

Tablets or scalpel: Pituitary hyperplasia due to primary hypothyroidism

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We describe a patient with pituitary hyperplasia due to primary hypothyroidism. Pituitary hyperplasia and pituitary masses cannot be reliably differentiated on imaging alone, despite significant improvement in imaging quality in recent years.

Case report

Our patient (18 years old) first noticed symptoms of reduced visual acuity two years before seeking medical advice (from an ophthalmologist) when he could not read the number plate of the car during his driving test. He also reported tiredness, lethargy, lack of concentration, slow mentation, and memory problems for the previous 2 years. He shaved once a week. He reported normal erectile function. The family history was positive for hypothyroidism in his mother.

He looked much younger than his age. He had male pattern body hair distribution; however, hair was sparse. His corrected visual acuities were 6/12 right and 6/24 left, and ocular examination was normal. His electrophysiology showed subtle delay in the pattern of visual evoked potentials on the right, with borderline responses on the left. Visual field testing with the Octopus perimeter showed subtle superotemporal defects bilaterally.

Investigations

Blood tests showed primary hypothyroidism with markedly high TSH, hypogonadotropic hypogonadism, low IGF-1, and hyperprolactinemia (Table). Random cortisol was low, but the stimulated cortisol rose to 738 nmol/l (normal value >550 nmol/l).

A CT scan of the head showed a mass in the sella turcica. An MRI scan confirmed a pituitary mass extending upward into the suprasellar cistern, elevating and compressing the optic chiasm (Figs. 1-5).

Treatment

Thyroxine replacement was started with monitoring of the patient's clinical condition and biochemical profile. Surgical treatment was to be considered only if there was deterioration in his visual fields. Frequent clinic visits were organized to properly monitor the treatment.

Outcome and followup

The patient made a tremendous improvement symptomatically and biochemically over a period of 3 months, with thyroid hormone replacement initially at a dose of 25 mcg, increased rapidly to 75 mcg. All of the pituitary hormone levels returned to the reference range, including testosterone and cortisol. MRI 3 months later (Fig. 6) showed a reduction in the size of the mass in the pituitary fossa such that it no longer displaced the optic nerves or chiasm. The possibility of a primary pituitary mass could not be excluded; however, there was a definite reduction in the size of the gland, which was no longer displacing the optic nerve or chiasm.

Clinical improvement continued during subsequent clinic visits. The patient's scan in ten months (Fig. 7) showed further reduction in the size of the pituitary gland, with persistent changes. He remains on thyroxine, and to date (12

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Dates	At presentation	3 weeks later	11 weeks later	10 months later
Random Cortisol nmol/l (171-536)	269	186	189	
Free T4 pmol/l (12.0-22.0)	0.7	3.9	10.8	15.5
Free T3 pmol/l (4.0-6.8)	<0.4			
TSH mIU/l(0.27-4.20)	>100	>100.00	3.83	1.53
LH IU/l (1.7-8.6)	2.0	2.3	3.2	
FSH IU/l (1.5-12.4)	5.7	5.5	1.7	
Prolactin mIU/l (86-324)	1134	1326	451	
Testosterone nmol/l, (7.6-31.4)	7.1	7.0	18.9	
Growth hormone needs units			0.4	
IgF-1 nmol/l (16.5-55.1),	10.3	11.2	30.4	
Glucose units		4.7		
Levothyroxine dose	Started 25 mcg/day	Increased to 75 mcg/day	On 75 mcg/day	75 mcg/day
Insulin tolerance test showed adequate cortisol reserves, which rose to 738nmol/l (normal response value >550 nmol/l).				

Table 1. Laboratory investigations

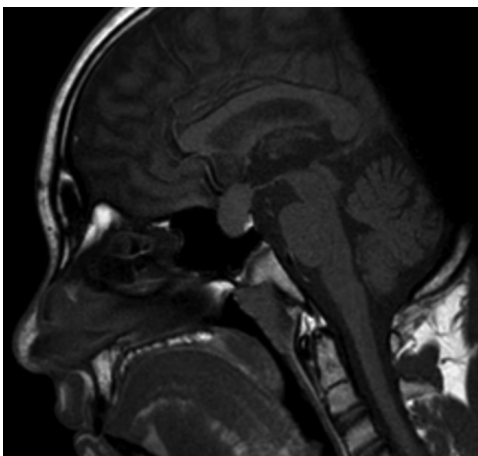
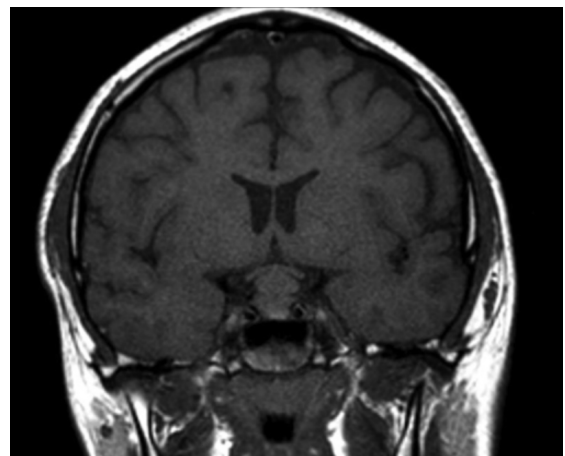


Fig. 1 (left). MRI scan image on presentation. Noncontrast, fat-saturated, T1-weighted sagittal view.

Fig. 2 (right). MRI scan on presentation. Post-contrast, fat-saturated, T1-weighted coronal view.



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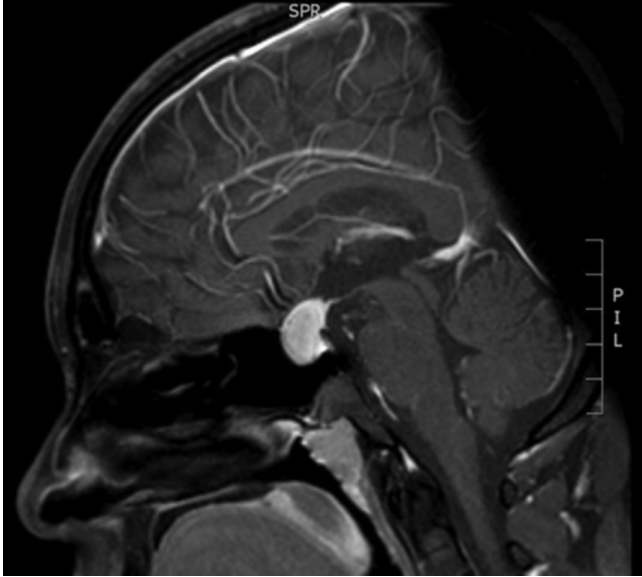


Fig. 3. MRI scan image on presentation. Postcontrast, fat-saturated, T1-weighted sagittal view showing homogeneous contrast uptake.

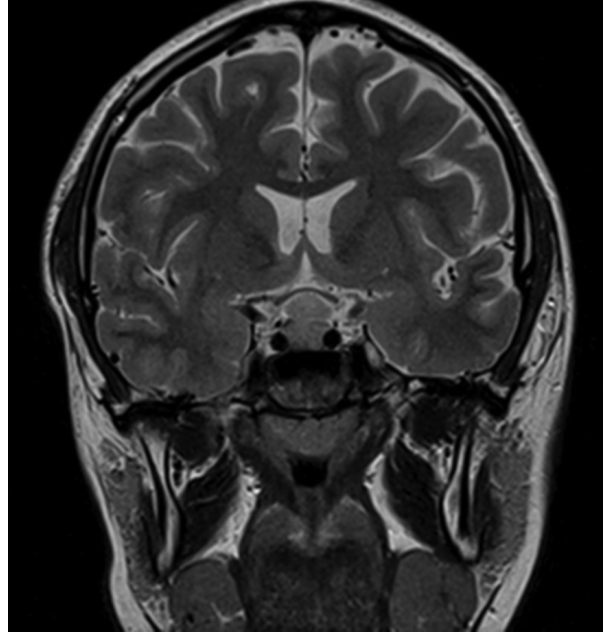


Fig. 5. MRI scan at presentation. T2 coronal section showing suprasellar extension and compression on optic chiasm.

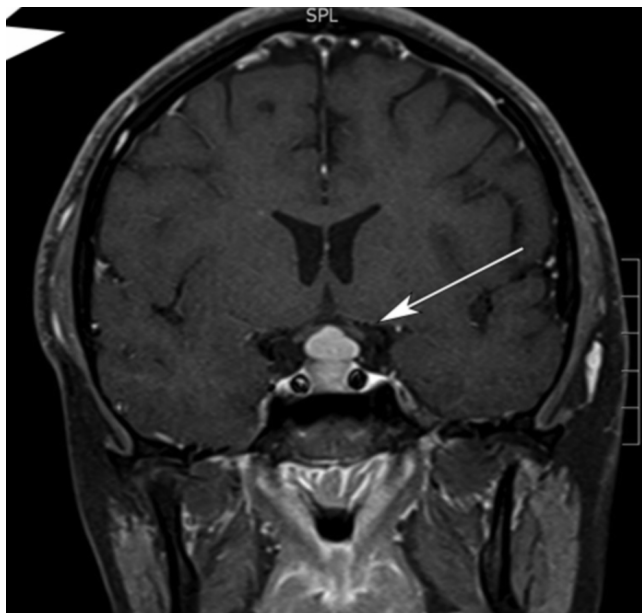


Fig. 4. MRI scan on presentation. Postcontrast, fat-saturated, T1-weighted coronal view showing nipple sign in the enlarged pituitary gland (arrow).

months since initiation of therapy), he has had no clinical symptoms or signs.

While pituitary hyperplasia is an uncommon diagnosis, the endocrinologist or neuroradiologist should consider it a possibility in the appropriate clinical scenario. A multidisciplinary approach helps in making these decisions and in providing appropriate treatment.

With the improvement in imaging techniques, we are increasingly coming across scenarios of abnormal findings on the imaging before the biochemical investigations. This case emphasizes the importance of complete biochemical investigations before interpreting imaging findings for endocrine diagnosis.

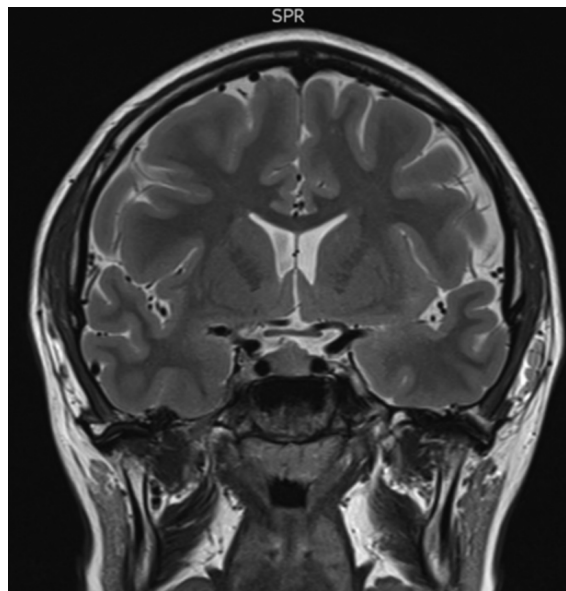


Fig. 6. MRI after three months. Noncontrast T2 coronal image. Note reduction in size of pituitary gland. Nipple sign is also reversing.

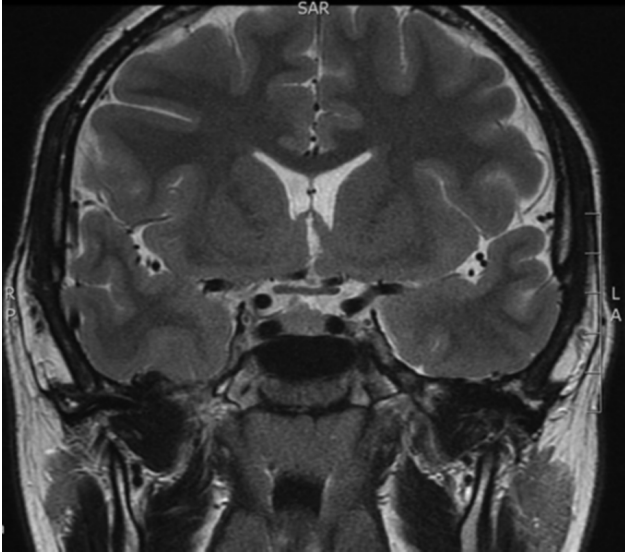


Fig. 7. MRI after ten months. Noncontrast T2 coronal image. Pituitary gland is smaller, with minimal residual changes.

Discussion

Primary hypothyroidism can lead to hypertrophy of thyrotroph cells in the adenohypophysis, resulting in enlargement of the anterior pituitary (1). It results from the loss of thyroxine feedback inhibition (2) and the subsequent overproduction of thyrotropin-releasing hormone (TRH) (3). Pituitary hyperplasia due to primary hypothyroidism occurs most frequently among all feedback tumors, reported as 33.3% (4). Despite continuing improvements in imaging techniques, it is not always possible to distinguish between pituitary adenomas and pituitary hyperplasia on CT or MRI scans. In this patient, TSH-producing adenoma and hyperplasia of anterior pituitary thyrotroph would be the most likely possibilities in view of the very high levels of TSH. The therapeutic option for primary hypothyroidism (thyroxine replacement) completely differs from that for TSHoma (usually, surgery).

Pituitary hyperplasia due to primary hypothyroidism is defined by an enlargement of the pituitary follicle, hyperplasia of hormone-producing cells, and changes of pituitary structure. The differences in ultrastructure between hyperplastic cells and normal pituitary cells are very obvious. Hyperplasia is always caused by pathological factors, and this is mostly found in primary hypothyroidism (5). The incidence of pituitary hyperplasia in patients with hypothyroidism varies from 25% to 81% (6); a high incidence (70%) is reported in patients with TSH levels ≥ 50 $\mu\text{IU/ml}$ (7). Because TRH (thyrotropin-releasing hormone) also has a weak stimulatory effect on lactotroph cells, mild to moderate hyperprolactinemia may occur in about three-quarters of patients (6). Children and young patients with pituitary hyperplasia and primary hypothyroidism do not usually present with symptoms secondary to sellar expansion (3%) but rather with symptoms of hypothyroidism (6). These

children present with reduced or arrested growth due to primary hypothyroidism, and growth hormone (GH) production may be decreased because thyroxine is one of the factors stimulating GH synthesis (8). Longstanding primary hypothyroidism may also lead to permanent pituitary damage, with insufficiency in one or more pituitary hormones (9). Thyroxine replacement therapy led to a reduction in the size of the gland in 85% of patients with pituitary hyperplasia (7). Surgery should be reserved for decompression of the optic chiasm or to obtain a pathological diagnosis in the case of a pituitary mass that does not respond to, or worsens under, thyroid hormone replacement (9).

MRI alone has proven unable to reliably differentiate between tumor and hyperplasia; however, a midline prominence of a pituitary mass with smooth contours (the “nipple sign”) has been proposed as suggestive of pituitary hyperplasia (10). This appearance has also been noticed in pituitary adenomas. Indeed, the most frequent radiologic finding in primary hypothyroidism, both by CT and MRI, is a pituitary mass with supra-sellar extension (11).

The enhancing pattern of pituitary masses on postcontrast scans could allow them to be differentiated from each other. Pituitary adenomas may be homogeneous or heterogeneous. Typically, they have a slightly lower signal than a normal gland on unenhanced, T1-weighted images. Contrast medium allows better visualisation of this difference. Hyperplastic glands show a homogeneous pattern on unenhanced T1- and T2-weighted images and enhance uniformly on postcontrast T1-weighted images, as hyperplasia affects the gland uniformly (12).

The MRI scan in this case shows diffuse enhancement of the pituitary gland on T1, postcontrast, fat-rich images. Pituitary macroadenomas (adenomas more than 1 cm in size) on the T1 sequence are mostly isointense to gray matter (13); however, larger lesions are often heterogeneous and vary in signal due to areas of cystic change/necrosis/hemorrhage. On a T1 sequence with gadolinium, the solid components often demonstrate moderate to bright enhancement. Normal pituitary tissues can be identified in some cases as a thin outer rim at the margin of macroadenomas.

Microadenomas (adenomas less than 1 cm in size) are usually isointense to a normal pituitary gland on a T1 sequence. Postcontrast T1 sequences demonstrate a rounded region of delayed enhancement compared to the rest of the gland (14). The delayed images are variable, ranging from hypo-enhancement (most common), to isointense to the rest of the gland, to hyperintense (retained contrast). The pituitary microadenomas are best visualized on earlier-phase, contrast-enhanced dynamic MR images, with a signal intensity lower than that seen on images of the normal pituitary gland (15).

Lymphocytic hypophysitis can also present as a pituitary mass that (on T1 sequence) is isointense with slight signal heterogeneity in the affected area, and the normal posterior pituitary bright spot may be absent (13). The affected area can variably enhance, usually homogeneously (16), and dural enhancement may be present (13) on the post-

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contrast, T1, fat-rich sequence. In addition, the infundibulum may be thickened (13). On a T2 sequence, hypointensity in parasellar region can be present and may be useful in differentiating the mass from a pituitary adenoma (17).

Pituitary venous congestion could also present as a pituitary mass, which could have a sequential enhancement pattern. In 1983, Bonneville et al (18) described the pituitary tuff sign, which is the initial enhancement of the secondary portal circulation at the insertion site of the infundibulum, with progressive centrifugal enhancement of the anterior pituitary lobe. Sakamoto et al (15) used sagittal and coronal planes for dynamic MR imaging of the normal pituitary gland. They found that, on the sagittal sections, the signal intensity increased first in the posterior lobe of the pituitary gland; this was followed by enhancement of the anterior lobe adjacent to the junction with the infundibulum. On the coronal sections of the anterior lobe, the anterior pituitary lobe at the junction with the infundibulum showed earliest enhancement, the middle portion showed slightly delayed enhancement, and the lateral portion of the anterior lobe enhanced last. They also noted that the washout of contrast medium from the posterior lobe was slightly faster than that from the anterior lobe.

Patients treated with thyroxine need MRI monitoring of their pituitary glands to confirm reduction in the size of the mass and subsequent complete resolution. The diagnosis needs to be revisited if the mass does not reduce in size following treatment with thyroxine. Our patient did show the nipple sign on his initial and subsequent MRI pituitary scans.

The clinical evolution of the response of pituitary hyperplasia to thyroxine should be monitored closely, because of the rare possibility of acute neurological manifestations, such as the development of pseudotumor cerebri and “paradoxical” thyroid-hormone-therapy-induced visual failure, or the possibility of an incidental nonthyrotropic pituitary tumor that does not regress on thyroxine therapy (19). In the case of marked regression of pituitary enlargement, without complete normalization in pituitary morphology, the clinical significance of a persistent minimal abnormality detectable by either CT or MRI remains unclear.

Our patient noticed improvement of his visual symptoms soon after the initiation of thyroxine therapy. His MRI 3 months after thyroxine therapy showed significant improvement, and a subsequent scan in 10 months showed further reduction in pituitary gland size. The residual changes are most likely the effects of longstanding hypothyroidism that in our patient may take longer to resolve completely or may persist indefinitely.

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