Pituitary hyperplasia mimicking pituitary macroadenoma in two adolescent patients with long-standing primary hypothyroidism: case reports and review of literature

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We report two cases with primary autoimmune hypothyroidism and an ectopic thyroid gland causing pituitary enlargement mimicking pituitary macroadenoma. One of the cases presented with complaints of headache and short stature and the other case with a complaint of menorrhagia. In both cases, the pituitary mass and symptoms resolved with levothyroxine replacement. Normal menses resumed. However, pituitary dynamic tests revealed persistent growth hormone and gonadotropin deficiency in one case and growth hormone deficiency in the other. To our knowledge, this is the first report in an adolescent of hypogonadotropic hypogonadism, growth hormone deficiency, and menorrhagia associated with pituitary hyperplasia secondary to primary hypothyroidism. The recognition of the association between reversible pituitary hyperplasia and primary hypothyroidism might eliminate unnecessary surgery.

Key words: pituitary macroadenoma, primary hypothyroidism, pituitary hyperplasia.

Thyrotroph hyperplasia secondary to hypothyroidism is a common cause of pituitary enlargement. Secondary pituitary enlargement in primary hypothyroidism in adults[1-4] and children can be due to both acquired[5-7] and congenital hypothyroidism[8,9]. Despite recent progress in imaging techniques, thyroid-stimulating hormone (TSH)-producing macroadenoma and hyperplasia of pituitary thyrotroph cells may be indistinguishable on magnetic resonance imaging (MRI). In such cases, the TSH response to thyrotropin-releasing hormone (TRH) and repeat MRI after thyroid hormone therapy may provide a definitive diagnosis. The recognition of the association between reversible pituitary hyperplasia and end-organ failure may eliminate unnecessary surgery[10,11].

We describe two adolescents with a pituitary hyperplasia extending to suprasellar area, which mimicked pituitary macroadenoma, and primary hypothyroidism. MRI revealed pituitary mass resolution with thyroxine replacement; however, pituitary dynamic function tests revealed growth hormone and gonadotropin (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]) deficiency in one patient and growth hormone deficiency in the other.

Case Reports

Case 1

A 14.5-year-old boy presented to his local hospital with headaches and delayed puberty. MRI of the pituitary showed a large pituitary mass consistent with a pituitary macroadenoma. Contrast enhancement with gadolinium-diethylenetriamine penta-acetic acid (DTPA) revealed homogeneous enhancement of the enlarged pituitary (Fig. 1). A provisional diagnosis of pituitary macroadenoma was made and the patient was referred for an endocrinology consultation before a planned

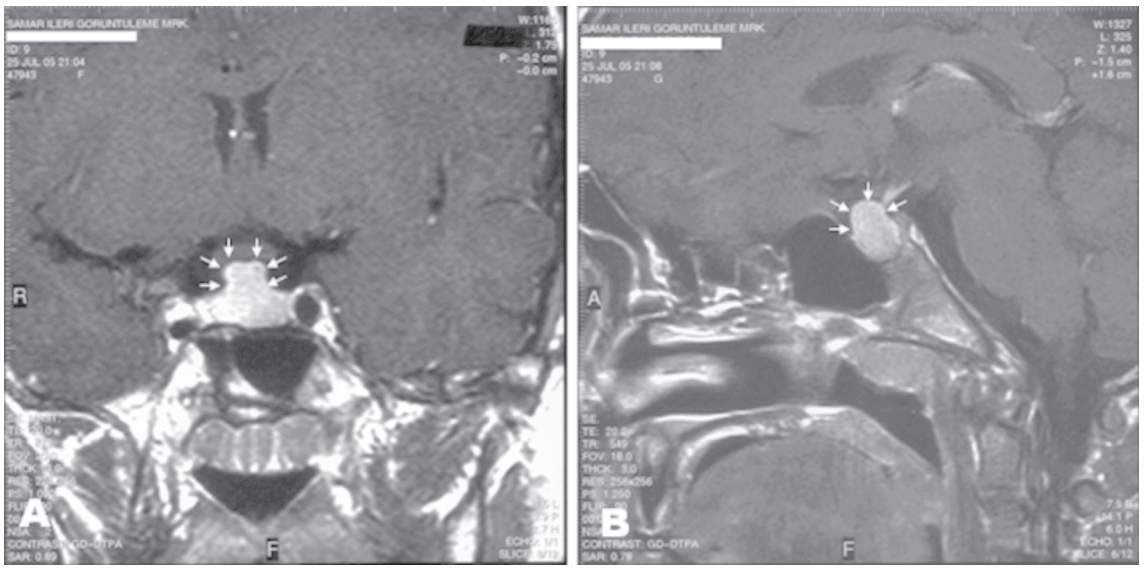

Fig 1. Pretreatment MRI of the pituitary gland. T_1-weighted coronal (A) and midsagittal (B) views of the pituitary demonstrating a large homogeneously enhancing sellar lesion with suprasellar extension (white arrows).

surgical adenomectomy. His symptoms included a notable mild headache, easy fatigability, extreme cold intolerance, and chronic constipation. The patient did not complain of visual acuity or visual field changes, polyuria, or polydipsia. His parents were concerned that he was the shortest student in his school; otherwise, the clinical history was unremarkable. The family history was non-contributory. On general examination, his body temperature was 35.8°C, pulse 72/min and regular, blood pressure 80/60 mmHg, height 135 cm (–3.6 SDs), and weight 39 kg (between 3rd-10th percentile). He had a pale, puffy, immature face with a poorly developed nasal bridge, and the thyroid gland was not palpable. He had failed to develop any secondary sexual traits. The results of the neurological examination were normal, including full visual fields on confrontational testing. The remainder of the clinical examination was normal. The results of his laboratory evaluations are shown in Table I. TSH and prolactin were assayed using appropriately diluted samples. Ultrasound of the thyroid revealed no thyroid gland in the normal position. A sublingual thyroid gland was revealed by ^{99m}Tc scintigraphy. Bone age was delayed five years compared to chronological age. The pituitary glycoprotein serum α-subunit level was 5.7 μg/L. The α-subunit/TSH molar ratio, which was calculated using the formula [(α-subunit in μg/L/TSH in mU/L) × 10] (12,13), was 0.17 (normal 0.5–5.0). Based on his clinical history and the results of the laboratory studies, a diagnosis of primary hypothyroidism was made, and his pituitary mass was attributed to secondary hyperplasia. Levothyroxine was commenced at 50 μg/day, increasing to 100 μg/day by two weeks. After three years of therapy, the patient was clinically and biochemically euthyroid, and his serum free T4 and TSH were within the normal range (21.9 pmol/L and 2.9 mU/L, respectively). The prolactin level decreased to 5.5 ng/ml and dynamic pituitary function tests revealed growth hormone, FSH, and LH deficiencies (Table II). Repeat MRI six months after levothyroxine replacement revealed complete resolution of the enlarged pituitary (Fig. 2).

Case 2

A 13-year-old girl presented with severe menorrhagia for six months. She also complained of cold intolerance, marked fatigue, sluggishness, and difficulty in school. Her medical history was unremarkable and she had no coagulation disorders. On general examination, she weighed 48 kg (50-75th percentile) and was 146 cm tall (3rd-10th percentile). She was a lethargic, sluggish, well-feminized girl. The thyroid gland was palpable. Her breasts were Tanner stage 4 bilaterally and her pubic hair was Tanner stage 3. Laboratory investigation revealed a serum estradiol of 118 pmol/L (3.2 ng/dl;

Table I. Results of the Hormonal Investigations of the Cases at Presentation

	Case 1	Case 2	Normal range
TSH, mU/L	334	232	0.5-5
Thyroxine (T_4), nmol/L	31.8	9.4	64-154
Free T_4, pmol/L	5.2	2.7	9-26
Prolactin, ng/ml	28	34	2-15
8 a.m. cortisol, nmol/L	490	345	150-650
8 a.m. corticotropin (ACTH), pmol/L	8	9	2-11
Thyroid peroxidase antibodies, IU/ml	12	855	0-35
Thyroglobulin antibodies, IU/ml	7	22	0-40
TSH responses to TRH administration			
0 min	333	234	
15 min	1863	580	
30 min	2010	456	
60 min	1992	372	
120 min	1965	306	

TSH: Thyroid-stimulating hormone. TRH: Thyrotropin-releasing hormone.

Table II. Dynamic Pituitary Function Tests After Three Years of Thyroxin Replacement

	Insulin tolerance test			Gn-RH stimulation test	
Time (min)	Glucose mmol/L	GH ng/mL	Cortisol nmol/L	FSH IU/L	LH IU/L
0	6	1.2	365	0.82	0.1
15	1.6	2	542	0.9	0.3
30	4.1	2.1	578	1.60	0.62
45	5.9	2.8	465	1.94	0.72
60	6.5	4.7	402	1.73	0.67

GH: Growth hormone (normal in GH stimulation tests >10 ng/ml). Cortisol (normal in hypoglycemic testing >495 nmol/L). FSH: Follicle-stimulating hormone (normal 2.4-11.0 mIU/ml). LH: Luteinizing hormone (normal 0.4-7.0 mIU/L). Gn-RH: Gonadotropin-releasing hormone.

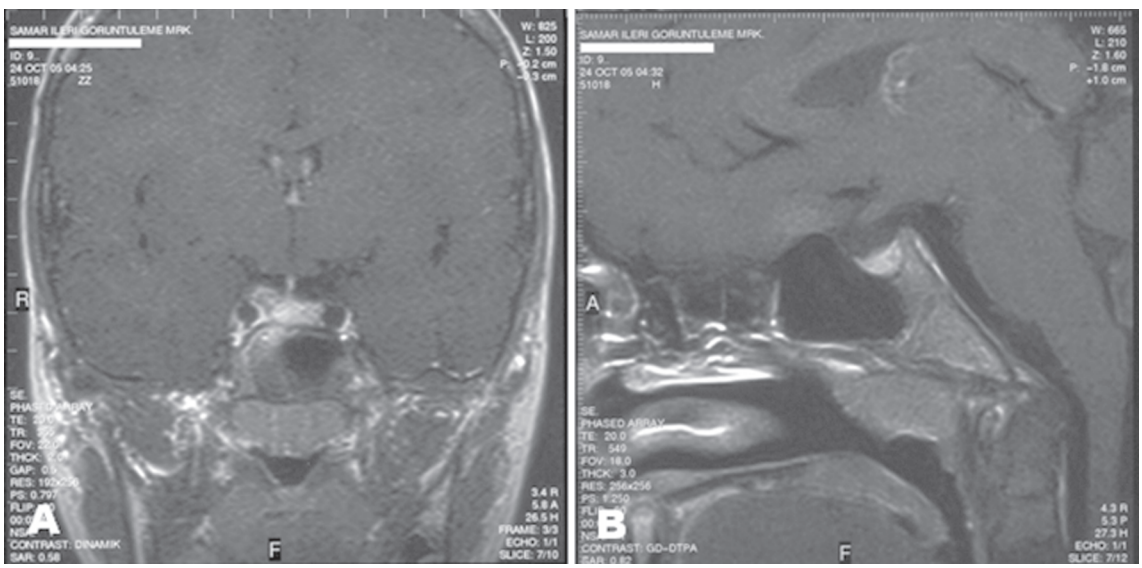

Fig. 2. Repeat MRI of the pituitary after six months of levothyroxine treatment. T_1-weighted coronal (A) and midsagittal (B) images show complete resolution of the pituitary enlargement.

consistent with Tanner stage 3), FSH 5.5 IU/L (Tanner stage 2 to adult), and LH 7.2 IU/L (Tanner stage 3–5). Baseline thyroid function tests, prolactin, and random cortisol levels are shown in Table I. Her bone age was 12 years. Thyroid ultrasonography revealed an enlarged thyroid gland with markedly heterogeneous echo texture, which was consistent with late-stage chronic thyroiditis. Her pituitary glycoprotein serum α-subunit level and α-subunit/TSH ratio were 0.9 μg/L and 0.03, respectively. Pituitary MRI revealed a homogeneously enhancing enlarged pituitary (height 11 mm) with suprasellar extension (Fig. 3). Based on the clinical history, laboratory findings, and MRI, a diagnosis of pituitary pseudo-adenoma secondary to primary hypothyroidism, consequent to chronic autoimmune (Hashimoto's) thyroiditis, was made. Levothyroxine was commenced at 50 μg/day for one week, increasing thereafter to 75–100 μg/day. After three years of thyroxine replacement, she was clinically and biochemical euthyroid (serum free thyroxine, 19.6 pmol/L; TSH, 3.2 mU/L), and regular menses resumed. The prolactin level decreased to 9.4 ng/ml, and dynamic pituitary function tests were performed (Table III). The insulin hypoglycemia test revealed a normal cortisol level and growth hormone deficiency. Repeat MRI showed complete resolution of the mass, with normalization of the pituitary gland (Fig. 4).

Discussion

Thyrotroph hyperplasia can be explained by the classical negative feedback loop in which reduced circulating levels of thyroid hormone result in overstimulation of thyrotrophs by TRH. Niépce[14] first recognized the possibility of increased

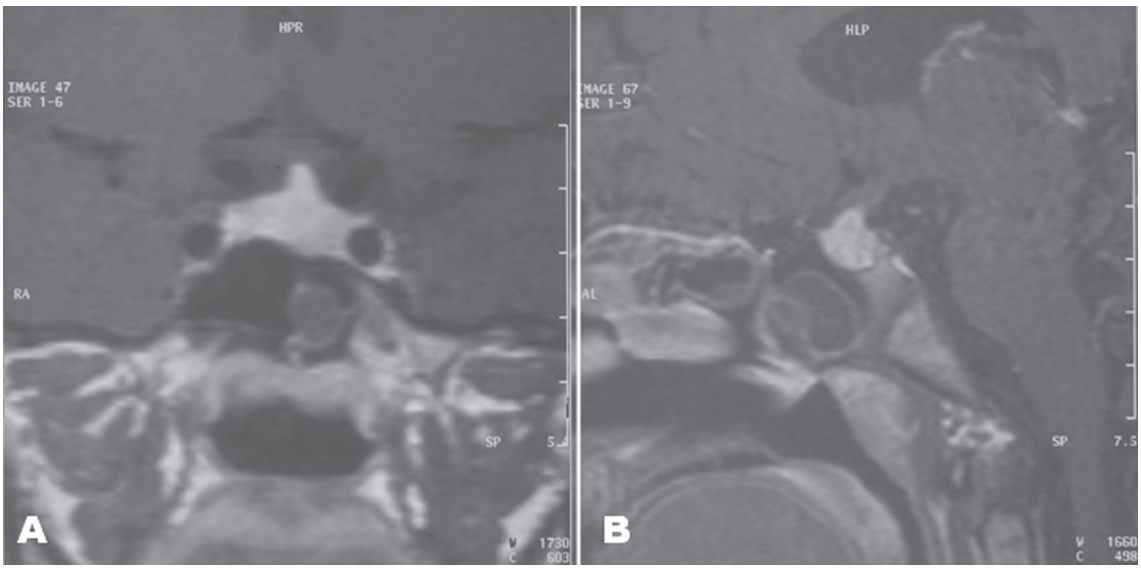

Fig. 3. Pretreatment MRI of the pituitary gland. T_1-weighted coronal (A) and midsagittal (B) images show an intrasellar, heterogeneously enhancing mass with suprasellar extension.

Table III. Dynamic Pituitary Function Tests After Three Years of Thyroxine Replacement

	Insulin hypoglycemia test			Gn-RH stimulation test	
Time (min)	Glucose mmol/L	GH ng/ml	Cortisol nmol/L	FSH IU/L	LH IU/L
0	6.1	0.1	385	7.2	5.5
15	1.5	2.9	590	8.2	19.1
30	5.1	2.1	532	11.3	20.3
45	5.6	1.6	469	9.2	20.4
60	6.3	1.3	447	9.2	19.2

GH: Growth hormone (normal in GH stimulation tests >10 ng/ml). Cortisol (normal in hypoglycemic testing >495 nmol/L). FSH: Follicle-stimulating hormone (normal 2.4-11.0 mIU/ml). LH: Luteinizing hormone (normal 0.4-7.0 mIU/L). Gn-RH: Gonadotropin-releasing hormone.

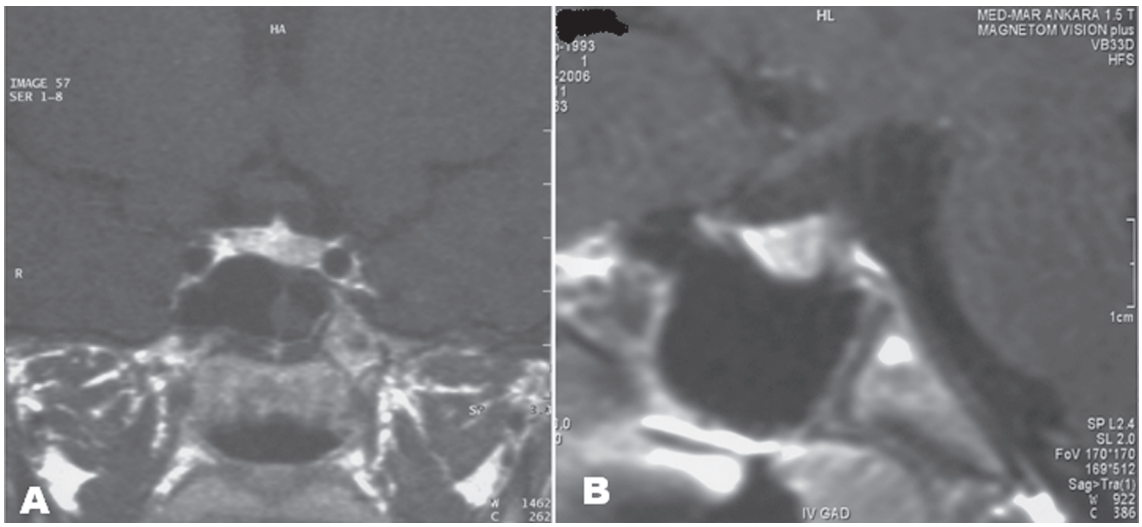

Fig. 4. Repeat MRI after six months of levothyroxine treatment. T_1-weighted coronal (A) and midsagittal (B) images show resolution of the pituitary enlargement.

pituitary size in primary hypothyroidism in 1851, at the autopsy of a cretin. Pituitary and sella enlargement in patients with long-standing primary hypothyroidism is well established[1-10]. Mild to moderate hyperprolactinemia is present in about three-quarters of patients[15]. The hyperprolactinemia in primary hypothyroidism is often attributed to the stimulatory effect of TRH on lactotropic cells[15,16] or from reduced hypothalamic dopamine content secondary to compression of hyperplastic pituitary gland on the pituitary stalk[1]. The pituitary enlargement associated with hypothyroidism responds well to medical treatment and complete regression of the pituitary mass can be confirmed by repeat MRI after thyroxine treatment. Interpretation of a pituitary mass without an endocrine investigation can lead to unnecessary surgery with potentially catastrophic results[1,10,11,17]. Despite recent progress in imaging, it is still difficult to distinguish between a pituitary adenoma and hyperplasia, even using high-resolution computerized tomography (CT) with contrast injection or MRI with gadolinium injection. The traditional diagnostic criteria for pituitary macroadenoma include homogeneous enlargement of the gland to a height greater than 10 mm, with or without erosion of the sellar floor, and deviation of the stalk[18]. The radiographic findings of macroadenoma overlap those of a diffusely enlarged pituitary gland. Therefore, pituitary imaging may be unable to reliably differentiate between pituitary adenoma and hyperplasia. Pituitary hyperplasia with long-standing primary hypothyroidism resolves completely with thyroxine therapy[2,3,19-21]. Repeat pituitary MRI after thyroxine therapy confirms the acute shrinkage of the hyperplasia, allowing the precise differentiation between hyperplasia and adenoma.

Thyroid-stimulating hormone-secreting adenomas constitute less than 5% of pituitary tumors in adults and are extremely rare in children[15]. The TSH levels in a TSH-secreting adenoma are often increased or inappropriately normal in the face of elevated T3 or T4 levels[15], while the thyroid hormone levels are hypothyroid in pituitary hyperplasia secondary to primary hypothyroidism. A baseline TSH level is insufficient to differentiate pituitary hyperplasia from a TSH-secreting tumor. Dynamic endocrine tests are helpful for differentiating a tumor from hyperplasia[15,22]. The TSH response to the TRH stimulation test in a TSH-secreting adenoma is blunted[22]. An elevated α-subunit/TSH molar ratio may be useful in the differential diagnosis of pituitary hyperplasia and a pituitary TSH-secreting adenoma[13,22]. The α-subunit/TSH molar ratio is often elevated (>1.0) in TSH-secreting adenomas[13,15]. The α-subunit and prolactin concentrations seen with pituitary hyperplasia never reach the levels seen in primary pituitary tumors. In our patients, baseline thyroid function tests were consistent with primary hypothyroidism secondary to an ectopic thyroid gland in Case 1, and with chronic autoimmune thyroiditis in Case 2.

The TSH responses to TRH stimulation tests revealed an exaggerated TSH response in both cases. The pituitary glycoprotein α-subunit/TSH molar ratio in Cases 1 and 2 was 0.17 and 0.03, respectively, countering the diagnosis of pituitary adenoma. In both cases, repeat pituitary MRI after levothyroxine therapy revealed complete regression of the pituitary mass. Based on the combined clinical findings, hormonal studies, and repeat MRI findings, the diagnosis of pituitary hyperplasia secondary to long-standing primary hypothyroidism was made. The recognition of this association may prevent unnecessary surgery, which can cause irreversible complications. This study indicated that the clinical history, basal hormone levels, dynamic endocrine tests, and repeat pituitary MRI after thyroxine replacement should be interpreted together to provide the precise diagnosis in a patient presenting with a pituitary mass.

The chief complaints reported at presentation in children with pituitary hyperplasia and primary hypothyroidism are associated with hypothyroidism (42%), abnormal puberty (45%; includes precocious or delayed puberty and gonadarche), mass compression (3%; includes headache or visual problems), prolactinoma (2%; includes amenorrhea or galactorrhea), and secondary hypoadrenocorticism[15]. On presentation, growth hormone deficiency was reported in 45% of the patients with pituitary hyperplasia; elevated FSH and LH in 13%; and low gonadotropins (FSH and LH) in 27%[15]. There are few reports on pituitary gland function after thyroxine replacement in children. Transient growth hormone deficiency[23,24], an empty sella, and hypopituitarism[25-27] have been reported. In our study, combined growth hormone, FSH, and LH deficiency persisted in Case 1, while growth hormone deficiency persisted in Case 2. Persistent growth hormone or gonadotropin deficiency might be attributed to pituitary enlargement causing compression of the pituitary stalk, resulting in decreased growth hormone or gonadotropins. As a pubertal disorder, menorrhagia has not been reported previously in an adolescent with pituitary hyperplasia. However, hypopituitarism and primary hypothyroidism may be coincidental in Case 1. To our knowledge, this is the first report of primary hypothyroidism (ectopic thyroid) leading to persistent hypogonadotropic hypogonadism and growth hormone deficiency in one case, and persistent growth hormone deficiency and reversible menorrhagia in the other. This rarity might be explained by neonatal screening for congenital hypothyroidism and the early diagnosis and therapeutic intervention in older children with hypothyroidism. Unfortunately, national neonatal screening for congenital hypothyroidism has been implemented only recently in Turkey.

In conclusion, to determine the final diagnosis quickly, safely, and reliably in a patient with a pituitary mass, the workup should include the clinical history, endocrine studies, pituitary glycoprotein serum α-subunit levels, TSH/α-subunit ratio, and repeat pituitary MRI after levothyroxine replacement (Table IV). In an adolescent presenting with menorrhagia, thyroid function should be evaluated before considering detailed tests. The dynamic pituitary function test should be repeated during the follow-up

Table IV. Diagnostic Criteria for TSH-Secreting Pituitary Macroadenoma and Pituitary Hyperplasia Secondary to Long-Standing Primary Hypothyroidism

	Macroadenoma	Pituitary hyperplasia
Related clinic findings	Hyperthyroidism	Hypothyroidism
Baseline TSH and TFTs	TSH ↑, T_4↑, fT_4↑, T3↑	TSH ↑/↑↑↑, T_4 ↓, fT_4↓, T3 N/↓
TSH response to TRH test	Blunted	Exaggerated
α-subunit levels (mg/L)[a]	Usually >5	Usually <5
Molar TSH/α-subunit ratio[a]	Usually >1.0	Usually <1.0
Repeat pituitary MRI after thyroxine trial[b]	No change[b]	Complete regression[c]

TFTs: Thyroid function tests. TSH: Thyroid-stimulating hormone. TRH: Thyrotropin-releasing hormone.
[a]The molar α-subunit/TSH ratio is calculated using the formula: Molar α-subunit/TSH ratio = [(α-subunit in μg/L divided by TSH in mU/L) × 10]. α-subunit, less than 3 μg/L in males and before menopause, less than 5 μg/L after menopause; α-subunit/TSH, if TSH is normal: ratio below 5.7 in normogonadotropic patients and below 29.1 in hypergonadotropic patients; if TSH is elevated: ratio below 0.7 in normogonadotropic patients and below 1.0 in hypergonadotropic patients[12,13].
[b]Reference 15
[c]Reference 3

period in all patients with pituitary hyperplasia. Long-standing primary hypothyroidism may lead to irreversible pituitary injury, which can lead to a deficiency in one or more pituitary hormones. Surgery should be reserved for decompression of the optic chiasm or to obtain a pathological diagnosis in the case of a pituitary mass not responding to, or worsening on, thyroid hormone replacement.

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