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CASE REPORT

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A fortunate bitten tongue—Hypothyroidism despite repeatedly normal plasma thyrotropin levels

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Key Clinical Message

Hypophyseal dysfunction may be overlooked by the currently generally accepted laboratory routine for the differential diagnosis in patients suffering from symptoms of depression or dementia.

Abstract

Hypothyroidism is an important cause of depression and potentially reversible cognitive impairment. Whereas the determination of the plasma concentration of thyrotropin (TSH) is generally considered part of the laboratory screening tests for dementia, the measurement of total or free triiodothyronine (T3, FT3), thyroxine (T4, FT4) and cortisol in plasma does not belong to the routine diagnostic workup in patients with depression or suspected dementia. In an 87-year-old lady suffering from increasingly poor general health, decreased fluid and food intake, mood depression and lack of energy, three measurements of plasma TSH produced normal values. A cranial computed tomography (cCT) 2 days prior to hospital admission had been assessed as apparently normal. A second cCT performed following a loss of consciousness complicated by tongue bite showed a hypophyseal tumor. Then, low plasma levels of FT3, FT4 and cortisol were found. Following hormone replacement and transsphenoidal tumor resection, the patient recovered rapidly. The present case report illustrates the pitfalls of measuring merely the TSH level in the detection of thyroid and hypophyseal dysfunction.

KEYWORDS

cognitive impairment, craniopharyngioma, depression, hypocortisolism, hypothyroidism

1 | INTRODUCTION

Hypothyroidism is an important cause of depression and potentially reversible cognitive impairment.[1] If not detected and treated within 6 months, it can cause the syndrome of dementia which is defined as disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgment for ≥6 months.[2] Hypothyroidism also appears to be associated with an increased risk of irreversible forms of dementia. Population-based Danish data based on the determination of thyroid

stimulating hormone [thyrotropin (TSH)] suggests that "every 6 months of elevated TSH increased the risk of dementia by 12%."[3] In an own study, approx. 15% of previously or newly diagnosed patients with cognitive impairment had some laboratory signs of thyroid dysfunction.[4] The determination of the plasma concentration of TSH is generally considered part of the laboratory screening tests for dementia in order to detect hypo- or hyperthyroidism (e.g.,[5–7]). Mainly for economic reasons, the measurement of total or free triiodothyronine (T3, FT3), thyroxine (T4, FT4) and cortisol in plasma does not belong to the routine diagnostic workup in patients with depression or suspected dementia. The present case report illustrates the pitfalls of this approach.

2 | CASE HISTORY/EXAMINATION

An 87-year-old woman suffered from increasingly poor general health, decreased fluid and food intake, mood depression and lack of energy for approx. three months. Upon hospital admission, her lung and heart examinations including her blood pressure were unremarkable, she had mild peripheral edema, was fully oriented and without focal neurological signs.

A cranial computed tomography (cCT) 2 days prior to hospital admission had been assessed as apparently normal, revealing only small vascular lesions.

3 | METHODS

Routine blood measurements showed no significant abnormalities, and plasma TSH measured 17 days before and on the first day in hospital was normal (Table 1).

Seven days following admission, the patient lost consciousness while seated. Shivering, cyanosis and a bitten tongue were noted. In a recumbent position, she rapidly regained consciousness. A repeat cCT to exclude an acute intracranial lesion, for example, a subdural haematoma, in the presence of a small epicranial contusion on her forehead revealed an intrasellar tumor 0.7 × 1.2 cm in size in contact with the optic chiasma (Figure 1), which had been overlooked on the first cCT scan. The ophthalmologist noted a temporal visual field defect of the left eye, which had not been noticed by the patient and which had not been detected by finger-perimetric visual field testing in the neurological examination. An electroencephalogram showed no activity typical of epilepsy, and the episode was interpreted as an orthostatic collapse.

Following the diagnosis of hypothyroidism by decreased plasma concentrations of FT3 and FT4 despite normal TSH levels and hypocortisolaemia despite normal plasma sodium and potassium concentrations, the patient was treated with hydrocortisone 40 mg/day divided into three doses and thyroxine 50 µg/day as a single dose. Because of the visual field defect of the left eye the tumor was resected transsphenoidally and was histologically classified as a craniopharyngioma. A B-Raf proto-oncogene, serine/threonine kinase (BRAF) mutation, the most frequent mutation in craniopharyngioma in adults, was excluded by polymerase chain reaction and subsequent DNA sequencing. Both children and both grandchildren did not develop a craniopharyngioma.

4 | OUTCOME AND FOLLOW-UP

After a short phase of postoperative diabetes insipidus, the patient recovered rapidly: during her geriatric rehabilitation program her Barthel activity in daily life (ADL) index[8] rose from a score of <20 on admission to 80 on discharge, and the Tinetti Performance Oriented Mobility Assessment (POMA)[9] increased from 4/28 to 15/28 points. She was discharged home with a good quality of life for the following 4 years.

TABLE 1 Laboratory findings in an 87-year-old woman with a pituitary tumor prior to thyroxine and cortisol replacement.

Day	Thyrotropin (TSH) [mU/l] normal 0.27–4.2	Free triiodothyronine (FT3) [pmol/L] normal 3.1–6.8	Free thyroxine (FT4) [pmol/L] normal 12.0–22.0	Cortisol 8 A.M. [µg/L] normal 50–250	Sodium [mmol/l] normal 135–145; potassium [mmol/L] normal 3.5–5.1
−17	1.08	Nd	Nd	Nd	Nd; 3.8
0	0.899	Nd	Nd	Nd	142; 3.3
12	2.240	2.66	4.06	10.0	137; 3.6

Note: The plasma prolactin level measured in the morning of day 12 was elevated [1261mIU/l (normal: <450mIU/l)], probably as a consequence of treatment with mirtazapine for depression. Day 0 = day of hospital admission.

Abbreviation: Nd, not determined.

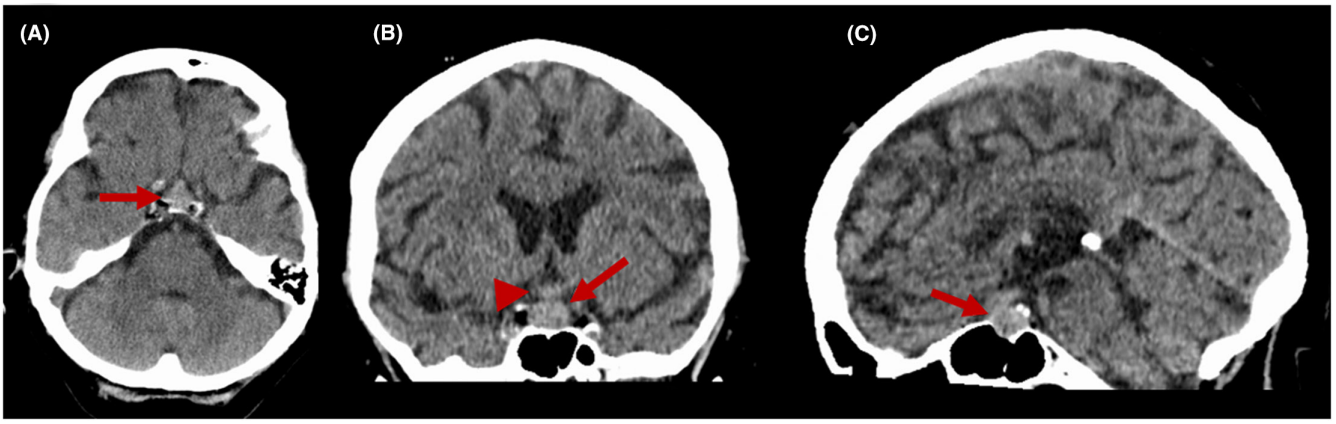

FIGURE 1 Hypophyseal tumor primarily overlooked in cranial computer tomography. Unenhanced computed tomography. (A) Transverse-axial image, (B) coronal and (C) sagittal reconstructions. The intra- and suprasellar hypophyseal tumor is marked by red arrows, the elevated optic chiasm by the red arrowhead.

5 | DISCUSSION

Pituitary tumors are not considered a typical disorder in older persons. Endocrine syndromes caused by hormone hypersecretion by active pituitary adenomas most frequently present earlier in life. Although particularly prevalent in older women, hypothyroidism is often overlooked clinically, because its symptoms can be misinterpreted as the consequences of aging in the presence of multimorbidity.[10,11] Primary hypothyroidism caused by thyroidal dysfunction, which can be diagnosed by high TSH plasma levels, is considered to be 1000 times more frequent than secondary hypothyroidism caused by pituitary diseases.[11] In patients older than 55 years, however, approximately 2% of all cases of hypothyroidism were caused by TSH deficiency.[12] In most cases of persons with pituitary tumors leading to central hypothyroidism, abnormally low TSH plasma concentrations are found. TSH levels, however, are not always subnormal.[13,14] In such conditions, normal basal TSH levels despite decreased levels of thyroxine and triiodothyronine, have previously been noted.[14,15] Moreover, studies in older persons have shown that primary hypothyroidism in this population may be associated with a weaker TSH response than in young individuals.[16] When visual fields are affected, transsphenoidal surgery—as performed in our patient—is the treatment of choice in order to maintain the patient's vision. As in younger patients, surgery beyond the age of 75 relying on an endoscopic transsellar approach is effective and safe with a 30-day postoperative mortality below 1%.[17] Craniopharyngiomas in adults are most frequently driven by BRAF V600E mutations.[18] These mutations may have therapeutic consequences,[19] but were excluded by molecular methods in the present case. A family history of craniopharyngioma was absent.

The case report presented indicates that hypothyroidism in patients with pituitary tumors can sometimes not be identified from the basal TSH level, since this can be normal. "It seems like the secretory capacity of even small remnants of thyrotropes are efficient to produce a ´normal´ amount of immunological active TSH."[10] Therefore, measurement of basal serum TSH and even of the TSH response to TSH releasing hormone (TRH) are insufficient measures in the assessment of patients with pituitary dysfunction. The possible need for replacement therapy must be assessed by repeated measurement of thyroid hormone levels, in particular FT4.

The most striking features of the present case are that (1) even three TSH determinations at 2-week intervals were normal, and (2) despite clear symptoms of hypothyroidism FT3 and FT4 were not measured, and (3) this patient also suffered from central hypocortisolism, although plasma sodium and potassium were normal. The case illustrates that the common practice of measuring merely plasma TSH to exclude hypothyroidism entails the risk of overlooking hypothyroidism caused by hypophyseal disease as an important reversible cause of depression and the dementia syndrome. We do not advocate the expansion of the clinical laboratory routine for patients with depression and suspected dementia to plasma FT3, FT4 and cortisol. Clinicians should, however, be aware that the current laboratory routine in the differential diagnosis of depression and dementia may overlook hypophyseal dysfunction, and laboratory examinations should be broadened in the case of the slightest suspicion of this condition.

AUTHOR CONTRIBUTIONS

Marija Djukic: Data curation; writing – original draft. **Johannes Gossner:** Data curation; methodology; writing – review and editing. **Jörg Larsen:** Data curation;

writing – review and editing. **Fatima Barbara König:** Data curation; writing – review and editing. **Hans-Ulrich Schildhaus:** Data curation; writing – review and editing. **Veit Rohde:** Data curation; methodology; writing – review and editing. **Roland Nau:** Conceptualization; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors have no commercial interests in the publication of this case.

DATA AVAILABILITY STATEMENT

Anonymized patient data will be provided by the corresponding author upon reasonable request, unless the anonymity of the patient is endangered.

ETHICS STATEMENT

Not applicable.

CONSENT

Written informed consent was obtained from the patient's closest relative to publish this report in accordance with the journal's patient consent policy.

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