Los Angeles Committee on Clinical Investigations.

Registry data on serum prolactin levels, endocrinological and auxological outcomes, and neuroradiographic findings were abstracted for this study. Subjects with an initial serum prolactin level through 2008 and known pituitary status (either hypopituitarism diagnosed at any time or confirmed normal pituitary hormones at age 5) were included. Serum prolactin levels were measured at or before the initial study visit ($\leq$ 3 years), and, if done at the initial study visit, were obtained under sedation with chloral hydrate. In addition, recent subjects

have had repeat measurements of prolactin levels at the time of their glucagon stimulation test or at the discretion of their primary endocrinologist. Referral laboratories and assays used for analyses varied depending on whether the laboratory tests were drawn as part of a study visit or by the primary endocrinologist. Thus, hyperprolactinemia was defined as above the upper limit of the laboratory-defined normal range for age. Hypopituitarism was defined as either being prescribed hormone replacement (GH, levo-thyroxine, hydrocortisone, and/or desmopressin) and/or having a subnormal stimulated peak serum GH level (<10 ng/mL after glucagon).

Auxological data were collected at annual study visits. BMI was calculated from the last available height and weight measurements in the database, and converted to standard deviation scores (SDS) using Epi Info Version 3.5.3 (a software program that calculates SDS using the 2000 Centers for Disease Control growth references) [18]. Using the guidelines of the Center for Disease Control, overweight was defined as a BMI between the 85th and 95th percentiles (>1.4 SDS) and obesity was defined as a BMI $>95^{\text{th}}$ percentile (>2.1 SDS).

Data were analyzed using Stata 11.0 (College Station, TX) to examine the association of initial serum prolactin with documented pituitary status and BMI SDS. Summary statistics were used, with median values and 5th and 95th percentiles if not normally distributed. Comparisons between groups were performed by the chi-square and Student's t-test, or, if continuous variables, by Pearson's correlation. The non-parametric analogs were used when appropriate. Odds ratios (OR) and the 95% confidence intervals (CI) were estimated using logistic regression. Statistical significance was defined as an alpha of 0.05, with two-sided alternative hypotheses.

RESULTS

Demographic and clinical characteristics of the sample are presented in the Table. Of the 125 subjects with an available initial serum prolactin level (measured at age 13.2 ± 9.3 months), 73% had an elevated value, 41.6 ± 21.1 ng/mL, and 27% had a normal value, 12.1 ± 4.5 ng/mL ($p<0.001$). Hyperprolactinemia was not associated with an absent septum pellucidum or hypoplastic corpus callosum. Subjects with an elevated initial prolactin level were more likely to have hypopituitarism [OR 2.45 (95% CI: 1.10, 5.48)]. The association was driven primarily by GH deficiency [OR 2.63 (95% CI: 1.14, 6.06)], as there were no significant associations with other types of pituitary deficiencies: hypothyroidism ($p=0.360$) and adrenal insufficiency ($p=0.574$).

A repeat prolactin level at an older age (44.4 ± 20.1 months) was available in 52.8% of subjects. Prolactin levels remained normal in all subjects with a normal initial prolactin level ($n=12$), and normalized in 61% (33/54) of subjects with an initially elevated prolactin level. There was no difference in the initial prolactin levels between those with persistent hyperprolactinemia (38.8 ± 14.8 ng/mL) and those that normalized (39.3 ± 16.7 ng/mL; $p=0.916$). Subjects with persistent hyperprolactinemia were more likely to have hypopituitarism (81% vs 55%; $p=0.048$) and GHD (76% vs 50%; $p=0.05$) than those that normalized.

BMI data at age 5 years (59.6 ± 5.5 months) were available for 112 subjects (89%); 31% were overweight and 20% were obese. Obesity did not correlate with elevated initial prolactin ($p=0.439$); there was no association among those with ($p=0.715$) and without ($p=1.00$) GH deficiency. The median BMI SDS was higher among subjects with an elevated initial prolactin (1.01; $-1.25, 3.26$) compared to those with a normal prolactin (0.39; $-1.1, 2.82$), although this only approached statistical significance ($p=0.091$). Persistent

hyperprolactinemia was not associated with BMI SDS ($p=0.589$). There was a statistically significant difference in the median BMI SDS between those with (1.14; -1.25, 3.26) and without GH deficiency (0.39; -1.1, 2.59) ($p=0.010$).

DISCUSSION

Hypopituitarism and obesity occur frequently in children with ONH, and currently it is difficult to predict which children with ONH will develop these co-morbidities. It is generally accepted that hyperprolactinemia is a marker of interrupted signaling between the hypothalamus and pituitary, but this is the first study to demonstrate that elevated initial serum prolactin levels may be a potential marker for hypopituitarism in children with ONH.

Hypopituitarism was least common among those with an initially normal serum prolactin level (44%; $n=15/34$). The prevalence of hypopituitarism was higher (66%) among those with an initially elevated prolactin, corresponding to a 2.5-fold increased likelihood of hypopituitarism. The prevalence of hypopituitarism was highest (81%) for those with a persistently elevated prolactin. An elevated serum prolactin was specific to GH deficiency in this study, which likely reflects the predominance of GH deficiency in ONH.

This study confirms the high prevalence of obesity (20%) at age 5 years in children with ONH, which is notably higher than the national reported prevalence of 10.4% ($p<0.001$) in children ages 2–5 years (NHANES 2007–2008) [19]. While obesity did not correlate with early hyperprolactinemia, the observed higher median BMI SDS between those with and without early hyperprolactinemia (1.0 vs 0.4; $p=0.09$) is still of clinical significance and also suggestive of underlying hypothalamic dysfunction. The increased BMI and prevalence of obesity are clearly concerning for future health implications.

Thirty-four percent of subjects with elevated initial prolactin levels did not have hypopituitarism. The young age of participants precluded the detection of hypopituitarism presenting later in life, for example, during puberty. Additionally, assessment of gonadotropin deficiency was not possible due to the young age of our subjects and absence of laboratory data from the mini-puberty of infancy [20]. Therefore, our prevalence of hypopituitarism may be an underestimation. There is the potential for false elevation of prolactin levels attributable to, for example, stress and sleep. Moreover, prolactin levels were collected under non-standardized conditions, were sent to different laboratories, and were measured using multiple assay methodologies, all of which may have affected their results. Prolactin levels are normally higher in the first few months of life, but decline to normal childhood values by 3 months of age. This was an unlikely source of bias since only one of our subjects had prolactin levels checked prior to 3 months of age.

A repeat serum prolactin level was not available for 48% of our study sample. Repeat measurements became more frequent over the past seven years, and were generally obtained at the time of the glucagon stimulation test performed as part of the registry. Subjects were less likely to have a repeat prolactin obtained if they were already receiving GH replacement therapy. The majority of these subjects had an elevated initial prolactin; therefore, the exclusion of these subjects from the subset analysis of repeat prolactin levels may have led to the underestimation of the association of prolactin levels with endocrinological and auxological outcomes.

In conclusion, early serum prolactin levels are often elevated in children with ONH. There is an association between early hyperprolactinemia and GH deficiency, but not other pituitary deficiencies, by age 5 years. However, there were also many subjects with normal early serum prolactin levels who subsequently developed hypopituitarism, indicating that screening for hypopituitarism is necessary regardless of early prolactin levels. Further

studies are needed to identify possible clinical and/or biochemical markers that could be used to predict hypopituitarism in children with ONH. Until then, it is important to screen these patients regularly for pituitary hormone deficiencies.

Acknowledgments

This research was 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.

Abbreviations

ONH	optic nerve hypoplasia
BMI	body mass index
GH	growth hormone
SDS	standard deviation score

REFERENCES

- 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; 148:85–88. [PubMed: 16423603]
- Blohme J, Tornqvist K. Visual impairment in Swedish children. II. Etiological factors. *Acta Ophthalmol Scand*. 1997; 75:199–205. [PubMed: 9197573]
- Hoyt CS. Optic nerve hypoplasia, changing perspective. *Aust NZ J Ophthalmol*. 1986; 14:325–331.
- 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. [PubMed: 16423602]
- Garcia-Filion P, Eppert K, Nelson M, Azen C, Geffner ME, Fink C, Borchert M. Neuroradiologic, endocrinologic, and ophthalmic correlates of adverse developmental outcomes in children with optic nerve hypoplasia: a prospective study. *Pediatrics*. 2008; 121:e653–e659. [PubMed: 18250116]
- Costin G, Murphree AL. Hypothalamic-pituitary function in children with optic nerve hypoplasia. *Am J Dis Child*. 1985; 139:249–254. [PubMed: 2983530]
- Ek U, Fernell E, Jacobson L. Cognitive and behavioural characteristics in blind children with bilateral optic nerve hypoplasia. *Acta Paediatrica*. 2005; 94:1421–1426. [PubMed: 16299874]
- Fink CF, Borchert MB. Optic nerve hypoplasia and autism: common features of spectrum diseases. *J Vis Impair Blind*. 2011 (in press).
- Reinehr T, Dobe M, Winkel K, Schaefer A, Hoffmann D. Obesity in disabled children and adolescents. *Dtsch Arztebl Int*. 2010; 107:268–275. [PubMed: 20458368]
- Van Cleave J, Gortmaker S, Perrin J. Dynamics of obesity and chronic health conditions among children and youth. *JAMA*. 2010; 303:623–630. [PubMed: 20159870]
- Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JA. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011; 96:273–288. [PubMed: 21296991]
- Greenman Y, Tordjman K, Stern N. Increased body weight associated with prolactin secreting pituitary adenomas: weight loss with normalization of prolactin levels. *Clin Endocrinol*. 1998; 48:547–553.
- Doknic M, Pekic S, Zarkovic M, Medic-Stojanoska M, Dieguez C, Casanueva F, Popovic V. Dopaminergic tone and obesity: an insight from prolactinomas treated with bromocriptine. *Eur J Endocrinol*. 2002; 147:77–84. [PubMed: 12088923]

14. dos Santos Silva CM, Barbosa FR, Lima GA, Warszawski L, Fontes R, Domingues RC, Gadelha MR. BMI and metabolic profile in patients with prolactinoma before and after treatment with dopamine agonists. *Obesity*. 2011; 19:800–805. [PubMed: 20559294]
15. Galluzi F, Salti R, Stagi S, La Cauza F, Chiarelli F. Reversible weight gain and prolactin levels--long-term follow-up in children. *J Pediatr Endocrinol Metab*. 2005; 18:921–924. [PubMed: 16279371]
16. Saranac L, Zivanovic S, Radovanovic Z, Kostic G, Markovic I, Miljkovic P. Hyperprolactinemia: differential clinical expression in childhood. *Horm Res Paediatr*. 2008; 73:187–192. [PubMed: 20197671]
17. Wang GJ, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, Netusil N, Fowler JS. Brain dopamine and obesity. *Lancet*. 2001; 357:354–357. [PubMed: 11210998]
18. Epi Info Version 3.5.3 (Software program). Atlanta, GA: Centers for Disease Control and Prevention; 2011.
19. Ogden C, Carroll M, Curtin L, Lamb M, Flegal K. Prevalence of high body mass index in US Children and Adolescents, 2007–2008. *JAMA*. 2010; 303:242–249. [PubMed: 20071470]
20. Nakamoto, JM.; Franklin, SL.; Geffner, ME. Puberty. In: Kappy, MS.; Allen, DB.; Geffner, ME., editors. *Pediatric Practice: Endocrinology*. New York: McGraw Hill Medical; 2010. p. 257-298.

Table

Demographics and clinical characteristics

Characteristics	% [*]	n/N
<i>Gender</i>		
Male	52	64/125
<i>Ethnicity</i>		
Caucasian	39	49/125
Hispanic	46	57/125
African-American	2	2/125
Asian/Pacific Islander	2	2/125
Other	6	7/125
Mixed	6	8/125
<i>Neuroradiographic Abnormalities</i> ^{**}		
Corpus Callosum Hypoplasia	44	52/118
Absent Septum Pellucidum	40	47/118
<i>Laterality</i>		
Bilateral	85	106/125
<i>Endocrinopathy</i> ^{**}		
Elevated serum prolactin	73	91/125
Hypopituitarism	60	75/125
GH deficiency	58	67/116
Central hypothyroidism	39	47/121
Adrenal insufficiency	31	38/122

^{*} Percentages are rounded up to the next integer and, thus, may not total 100.

^{**} Percentages are not mutually exclusive. The total number of subjects varies depending on available results.