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LETTER TO THE EDITOR

Differentiating nonthyroidal illness syndrome from central hypothyroidism in the acutely ill hospitalized patient

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To the Editor,

The goal of thyroid testing in critically, or acutely ill, hospitalized patients is to identify thyroid disorders that could be positively influenced by therapy. In the absence of a history of thyroid disease, low thyroid function laboratory values in hospitalized patients are often attributable to nonthyroidal illness syndrome [1]. Unfortunately, thyroid hormone supplementation does not reduce the high mortality associated with nonthyroidal illness syndrome [2]. Thus, the utility of routine thyroid function testing of hospitalized patients can be questioned because testing rarely leads to a beneficial therapeutic intervention.

Laboratory findings of low thyroid hormone and low thyrotropin levels are similarly observed in patients with central hypothyroidism. Without known pre-existing underlying pituitary or hypothalamic disease, however, it would be extremely rare to diagnose central hypothyroidism by routine laboratory testing of acutely ill patients. A case is presented of an acutely ill man who clinically presents with aseptic meningitis. When low free T4, free T3, and TSH levels were discovered, treating physicians had to consider nonthyroidal illness syndrome versus central hypothyroidism in the differential diagnosis. Distinguishing between these diagnoses is of paramount importance because the prognosis and treatment options vary markedly between these two disorders.

A 76-year-old man with no known prior history of thyroid or pituitary disease presented to an outside hospital with sudden onset of severe headache, nausea, vomiting, and intermittent fevers up to 40.9 °C. He denied having any vision impairment. He was empirically treated with intravenous antibiotics for possible bacterial meningitis. Over the next 2 weeks, the patient became delirious and was transferred to our hospital. His past medical history included a 15-year history of well-controlled hypertension and type 2 diabetes mellitus. His home medications were atenolol and glibenclamide. Physical examination revealed a disoriented man. His vital signs were temperature 40.9 °C, blood pressure 117/42 mmHg, heart rate 96 bpm, respiratory rate 26/min, and oxygen saturation 100 % breathing room air. There was no thyromegaly and no delayed reflexes. There was no gynecomastia. Testicular size was normal. There was a normal distribution of facial, chest, and pubic hair. Ophthalmologic exam showed no papilledema. Laboratory findings were mild leukocytosis of 12.8 (4.3–10.0 $\times$ 10^3 cells/μl) and unremarkable differential. Lumbar puncture fourth tube showed RBC 874/μl, WBC16/μl, 92 % lymphocytes, 96 % mononuclear cells, and CSF protein 99 mg/dl (45–60 mg/dl); consistent with non-bacterial meningitis. Viral, bacterial, and fungal cultures were negative. Thyrotropin (TSH) was <0.01 μIU/ml (0.47–4.68 μIU/ml), free thyroxine (FT4) was 0.6 ng/ml (0.8–2.3 ng/ml) and free triiodothyronine (FT3) was 1.5 pg/ml (2.8–5.3 pg/ml). The patient was not taking medications known to lower TSH levels.

Consultation with the endocrinology service was requested. The differential diagnoses considered were nonthyroidal illness syndrome versus central hypothyroidism. Treatment with thyroid hormone was questioned.

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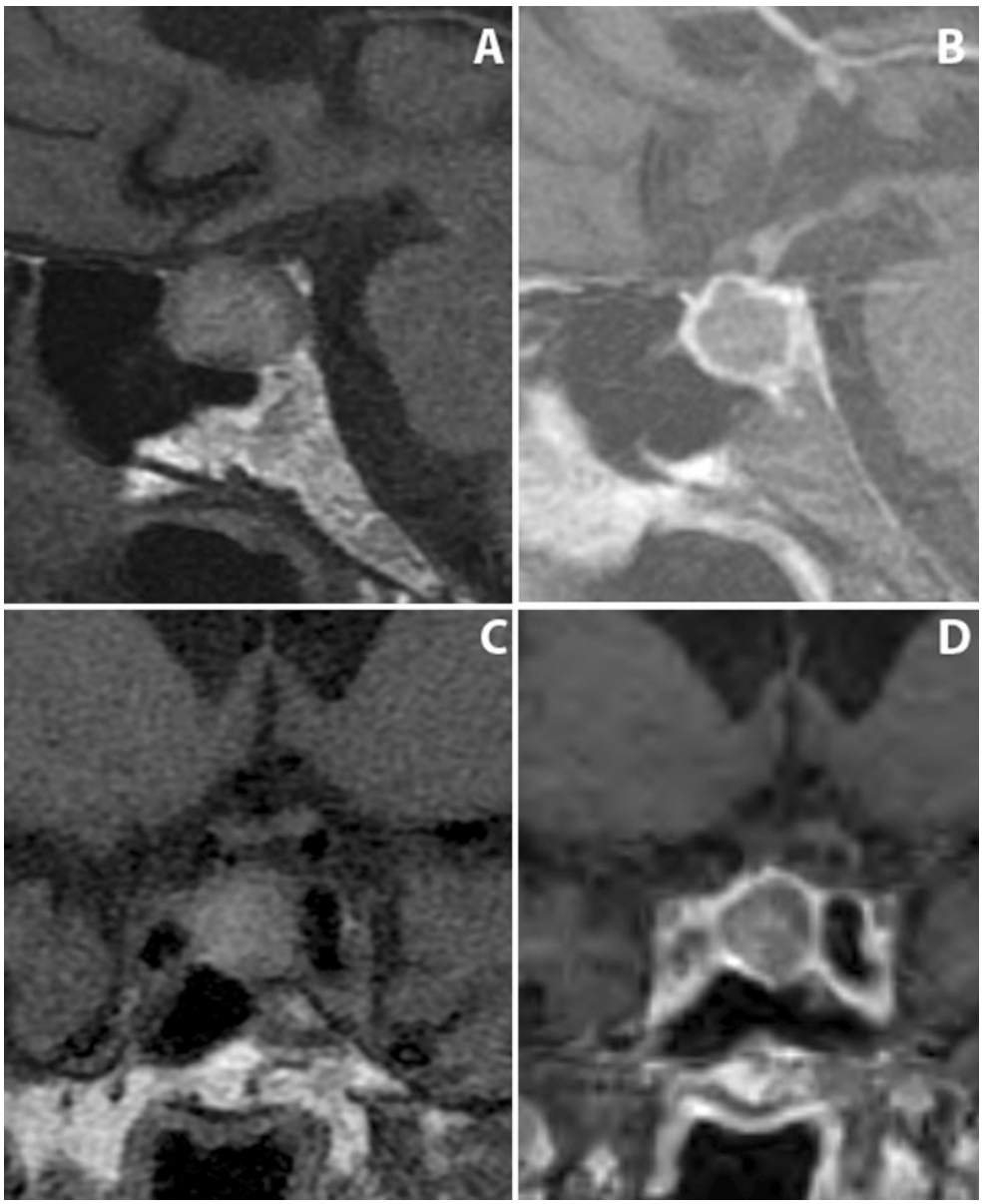

Fig. 1 MRI of patient's pituitary. **a** The T1-weighted sagittal image pre-contrast identified a 1.4-cm pituitary macroadenoma. **b** The sagittal image post-contrast was notable for peripheral enhancement of the pituitary, without central enhancement. **c** The coronal image pre-contrast again identified a diffuse hyperintensity in the sella and enlarged pituitary gland without optic chiasm impingement. **d** The coronal image post-contrast was again notable for a peripheral "pituitary ring sign" suggestive of pituitary apoplexy

Further endocrine testing demonstrated an undetectable serum prolactin. Total testosterone concentration was 2 ng/dl (275–900 ng/dl). Patient's morning serum cortisol level was 0.5 μg/dl and maximally increased to only 6.9 μg/dl following 250 μg cosyntropin. The patient's hypernatremia of 146 (136–145 mmol/l), high serum osmolality of 305 (275–299 mOsm/kg), relatively low urine specific gravity of 1.003 (1.003–1.040), and relatively dilute urine osmolality of 245 (50–1200 mOsm/kg) suggested vasopressin insufficiency. Consistent with central diabetes insipidus, DDAVP increased urine osmolality to 416 mOsm/kg. Brain MRI demonstrated a 1.4-cm pituitary adenoma with peripheral enhancement consistent with the "Pituitary Ring Sign" characteristic of pituitary apoplexy (Fig. 1). The patient was treated with 100 mg of hydrocortisone every 8 h, 100 μg of levothyroxine daily, 0.1 mg of DDAVP bid, and testosterone cypionate 200 μg every 2 weeks. His condition improved promptly and markedly upon initiation of treatment, and he was discharged from the hospital.

For nonthyroidal illness syndrome, usual laboratory findings are a low T3 level, and low or low-normal TSH level with or without a low FT4 level. The presented

patient's undetectable TSH level is more consistent with central hypothyroidism, but not incompatible with nonthyroidal illness syndrome since undetectable TSH levels occur in up to 7 % of patients with documented nonthyroidal illness syndrome [3].

For the acutely ill hospitalized patient without known pre-existing thyroid or pituitary dysfunction, differentiating between the very rare cases of new onset central hypothyroidism from the much more common nonthyroidal illness syndrome can be difficult based on routine thyroid tests alone. Although it is not cost effective to perform a full pituitary evaluation for all acutely ill hospitalized patients, suspicion for central hypothyroidism should be raised when the patient presents with a history of headache, nausea, vomiting, visual changes, head trauma, infiltrative diseases, known cancer, abnormal water balance, or stigmata of gonadal insufficiency. Differentiating between central hypothyroidism and nonthyroidal illness syndrome is of critical importance due to the vastly different prognosis, management, and expected responses to treatment.

Conflict of interest The authors declare that they have no conflict of interest.

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