Original Article

PITUITARY ENLARGEMENT IN PATIENTS WITH PRIMARY HYPOTHYROIDISM

Nahla M. Khawaja, MD, Bassam M. Taher, MD, Muries E. Barham, MD, Abeer A. Naser, BSc, Azmy M. Hadidy, MD, Azmi T. Ahmad, MD, Hanan A. Hamamy, MD, Nakhleh A. Yaghi, MD, and Kamel M. Ajlouni, MD, FACP, FACE

ABSTRACT

Objective: To assesses the frequency and degree of pituitary hyperplasia in patients with primary hypothyroidism, the association of pituitary enlargement with disease severity, and the response to treatment.

Methods: Between April 2002 and August 2004 at the National Center for Diabetes, Endocrinology and Genetics in Amman, Jordan, 53 patients (49 female and 4 male subjects) with primary hypothyroidism and serum thyrotropin (thyroid-stimulating hormone or TSH) levels of ≥50 μIU/mL were encountered. Initial and follow-up investigations included thyroid function tests, serum prolactin levels, and magnetic resonance imaging (MRI) of the pituitary. Visual field examination was requested for all patients with pituitary enlargement (and adequately completed in 24).

Results: Pituitary enlargement on MRI was found in 37 of the 53 patients (70%), with 31 of the 37 patients (84%) having TSH levels of ≥100 μIU/mL. After thyroxine treatment, 85% of the patients with pituitary enlargement who underwent a follow-up MRI showed a decrease in size of the gland. About half of the patients were referred to our facility with the diagnosis of hypothyroidism; presenting features in the rest of the patients included galactorrhea, menstrual irregularities, learning disability, short stature, precocious puberty, ovarian hyperstimulation syndrome, headaches, visual field defects, and dry ichthyotic skin.

Conclusion: The association between pituitary gland enlargement and primary hypothyroidism should be kept in mind when pituitary hyperplasia is detected on MRI, before unwarranted and drastic interventions are initiated.
(Endocr Pract. 2006;12:29-34)

Abbreviations:
MRI = magnetic resonance imaging; **TSH** = thyroid-stimulating hormone (thyrotropin)

INTRODUCTION

The association between primary hypothyroidism and pituitary gland enlargement has been recognized since 1851; Niepce first described this association at autopsy in patients with cretinism (1). Several case reports have subsequently been published in the literature (1-11). Yamada et al (1) observed that the magnitude of the increase in the size of the sella turcica correlated with the increase in the serum level of thyrotropin (thyroid-stimulating hormone or TSH). The increase in pituitary mass may be interpreted as the cause rather than the result of an endocrinopathy if the pathophysiologic factors underlying the anatomic changes are not considered (11). Overlooking the diagnosis of primary hypothyroidism in the presence of an enlarged pituitary gland could lead to a wide range of inappropriate management decisions.

This study was initiated after we noted that several patients who were referred to our center for evaluation of pituitary enlargement had severe primary hypothyroidism. In the current study, we assess the frequency and degree of pituitary hyperplasia in patients with primary hypothyroidism, the association of pituitary enlargement with disease severity, and the response to treatment. The lack of neonatal screening in Jordan, as well as the delayed diagnosis of primary hypothyroidism in adults, creates a setting for long-standing primary hypothyroidism to result in higher TSH levels and to be accompanied by a higher incidence of pituitary hyperplasia.

PATIENTS AND METHODS

Study Cohort

Between April 2002 and August 2004, 3,521 patients had thyroid function tests performed at the endocrine clinic of the National Center for Diabetes, Endocrinology and Genetics in Amman, Jordan. Patients underwent such tests

Submitted for publication May 27, 2005
Accepted for publication August 18, 2005
From the Department of Internal Medicine, National Center for Diabetes, Endocrinology and Genetics, Amman, Jordan.
Address correspondence and reprint requests to Dr. Kamel M. Ajlouni, Department of Internal Medicine, National Center for Diabetes, Endocrinology and Genetics, P.O. Box 13165, Amman, Jordan 11942.
© 2006 AACE.

when the presence of a thyroid disorder was suspected or as part of the battery of studies performed for patients with short stature, diabetes mellitus, or age exceeding 40 years. All patients with primary hypothyroidism and TSH levels ≥50 μIU/mL, regardless of age or sex, were included in the study, whereas patients with postablative hypothyroidism or with central nervous system disorders were excluded. The study period was planned to extend for 2 years or until a minimum of 50 patients had been recruited, whichever criterion was satisfied first. The number of patients fulfilling the criteria of the study was 53 (49 female and 4 male patients), with ages ranging from 10 months to 70 years.

Laboratory, Imaging, and Other Studies

Initial hormonal assessment included determination of levels of free thyroxine, free triiodothyronine, TSH, and prolactin as well as presence of antimicrosomal antibodies. Measurements were done with use of a microparticle enzyme immunoassay commercially available from Abbott Laboratories.

Serial free thyroxine, free triiodothyronine, TSH, and prolactin levels were determined every 2 months. Magnetic resonance imaging (MRI) was done to assess the size of the pituitary gland at presentation; 3-mm sections were obtained in every patient (with and without use of contrast medium) in T1 sagittal as well as T1 and T2 coronal views. Pituitary enlargement was defined as a height of the pituitary gland in excess of 9 mm. The volume of the pituitary gland was calculated by using the following Dichori and Nelson formula: volume = ½ × length × width × height (2,3). In patients with pituitary enlargement, follow-up MRI was done 6 to 12 months after initiation of thyroxine treatment. Visual field examination was performed by an ophthalmologist (using Goldman's perimetry method) in patients with an enlarged pituitary gland on MRI.

Statistical Analysis

Patients were divided into two groups—those with TSH levels between 50 and 99 μIU/mL and those with TSH levels ≥100 μIU/mL. Statistical analysis was performed, and Yates method of continuity correction was used.

RESULTS

Thyroid function tests were done in 3,521 patients seen at our medical facility during the previously indicated study period; the results are shown in Table 1. Fifty-three patients who had TSH levels ≥50 μIU/mL were eligible for inclusion in the study. Of the 53 patients, 49 (92%) were female subjects; almost half (47%) of the study participants were between the ages of 20 and 40 years. The sex and age-group distributions of the patients are summarized in Table 2. Pituitary enlargement on MRI was detected in 16 of 18 patients (89%) younger than or equal to 20 years of age and in 21 of 35 patients (60%) older than 20 years. The symptoms and clinical features at presentation of the patients are outlined in Table 3. Hypothyroidism was diagnosed in only 26 patients (49%) before thyroid function testing was performed. Among female patients, 22% presented with menstrual irregularities, infertility, and galactorrhea, and dopamine agonists were prescribed for presumed prolactinoma in some of them. Surgical intervention was scheduled for 4 patients with a diagnosis of pituitary adenoma before the pituitary hyperplasia was ultimately attributed to primary hypothyroidism. Surgical intervention for pituitary adenoma remained an option in an adolescent girl in whom severe primary hypothyroidism was associated with headaches; visual field defects and the massive pituitary enlargement showed limited and slow regression with thyroxine treatment.

Two prepubertal girls presented with irregular menses, premature breast development, and multicystic ovaries detected on ultrasound examination. Unilateral oophorectomy was performed in one girl because of the erroneous diagnosis of ovarian cancer before her precocious puberty was correctly ascribed to severe primary hypothyroidism (12). Two young female patients presented with ovarian enlargement and abdominal pain, and ovarian cancer was diagnosed in one of them. Fortunately, she was spared the planned total abdominal hysterectomy and bilateral salpingo-oophorectomy after primary hypothyroidism was diagnosed (13).

Among 2 girls with dry ichthyotic skin changes, one had been diagnosed as having zinc deficiency. Treatment with zinc for several years, however, had yielded no improvement.

All 4 male patients in this series had the classic symptoms of hypothyroidism.

An enlarged pituitary gland on MRI with convex upper surface was detected in 37 of 53 patients (70%),

Table 1
Distribution of TSH Levels
Among 3,521 Patients Tested*
Between April 2002 and August 2004†

TSH level (μIU/mL)	Patients	
	No.	%
<5	3,098	88
5-<10	200	5.7
10-<50	163	4.6
50-99	23	0.6
≥100	37	1.1
Total	3,521	100

*At the National Center for Diabetes, Endocrinology and Genetics, Amman, Jordan.
†TSH = thyroid-stimulating hormone (thyrotropin).

Table 2
Sex and Age-Group Distributions of Study Patients With TSH Levels ≥50 μIU/mL, Stratified by Pituitary Enlargement*

Factor	Patients with pituitary enlargement	Patients with no pituitary enlargement	Total
Total no. (%)	37 (70)	16 (30)	53
Sex			
Male	3	1	4
Female	34	15	49
Age (yr)			
0-12	9	1	10
>12-20	7	1	8
>20-40	16	9	25
>40	5	5	10

*TSH = thyroid-stimulating hormone (thyrotropin).

with 31 of the 37 (84%) having TSH levels of ≥100 μIU/mL. Patients with TSH levels of ≥100 μIU/mL were found to be 8.6 times more likely to have an enlarged pituitary gland in comparison with patients who had TSH levels of 50 to 99 μIU/mL (odds ratio, 8.6; 95% confidence interval, 2.2 to 33). Suprasellar extension was noted on MRI in 29 of the 37 patients (78%) with pituitary enlargement.

Galactorrhea was present in 47% of the patients with an enlarged pituitary gland and in 40% of patients with a pituitary size within normal range. The difference was not statistically significant (odds ratio, 1.2; 95% confidence interval, 0.38 to 4.2).

The prolactin levels did not correlate with the TSH levels in this study. The highest prolactin level was 101 ng/mL in a 10-month-old child who was hypoactive and had a TSH level of 337 μIU/mL.

Visual field examination was requested for all patients with pituitary enlargement, but it was adequately done in only 24 patients. Lack of cooperation was the cause of inadequate study results in the rest. Constricted visual fields were found in 2 of the 24 patients (8%). Both patients were female subjects who presented with typical symptoms of hypothyroidism. The first patient had a pretreatment TSH level of 100 μIU/mL and an initial pituitary volume of 1,188 mm^3 (pituitary height, 11 mm). After treatment, her TSH level and pituitary volume were 0.27 μIU/mL and 231 mm^3 (height, 6 mm), respectively. The second patient had a pretreatment TSH level of 632 μIU/mL and an initial pituitary volume of 1,040 mm^3 (height, 13 mm). After treatment, her TSH level and pituitary volume were 1.01 μIU/mL and 770 mm^3 (height, 10 mm), respectively. Repeated assessment of visual fields 6 months after initiation of thyroxine therapy revealed no change in the defect despite adequate thyroxine treatment in the second patient.

After thyroxine therapy, MRI of the pituitary gland was repeated in 26 patients with an initially enlarged gland. Normalization of the pituitary hyperplasia was evident in 11 of the 26 patients (42%), a decrease in the size of the pituitary gland was evident in 5 patients (19%), and a partially empty sella was seen in 6 patients (23%). One patient (4%) had no change in the pituitary size despite adequate thyroxine treatment. Three patients (12%) were noncompliant with therapy; one of them had no change in the size of the pituitary gland, and the other 2 had further enlargement of the gland (Table 4).

DISCUSSION

The hypothyroid state causes an elevation in the serum levels of thyrotropin-releasing hormone and hyperplasia of the thyrotropin-producing cells, in conjunction with subsequent enlargement of the pituitary gland (2,14,15). Progression of hyperplasia of the anterior pituitary may be rapid, occurring with acute development of hypothyroidism in patients who receive radioiodine therapy for thyroid carcinoma (2). Enlargement of the pituitary and sella turcica in patients with primary hypothyroidism has previously been reported, and a positive correlation was noted between the volume of the sella turcica and the TSH levels (1). Similar findings were reported in cases of congenital hypothyroidism (4). Smallridge (14), in a 1987 review of the clinical, pathologic, and surgical literature, found that the reported incidence of pituitary enlargement in patients with primary hypothyroidism was less than 1%. In 1996, Beck-Peccoz et al (15) reviewed 210 published cases from 97 studies; those investigators noted that the

Table 3
Presenting Features Among 53 Patients
With TSH Levels ≥50 μIU/mL, Stratified by Pituitary Enlargement*

Symptom or clinical finding	Patients (no.)		
	With pituitary enlargement	With no pituitary enlargement	Total
Clinical diagnosis of hypothyroidism	19	7	26
Learning disability	2	0	2
Short stature	2	0	2
Goiter	3	4	7
Galactorrhea and menstrual irregularities†	6	5	11
Precocious puberty†	2	0	2
Ovarian enlargement†	2	0	2
Dry skin (ichthyosis)	1	0	1
Total no.	37	16	53

*TSH = thyroid-stimulating hormone (thyrotropin).
†In female patients only.

reported studies were extremely uneven in the depth of analysis and the focus, depending on the year of publication and the specialty of the authors. The findings at presentation in our series of patients were comparable to the cumulative findings in that review (15). For example, hypothyroidism was the dominant presentation in 38% of adults and 42% of children in that previous review (15); in our current series, this presentation was noted in 49% of all patients. Precocious puberty was seen among children in both our series and that review; one of our patients underwent drastic unwarranted interventions. Although ovarian enlargement in postpubertal female patients was not reported in the aforementioned review, it was seen in 2 of our patients. Our study focused primarily on the association between TSH levels and pituitary enlargement. All patients with hypothyroidism and TSH levels ≥50 μIU/mL were included in our study, irrespective of the mode of presentation, and were studied by a unified protocol. Imaging was done by MRI, which provides the best visualization of the hypothalamic-pituitary anatomy. We found pituitary enlargement in 70% of patients with TSH levels ≥50 μIU/mL, with a statistically significant positive correlation between the size of the enlarged pituitary gland and the TSH levels ($P = 0.002$). Radiologic studies in the reviewed series displayed heterogeneity in the groups studied and in the results; the incidence of pituitary enlargement in patients with hypothyroidism varied from 25% to 81% (15).

Thyrotropin-releasing hormone has the ability to stimulate prolactin-producing cells (lactotrophs) (9). Patients with primary hypothyroidism can present with galactorrhea, infertility, menstrual irregularities, and pituitary enlargement. This combination of findings can be misdiagnosed as the presence of a prolactinoma, and inappropriate management may subsequently be initiated (4-9,14,15). Dopamine agonists could restore fertility in such patients, and pregnancy could occur while hypothyroidism persists (16), with its recognized hazards to the fetus.

In this study, 11 of 49 female patients with TSH levels ≥50 μIU/mL presented with menstrual irregularities, galactorrhea, primary infertility, and pituitary enlargement. We found no significant correlation between TSH and prolactin levels in our patients with primary hypothyroidism, but a clear association between elevated serum prolactin levels and primary hypothyroidism has been seen in previous studies (17). Two female children in our series presented with features of precocious puberty caused by primary hypothyroidism (12), a picture that had been described previously by Van Wyck and Grumbach (18). At presentation, both patients had menstruation and breast development but no pubic hair, and their luteinizing hormone and follicle-stimulating hormone response to gonadotropin-releasing hormone stimulation was prepubertal. Both patients had an enlarged pituitary gland on MRI initially and subsequent cessation of menses and reduction in the size of the pituitary gland after thyroxine treatment. Failure to detect the presence of hypothyroidism in a menstruating child may lead to inappropriate management.

Two female patients in our series had features of ovarian hyperstimulation syndrome caused by primary hypothyroidism, which improved with thyroxine treatment. Therefore, unnecessary surgical interventions were avoided. We had previously reported one of these cases (13).

Pituitary enlargement attributable to primary hypothyroidism was reported to cause visual field defects because of compression of the optic chiasm (19,20);

Table 4
Age, Sex, TSH and Prolactin Levels, and Pretreatment and Posttreatment Pituitary Gland Size and Height in 26 Patients Who Had a Follow-Up MRI for Assessment of Pituitary Gland Volume Changes*

Case	Age (yr)	TSH (μIU/mL)	Prolactin (ng/mL)	Pretreatment pituitary volume (mm^3) on MRI (vertical height in mm)	Posttreatment pituitary volume (mm^3) on MRI (vertical height in mm)	% reduction in pituitary volume
1	10	50	…	264 (11)	672 (14)	+155†
2	19	65	16	1,080 (12)	675 (9)	38
3	46	69	…	539 (14)	490 (10)	9
4	41	71	24	672 (12)	216 (9)	68
5	12	75	…	520 (10)	432 (8)	17
6	32	>100‡	49	1,188 (11)	231 (6)	81
7	9	>100‡	54	1,120 (14)	234 (9)	79
8	33	>100‡	16	420 (10)	240 (8)	43
9	40	>100‡	11	600 (12)	243 (9)	60
10§	10	>100‡	7	520 (10)	288 (8)	45
11	32	>100‡	69	726 (11)	423 (7)	42
12	8	>100‡	74	924 (12)	440 (8)	52
13	32	>100‡	33	1,045 (11)	600 (8)	43
14	28	>100‡	12	1,482 (12)	819 (7)	45
15	30	120	…	1,000 (20)	352 (11)	65
16	19	145	16	720 (10)	720 (10)	0
17	30	157	50	1,072 (15)	1,072 (15)	0†
18§	56	190	12	599 (10)	320 (8)	47
19	32	191	…	1,404 (12)	480 (5)	66
20	26	195	36	585 (13)	840 (12)	+44†
21	20	230	…	1,040 (13)	240 (8)	77
22	33	261	87	1,100 (11)	997.5 (7)	9
23	65	269	28	312 (13)	120 (8)	62
24	26	632	34	1,040 (13)	770 (10)	26
25	4	1,645	100	2,176 (16)	408 (8)	81
26	19	4,191	38	1,567 (11)	357 (7)	77

*MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone (thyrotropin). Volume = ½ × length × width × height.
†Patients were noncompliant with treatment.
‡The thyroid-stimulating hormone measurement was done without further dilution.
§Male patients; the rest are female patients.

thyroxine treatment usually yields improvement. In our series, 2 of 24 patients (8%) who underwent visual field examination had constricted visual fields. Reassessment of visual fields 6 months after initiation of thyroxine therapy revealed no change in the defect, despite adequate thyroxine treatment in 1 of the 2 patients. The explanation for lack of visual field improvement in this patient may be the use of low doses of thyroid hormone that inhibit the release of TSH but not its synthesis; thus, pituitary TSH content may increase (19).

Repeated pituitary MRI in 26 patients showed regression of the volume of the pituitary gland in 22 (85%) of them, a finding that is consistent with outcomes in other studies (4,10,11,20-22). Regression of pituitary enlarge-

ment can be rapid—within 1 week after initiation of thyroid hormone replacement therapy (23).

CONCLUSION

The current study shows the high incidence of pituitary enlargement in patients with primary hypothyroidism. The potential for regression of the pituitary enlargement with successful thyroxine replacement therapy is also emphasized.

Assessment of thyroid function is imperative in the evaluation of any patient with an enlarged pituitary gland in order to avoid errors in diagnosis, which can result in complex, unnecessary, and even harmful therapeutic interventions. Misdiagnosis of a prolactinoma is of particular concern in this setting. This study also draws attention to some unusual clinical presentations of primary hypothyroidism, such as precocious puberty and ovarian hyperstimulation syndrome.

REFERENCES

1. **Yamada T, Tsukui T, Ikejiri K, Yukimura Y, Kotani M.** Volume of sella turcica in normal subjects and in patients with primary hypothyroidism and hyperthyroidism. *J Clin Endocrinol Metab*. 1976;42:817-822.
2. **Shimono T, Hatabu H, Kasagi K, et al.** Rapid progression of pituitary hyperplasia in humans with primary hypothyroidism: demonstration with MR imaging. *Radiology*. 1999;213:383-388.
3. **Takano K, Utsunomiya H, Ono H, Ohfu M, Okazaki M.** Normal development of the pituitary gland: assessment with three-dimensional MR volumetry. *AJNR Am J Neuroradiol*. 1999;20:312-315.
4. **Desai MP, Mehta RU, Choksi CS, Colaco MP.** Pituitary enlargement on magnetic resonance imaging in congenital hypothyroidism. *Arch Pediatr Adolesc Med*. 1996;150: 623-628.
5. **Brandle M, Schmid C.** Galactorrhoea and pituitary mass: a typical prolactinoma? *Postgrad Med J*. 2000;76:232-234.
6. **Chan AW, MacFarlane IA, Foy PM, Miles JB.** Pituitary enlargement and hyperprolactinaemia due to primary hypothyroidism: errors and delays in diagnosis. *Br J Neurosurg*. 1990;4:107-112.
7. **Ozbey N, Sariyildiz E, Yilmaz L, Orhan Y, Sencer E, Molvalilar S.** Primary hypothyroidism with hyperprolactinaemia and pituitary enlargement mimicking a pituitary macroadenoma. *Int J Clin Pract*. 1997;51:409-411.
8. **Poretsky L, Garber J, Kleefield J.** Primary amenorrhea and pseudoprolactinoma in a patient with primary hypothyroidism: reversal of clinical, biochemical, and radiologic abnormalities with levothyroxine. *Am J Med*. 1986;81:180-182.
9. **Pioro EP, Scheithauer BW, Laws ER Jr, Randall RV, Kovacs KT, Horvath E.** Combined thyrotroph and lactotroph cell hyperplasia simulating prolactin-secreting pituitary adenoma in long-standing primary hypothyroidism. *Surg Neurol*. 1988;29:218-226.
10. **Young M, Kattner K, Gupta K.** Pituitary hyperplasia resulting from primary hypothyroidism mimicking macroadenomas. *Br J Neurosurg*. 1999;13:138-142.
11. **Atchison JA, Lee PA, Albright AL.** Reversible suprasellar pituitary mass secondary to hypothyroidism. *JAMA*. 1989;262:3175-3177.
12. **Taher BM, Ajlouni HK, Hamamy HA, Shegem NS, Madanat AY, Ajlouni KM.** Precocious puberty at an endocrine centre in Jordan. *Eur J Clin Invest*. 2004;34:599-604.
13. **Taher BM, Ghariabeh RA, Jarrah NS, Hadidy AM, Radaideh AM, Ajlouni KM.** Spontaneous ovarian hyperstimulation syndrome caused by hypothyroidism in an adult. *Eur J Obstet Gynecol Reprod Biol*. 2004;112:107-109.
14. **Smallridge RC.** Thyrotropin-secreting pituitary tumors. *Endocrinol Metab Clin North Am*. 1987;16:765-792.
15. **Beck-Peccoz P, Brucker-Davis F, Persani L, Smallridge RC, Weintraub BD.** Thyrotropin-secreting pituitary tumors. *Endocr Rev*. 1996;17:610-638.
16. **Mroueh AM, Siler-Khodr TM.** Ovarian refractoriness to gonadotropins in cases of inappropriate lactation: restoration of ovarian function with bromocriptine. *J Clin Endocrinol Metab*. 1976;43:1398-1401.
17. **Fish LH, Mariash CN.** Hyperprolactinemia, infertility, and hypothyroidism: a case report and literature review. *Arch Intern Med*. 1988;148:709-711.
18. **Van Wyck JJ, Grumbach MM.** Syndrome of precocious menstruation and galactorrhea in juvenile hypothyroidism: an example of hormonal overlap in pituitary feedback. *J Pediatr*. 1960;57:416-435.
19. **Yamamoto K, Saito K, Takai T, Naito M, Yoshida S.** Visual field defects and pituitary enlargement in primary hypothyroidism. *J Clin Endocrinol Metab*. 1983;57:283-287.
20. **Pita JC Jr, Shafey S, Pina R.** Diminution of large pituitary tumor after replacement therapy for primary hypothyroidism. *Neurology*. 1979;29:1169-1172.
21. **Silver BJ, Kyner JL, Dick AR, Chang CH.** Primary hypothyroidism: suprasellar pituitary enlargement and regression on computed tomographic scanning. *JAMA*. 1981;246:364-365.
22. **Jawadi MH, Ballonoff LB, Stears JC, Katz FH.** Primary hypothyroidism and pituitary enlargement: radiological evidence of pituitary regression. *Arch Intern Med*. 1978; 138:1555-1557.
23. **Sarlis NJ, Brucker-Davis F, Doppman JL, Skarulis MC.** MRI-demonstrable regression of a pituitary mass in a case of primary hypothyroidism after a week of acute thyroid hormone therapy. *J Clin Endocrinol Metab*. 1997;82: 808-811.