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The Prevalence and Volumetry of Pituitary Cysts in Children with Growth Hormone Deficiency and Idiopathic Short Stature

Nicholas Krasnow
New York Medical College

Bradley Pogostin

James Haigney
New York Medical College

Brittany Groh
New York Medical College

Winston Weiler

See next page for additional authors

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Nicholas Krasnow, Bradley Pogostin, James Haigney, Brittany Groh, Winston Weiler, Michael Tenner, Marion Kessler, Michael Frey and Richard A. Noto*

The prevalence and volumetry of pituitary cysts in children with growth hormone deficiency and idiopathic short stature

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Abstract

Background: Pituitary cysts have been speculated to cause endocrinopathies. We sought to describe the prevalence and volumetry of pituitary cysts in patients with growth hormone deficiency (GHD) and idiopathic short stature (ISS).
Methods: Six hundred and eighteen children evaluated for growth failure at the Division of Pediatric Endocrinology at New York Medical College between the years 2002 and 2012, who underwent GH stimulation testing and had a brain magnetic resonance imaging (MRI) prior to initiating GH treatment were randomly selected to be a part of this study. High resolution MRI was used to evaluate the pituitary gland for size and the presence of a cyst. Cyst prevalence, cyst volume and percentage of the gland occupied by the cyst (POGO) were documented.
Results: Fifty-six patients had a cyst, giving an overall prevalence of 9.1%. The prevalence of cysts in GHD patients compared to ISS patients was not significant (13.5% vs. 5.7%, $p = 0.46$). Mean cyst volume was greater in GHD patients than ISS patients (62.0 mm^3 vs. 29.4 mm^3, $p = 0.01$). POGO for GHD patients was significantly greater ($p = 0.003$) than for ISS patients ($15.3\% \pm 12.8$ vs. $7.1\% \pm 8.0$). Observers were blinded to patient groups.
Conclusions: GHD patients had a significantly greater volume and POGO compared to ISS patients. This raises the question of whether cysts are implicated in the pathology of growth failure.

Keywords: endocrinopathy; growth disorders; growth hormone deficiency; growth hormone stimulation test; hypopituitarism; magnetic resonance imaging; pituitary; pituitary disease; pituitary volume; short stature.

Introduction

High resolution magnetic resonance imaging (MRI) evaluation of the pituitary gland has become essential in the assessment of the growth hormone deficient (GHD) child [1–3]. This new MRI technique allows for greater detailed observations to be made [4–6]. As a result, the endocrinologist may discover new and more frequent radiographic findings, including pituitary cysts [7–9]. We have previously shown a 14.6% prevalence of pituitary cysts in pediatric patients [Abstract: Incidence and volumetry of pituitary cysts in normal children]. One could easily speculate that compression of the pituitary by cysts may cause dysfunction in secretion in the somatotrophs and other cells of the pituitary gland [10–12]. This study sought to compare the prevalence and volumetry of pituitary cysts between GHD and idiopathic short stature (ISS) children.

Subjects and methods

Subjects

All children evaluated for growth failure seen in the Division of Pediatric Endocrinology at New York Medical College from 2002 to 2012, who had a bone age demonstrating open growth plates and had high resolution MRI and GH stimulation testing performed were considered for this study. Growth failure was defined as having a height less than 2.0 standard deviations below the mean on the Centers for Disease Control (CDC) growth curve, a subnormal growth velocity for at least 6 months and/or a predicted adult height greater than 5.08 cm discrepant from the mid-parental height. A GH peak of less than or equal to 10 ng/mL on stimulation was defined as GHD. Those with

***Corresponding author: Richard A. Noto,** MD, Diabetes and Endocrine Center for Children and Young Adults, 755 North Broadway, Suite 400, Sleepy Hollow, NY 10591, USA; and Department of Pediatrics, Division of Pediatric Endocrinology, New York Medical College, Valhalla, NY, USA, Work: +1 914 366 3400, Fax: +1 914 366 3407, E-mail: Richard_Noto@bchphysicians.org
Nicholas Krasnow, Bradley Pogostin, James Haigney, Brittany Groh, Winston Weiler, Marion Kessler and Michael Frey: Department of Pediatrics, Division of Pediatric Endocrinology, New York Medical College, Valhalla, NY, USA
Michael Tenner: Department of Radiology, New York Medical College, Valhalla, NY, USA

levels greater than 10 ng/mL were classified as ISS. The secretagogues utilized during the GH stimulation test were clonidine and levodopa. Clonidine was administered at 0.004 mg/kg by mouth with 0.05 or 0.1 mg tablet, and 7–10 mg/kg of levodopa was administered by mouth with 125, 250, 375, or 500 mg tablet. GH levels were measured at our in-house endocrine laboratory via the chemiluminescent assay technique [13]. Patients were separated into two groups. Group 1 was considered the prepubertal patients, as defined by an age ≤11 years. Group 2 was considered the pubertal patients, as defined by an age >11 years. Patients with Turner syndrome, *SHOX* gene mutation, Cushing's syndrome, hypothyroidism, other anterior pituitary hormone deficiencies and malnutrition were excluded from this study. As this was a retrospective study of pre-existing data accumulated in our division, it was not necessary to obtain informed consent.

Magnetic resonance imaging (MRI)

MRI scans were taken on a Philips 1.5 Tesla MRI system (Koninklijke Philips N. V. Amsterdam, The Netherlands). Post-gadolinium contrast brain MRIs with special attention to the pituitary gland were reviewed for the presence of pituitary cysts. Image slices of 1–2 mm thickness were used for both sagittal and coronal images. Fluid-filled lesions were defined as cysts and were only distinguishable by size, and an identified mass was considered an adenoma and excluded from the study. Patients were referred for dynamic scanning when a lesion could not be classified otherwise. Pituitary and cyst length and height were measured using mid-sagittal images, while width was obtained using coronal images at the level of the pituitary stalk entrance into the gland. Pituitary volumes and cyst volumes were calculated using the ellipsoidal formula $(l \times w \times h)/2$. Percentage of the gland occupied by the cyst (POGO) was calculated with the formula (cyst volume/pituitary volume) $\times 100$. A cyst with a POGO less than 15% was defined as a small cyst, and a POGO greater than 15% was defined as a large cyst.

Statistical analysis

All statistical analyses were performed using IBM SPSS software (IBM Corp. Armonk, NY, USA). Continuous variables were compared using the two-tailed Student's t-test and were presented as the mean ± standard deviation. Categorical variables were compared using the chi-squared (χ^2) test. A p-value <0.05 was considered statistically significant.

Ethical approval

The research related to human use has complied with all the relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration. The Institutional Review Board of New York Medical College approved this cross-sectional retrospective study.

Results

Table 1 depicts the prevalence of cysts stratified by the demographics of sex and age groups. Table 2 compares cyst volume and POGO, separated by diagnosis and age groups. Table 3 compares cyst volume and POGO, stratified by sex and diagnosis. Table 4 displays the prevalence of large and small cysts by diagnosis.

Six hundred and eighteen patients met the criteria for inclusion in the study. Of these patients, 393 were male (64%) and 225 were female (36%). Two hundred and sixty-six patients had GHD (43%), of which 181 were male (68%)

Table 1: Demographics and prevalence of pituitary cysts.

	Total					GHD			ISS		
	Total	Male	Female	≤11	>11	Total	Male	Female	Total	Male	Female
n	618	393	225	233	385	266	181	85	352	212	140
# with cyst	56	39	17	23	33	36	27	9	20	12	8
Prevalence, %	9.1	9.9	7.5	9.87	8.57	13.5	14.9	10.6	5.7	5.7	5.7
Mean age	11.5	11.9	10.7	7.6	13.7	11.3	11.8	10.3	11.6	11.9	11.0
(SD age)	(3.4)	(3.5)	(3.2)	(2.9)	(2.0)	(3.4)	(3.5)	(3.2)	(3.4)	(3.5)	(3.1)

SD, standard deviation; GHD, growth hormone deficiency; ISS; idiopathic short stature.

Table 2: Cyst volume and POGO, separated by diagnosis and age group.

	Cyst patients	GHD	ISS	≤11	>11
n	56	36	20	23	33
Mean cyst volume (SD)	51.1 (±58.9)	62.0 (±67.2)	29.4 (±38.4)	39.8 (±31.1)	58.7 (±71.3)
p-Value			0.01		0.19
Mean POGO (SD)	11.7% (±11.3)	15.3% (±12.8)	7.1% (±8.0)	13.1% (±12.6)	10.8% (±10.4)
p-Value			0.003		0.46

SD, standard deviation; POGO, percentage of the gland occupied by the cyst; GHD, growth hormone deficiency; ISS; idiopathic short stature.

Table 3: Volumetry of pituitary cysts by sex and diagnosis.

	GHD male	ISS male	GHD female	ISS female
n	27	12	9	8
Mean cyst volume (SD)	68.9 (±74.9)	29.5 (±46.7)	41.3 (±29.6)	29.2 (±24.1)
p-Value		0.03		0.27
Mean POGO (SD)	16.4% (±14.3)	6.7% (±9.0)	11.8% (±5.6)	7.8% (±6.6)
p-Value		0.009		0.16

SD, standard deviation; GHD, growth hormone deficiency; ISS; idiopathic short stature; POGO, percentage of the gland occupied by the cyst.

Table 4: Prevalence of large versus small pituitary cysts in the different patient diagnoses.

	Cyst patients	GHD	ISS
Small cysts	66.1%	55.6%	85.0%
p-Value			0.04
Large cysts	33.9%	44.4%	15.0%
p-Value			0.04

GHD, growth hormone deficiency; ISS; idiopathic short stature.

and 85 were female (32%). Three hundred and fifty-two had ISS (57%), of which 212 were male (60%) and 140 were female (40%).

Prevalence

Of the 618 patients studied, 56 had cysts, resulting in an overall prevalence of 9.1% (Table 1). GHD patients were found to have a prevalence of 13.5% compared to 5.7% for ISS patients ($p = 0.46$). This difference was not significant. The prevalence between males and females of the entire cohort was not significant (9.9% and 7.5%, $p = 0.79$). When analyzed by age, 9.87% of prepubertal patients (group 1) showed pituitary cysts, while 8.57% of pubertal patients (group 2) demonstrated a cyst ($p = 0.59$, Table 1). The difference in prevalence between age groups was not significant.

Cyst volume

Cyst analysis showed a significant difference between cyst volume in GHD patients (mean 62.0 $mm^3 \pm 67.2$, median 48.9) vs. ISS patients (mean 29.4 $mm^3 \pm 38.4$, median 16.5) ($p = 0.01$). For males, the difference in cyst volume between GHD patients (mean 68.9 $mm^3 \pm 74.9$, median 53.7) and ISS patients (mean 29.5 $mm^3 \pm 46.7$, median 14.5) was significant ($p = 0.03$). Cyst volume was greater in GHD females (mean 41.3 $mm^3 \pm 29.6$, median 34.5) than in ISS females (mean 29.2 $mm^3 \pm 24.1$, median 19.9), but this difference was not significant ($p = 0.27$). The group 2 patients had a larger cyst volume (58.67 $mm^3 \pm 71.29$ mm^3) than the group 1 patients (39.76 $mm^3 \pm 31.08$ mm^3). This difference was not significant ($p = 0.19$, Table 2).

POGO

The mean POGO of the cyst for GHD patients was 15.3% ± 12.8 (median 13.5) and for ISS it was 7.1% ± 8.0 (median 4.8). The difference between these two groups was statistically significant ($p = 0.003$). For males, the difference in POGO between the GHD (mean 16.4% ± 14.3, median 13.5) and ISS (mean 6.7% ± 9.0, median 4.1) groups was significant ($p = 0.009$). For females, the difference in POGO between the GHD (mean 11.8% ± 5.6, median 10.9) and ISS (mean 7.8% ± 6.6, median 5.4) groups was not significant ($p = 0.16$). Mean POGO in group 1 patients was 13.08% ± 12.6 and mean POGO in group 2 patients was 10.77% ± 10.4. This difference was not significant ($p = 0.46$, Tables 2 and 3).

In patients who had a pituitary cyst, 66.1% had a small cyst. For GHD and ISS patients with a cyst, small cysts were found in 55.6% and 85%, respectively. This difference was significant ($p = 0.04$). Large cysts were found in 33.9% of all patients with a cyst. For GHD and ISS patients with a cyst, large cysts were found in 44.4% and 15%, respectively. There was a significant difference between the percentage of GHD patients and ISS patients with large cysts ($p = 0.04$, Table 4).

Discussion

To the best of our knowledge, the data presented here is the first study to assess cyst prevalence and volumetry in children with GHD and ISS. Pituitary cysts have been speculated to cause a variety of clinical findings, including anterior pituitary dysfunction, visual field defects, and headaches [11, 14–23]. This pathology may be caused by cyst compression of the adenohypophysis [10–12]. Because somatotrophs are the most abundant cell type of the pituitary

gland, they are the most likely to be affected by a cyst [10, 24, 25]. Given this relationship, one might hypothesize that children with poor growth may have a higher prevalence of cysts than the general pediatric population. However, in a recently completed study, we found a general pediatric population prevalence of cysts of 14.6%. This is greater than the 9.1% prevalence found in this study for short children. This tends to negate the hypothesis that cyst prevalence itself is related to poor growth and GHD. However, the difference in prevalence between our two studies is not comparable because higher resolution MRIs were utilized in the normal children study. Improved MRI technology may allow for more cysts of smaller size to be detected. The difference in cyst prevalence between GHD, ISS, and normal stature children warrants further investigation.

Cyst size may be a causative factor in cyst related pituitary dysfunction. We found the mean cyst volume and POGO of cysts in GHD children to be significantly larger than in ISS children, implicating larger cysts with increasing pituitary dysfunction. Furthermore, the volume and POGO of cysts in normal children [10] tended to be smaller than those of this study, with a mean volume and POGO of 17.28 mm^3 and 4.87%, respectively, in comparison to GHD (62 mm^3, 15.3%) and ISS (29.4 mm^3, 7.1%) patients.

Although cyst volume was greater in pubertal patients than prepubertal patients ($p = 0.19$), the difference in POGO between age groups was not significant ($p = 0.46$). This is likely because the pituitary size increases significantly in adolescence [26, 27]. If the POGO does not change, that is potentially indicative of only an increase in pituitary size, not an increase of cyst impingement on the gland.

From this data, we speculate that small cysts may be of a physiologic nature that come and go, but as cysts become larger, they may have a negative effect on pituitary secretion and cause problems with normal growth, with the larger cysts causing GHD.

It should be noted that the difference in POGO was not significant between GHD and ISS females. This is likely due to a lower number of females in our study. As our study was retrospective, we were unable to account for pubertal stage. We acknowledge that careful Tanner staging is essential to future research. Additional research looking at pituitary cysts and GH production in children may include genetic analysis.

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Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission. Nicholas Krasnow analyzed and collated the data and drafted the initial manuscript. Bradley Pogostin, James Haigney, Brittany Groh and Winston Weiler analyzed and collated the data. Michael Tenner helped conceptualize and design the study, interpreted each MRI, and measured pituitary and cyst volumes. Marion Kessler analyzed and collated the data and revised the manuscript for final submission. Michael Frey ran the assays for the growth hormone levels. Richard Noto conceptualized and designed the study, analyzed and collated data, and revised the manuscript for final submission. The authors would like to thank the late Dr. Marion Kessler for her extensive work on the production of this investigation. Dr. Kessler was critical in the conception, design, and execution of this study, as well as in drafting the manuscript. She tragically passed away just before acceptance of this paper. She will be greatly missed.

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References

1. Maghnie M, Lindberg A, Koltowska-Haggstrom M, Ranke MB. Magnetic resonance imaging of CNS in 15,043 children with GH deficiency in KIGS (Pfizer International Growth Database). Eur J Endocrinol 2013;168:211–7.
2. Arslanoglu I, Kutlu H, Isguven P, Tokus F, Isik K. Diagnostic value of pituitary MRI in differentiation of children with normal growth hormone secretion, isolated growth hormone deficiency and multiple pituitary hormone deficiency. J Pediatr Endocrinol Metab 2001;14:517–23.
3. Xu C, Zhang X, Dong L, Zhu B, Xin T. MRI features of growth hormone deficiency in children with short stature caused by pituitary lesions. Exp Ther Med 2017;13:3474–8.
4. Sobol WT. Recent advances in MRI technology: implications for image quality and patient safety. Saudi J Ophthalmol 2012;26:393–9.
5. Wood R, Bassett K, Foerster V, Spry C, Tong L. 1.5 Tesla magnetic resonance imaging scanners compared with 3.0 Tesla magnetic resonance scanners: systematic review of clinical effectiveness. Ottawa: Canadian Agency for Drugs and Technologies in Health, 2011 (CADTH Rapid Response Report).
6. Castillo M. Pituitary gland: development, normal appearances, and magnetic resonance imaging protocols. Top Magn Reson Imaging 2005;16:259–68.
7. Sanno N, Oyama K, Tahara S, Teramoto A, Kato Y. A survey of pituitary incidentaloma in Japan. Eur J Endocrinol 2003;149:123–7.
8. Hall WA, Luciano MG, Doppman JL, Patronas NJ, Oldfield EH. Pituitary magnetic resonance imaging in normal human volunteers: occult adenomas in the general population. Ann Intern Med 1994;120:817–20.

9. Soule SG, Jacobs HS. The evaluation and management of subclinical pituitary disease. Postgrad Med J 1996;72: 258–62.
10. Kunwar S, Wilson CB. Pediatric pituitary adenomas. J Clin Endocrinol Metab 1999;84:4385–9.
11. Aho CJ, Liu C, Zelman V, Couldwell WT, Weiss MH. Surgical outcomes in 118 patients with Rathke's cleft cysts. J Neurosurg 2005;102:189–93.
12. Furtado SV, Venkatesh PK, Ghosal N, Hegde AS. Reduction in size of a large Rathke's cleft cyst on treatment with low dose of corticosteroid. Horm Metab Res 2010;42:227–9.
13. Siemens immulite. Los Angeles, CA, USA: Siemens Healthcare Diagnostics Inc., 2002.
14. Mukherjee JJ, Islam N, Kaltsas G, Lowe DG, Charlesworth M, et al. Clinical, radiological and pathological features of patients with Rathke's cleft cysts: tumors that may recur. J Clin Endocrinol Metab 1997;82:2357–62.
15. El-Mahdy W, Powell M. Transsphenoidal management of 28 symptomatic Rathke's cleft cysts, with special reference to visual and hormonal recovery. J Neurosurg 1998;42: 7–16.
16. Isono M, Kamida T, Kobayashi H, Shimomura T, Matsuyama J. Clinical features of symptomatic Rathke's cleft cyst. Clin Neurol Neurosurg 2001;103:96–100.
17. Kim JE, Kim JH, Kim OL, Paek SH, Kim DG, et al. Surgical treatment of symptomatic Rathke cleft cysts: clinical features and results with special attention to recurrence. J Neurosurg 2004;100:33–40.
18. Nishioka H, Haraoka J, Izawa H, Ikeda Y. Magnetic resonance imaging, clinical manifestations, and management of Rathke's cleft cyst. Clin Endocrinol 2006;64:184–8.
19. Kanter AS, Sansur CA, Jane JA, Laws ER. Rathke's cleft cysts. Front Horm Res 2006;34:127–57.
20. Zada G. Rathke's cleft cysts: a review of clinical and surgical management. Neurosurg Focus 2011;31:E1.
21. Trifanescu R, Stavrinides V, Plaha P, Cudlip S, Byrne JV, et al. Outcome in surgically treated Rathke's cleft cysts: long-term monitoring needed. Eur J Endocrinol 2011;165:33–7.
22. Jahangiri A, Molinaro AM, Tarapore PE, Blevins L, Auguste KI, et al. Rathke cleft cysts in pediatric patients: presentation, surgical management, and postoperative outcomes. Neurosurg Focus 2011;31:E3.
23. Potts MB, Jahangiri A, Lamborn KR, Blevins LS, Kunwar S, et al. Suprasellar Rathke cleft cysts: clinical presentation and treatment outcomes. J Neurosurg 2011;69:1058–69.
24. Marieb EN, Wilhelm PB, Mallatt J. Human anatomy. Glenview, IL: Pearson Education, Inc., 2014:526.
25. Gardner DG, Shoback D. Greenspan's basic and clinical endocrinology. New York, NY: McGraw-Hill Companies, Inc., 2011:69.
26. Han X, Xiu J, Huang Z, Zhang J, Zhang Z, et al. Three-dimensional magnetic resonance volumetry of the pituitary gland is effective in detecting short stature in children. Exp Ther Med 2014;8:551–6.
27. Takano K, Utsunomiya H, Ono H, Ohfu M, Okazaki M. Normal development of the pituitary gland: assessment with three-dimensional MR volumetry. Am J Neuroradiol 1999;20:312–5.