CASE REPORT

Where art thou pituitary?

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SUMMARY

A middle-aged woman presented with premature menopause and recurrent episodes of vomiting with hyponatraemia. Since primary causes of hormone deficiencies were the only studies initially evaluated, there was a delayed diagnosis. Pituitary tropic hormones (serum thyroid stimulating hormone/follicle stimulating hormone/luteinising hormone), inappropriately low for low-level of target hormones (free thyroxine/oestradiol), led to detailed evaluation of trophic hormone deficiencies by pituitary stimulation. The pituitary stimulation by insulin challenge test confirmed secondary (pituitary) hypofunction. Pituitary imaging revealed an uncommon cause of hypopituitarism, which is discussed in this case report.

BACKGROUND

Secondary hormone deficiencies, that is, target endocrine gland (thyroid, adrenals, ovaries/testes) hypofunction secondary to pituitary trophic hormone (thyroid stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), follicular stimulating hormone (FSH)/luteinising hormone (LH)) deficiencies are uncommon. In addition, over-reliance on trophic hormone levels (eg, serum TSH) alone, failure to use free hormone levels (eg, total thyroxine (T4) instead of free T4) and failure to notice the larger picture (pituitary trophic hormones inappropriately low for low target hormones, eg, normal FSH/LH for clinically overt hypogonadism) often lead to delayed diagnosis. Additionally, hyperfunctioning pituitary adenomas or symptomatic pituitary masses may obscure incipient trophic hormone deficiencies. This case report aims to sensitise clinicians to the not so obvious secondary (pituitary) endocrine deficiencies.

CASE PRESENTATION

A 40-year-old woman was referred with recurrent episodes of vomiting and abdominal pain associated with severe hyponatraemia and hypotension (responsive to intravenous fluids and steroids). She also had amenorrhoea for the past 1 year. Her obstetric history was significant for two full-term pregnancies with caesarean sections performed for borderline pelvis with cephalopelvic disproportion. However, the postpartum periods were uneventful with normal lactation.

A detailed evaluation of the patient's past medical records was conducted. Her previous laboratory evaluation reports revealed normal body mass index (21.4 kg/m²), microcytic anaemia (haemoglobin—7.6 g%), normal blood sugars and normal liver function tests with severe hyponatraemia on

multiple occasions. Her evaluation for primary hormone deficiencies (primary hypothyroidism and Addisonian crisis) showed free T4 as low normal with serum TSH within normal limits and her 8:00 serum cortisol was 10.95 ng/dL. To rule out probable gastrointestinal or raised intracranial tension (ICT) as causes of the recurrent vomiting, she was evaluated with ultrasonography of the abdomen, CT of the abdomen and head, and upper gastrointestinal endoscopy; these turned out to be normal. Her fundus was within normal limits. Her serum ferritin was 268.1 ng/mL and total iron binding capacity was low normal with normal serum iron levels. The anaemia was perceived to be that of chronic disease with functional iron deficiency.

With the history and investigations outlined above, the patient was further investigated at our tertiary centre, for central endocrine deficiencies. Her serum FSH (9.26 mIU/mL (normal range: 19.3–100.6; postmenopausal) and LH (3.74 mIU/mL (normal range: 15.9–54; postmenopausal) were low with low oestradiol levels. Her free T4 was low (0.26 ng/dL (normal range 0.8–2.7 ng/dL)) with serum TSH in normal range. Her serum prolactin was normal (3.96 ng/mL (normal range: 2.8–29.2 ng/mL)). Thus, with pituitary trophic hormones inappropriately low, anterior pituitary deficit was suspected.

MRI of the pituitary fossa revealed non-visualisation of the anterior pituitary, with cerebrospinal fluid (CSF)-filled sella (Where art thou Pituitary!!) (figure 1). The posterior pituitary showed normal hyperintense signal on

Figure 1 Non-visualisation of anterior pituitary with cerebrospinal fluid filled sella on MRI.

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Figure 2 Failure of serum growth hormone and cortisol to rise even after maximum stimulation at 60 min (capillary blood glucose <40 mg%) in insulin challenge test.

T1-weighted image, which in the absence of polydipsia/polyuria and secondary hypernatraemia, clinically ruled out diabetes insipidus. After obtaining informed consent from the patient, growth hormone (GH) and cortisol stimulation test with insulin challenge was carried out in the intensive care setting. In the insulin challenge test, target hypoglycaemia was achieved (<40 mg%), which was promptly reversed with intravenous glucose and hydrocortisone. At baseline and at peak stimulation, serum GH, serum cortisol and serum ACTH were grossly low (figure 2). This confirmed the deficiencies of GH and ACTH.

In the absence of any history of pituitary apoplexy, pituitary adenoma, surgery or irradiation, a diagnosis of primary empty fossa syndrome with anterior pituitary hypofunction was made.

TREATMENT

The patient was initiated on hormone replacement therapy (HRT) that included daily tablet hydrocortisone (10 mg at 8:00

and 5 mg at 16:00), tablet levothyroxine (75 µg) and calcium/vitamin D supplements. GH was not initiated because of economic non-viability. The patient was advised HRT for hypogonadism after explaining to her the possible risks and benefits associated with it. However, she did not consent to receive HRT.

OUTCOME AND FOLLOW-UP

The patient's clinical response was used as a guide for corticosteroid replacement therapy. The serum free T4 was kept in the upper half of the normal range. With this regimen, she clinically improved and had no clinical episodes of Addisonian crisis since.

DISCUSSION

Empty sella is a clinical entity characterised by more than 50% of the sella filled with CSF and a pituitary gland thickness of

Table 1 Comparison of patient characteristics in a large series of primary empty sella patients

Parameters	Marinis <i>et al</i> ⁵	Guitelman <i>et al</i> ²	Gallardo <i>et al</i> ⁶	Ghatnatti <i>et al</i> ⁷
Number of cases	213	175	73	24
F:M ratio	4:1	6:1	4:1	3:1
Mean age (in years)	51.8±2.1	48.2±14	—	40.6±9.4
Mean BMI (in kg/m ²)	27.3±3.5	—*	—*	26.4±4.2
Multiparity	57%	58.3%	—	83.3%
Endocrine abnormalities				
Overall prevalence	19%	28%	55.3%	50%
Anterior hypopituitarism	4.2%	12%	15.8%	—
Hyperprolactinaemia	10%	12%	26.3%	20.8%
Isolated GH deficiency	3.7%(8)	—	—	12.5%
Neurological abnormalities				
Overall	47.9%			
Headache	40%	59.4%	69.7%	50%
Raised ICT	9.85%	—	—	12.5%
Rhinorrhoea	6.5%	—	11.8%	—
Ophthalmological abnormalities				
Visual disturbances	17.8%	13.7%	—	—
Imaging				
Partial empty sella	138	54	—	—
Total empty sella	75	121	—	—

*Obesity—49.5% (Guitelman *et al*) and 38.2% (Gallardo *et al*).

BMI, body mass index; F, female; GH, growth hormone; ICT, intracranial tension; M, male.

<2 mm. It is labelled primary when there is no history of secondary aetiology, for instance, pituitary adenomas, irradiation and surgery or pituitary apoplexy. Primary empty sella (PES) may present itself as an incidental radio imaging finding to severe anterior hypopituitarism or raised ICT with CSF rhinorrhoea. The term 'empty sella' was first coined by Busch¹ for autopsy findings of the severely flattened pituitary gland against the floor of the sella, without any history of pituitary disease. Various autopsy and neuroradiological findings show the prevalence of empty sella to be 5.5–35%.² Foresti *et al*³ reported PES in 12.8% of cases, in a series of 500 consecutive patients with MRI unrelated to sellar or parasellar pathology. Thus, there is high prevalence of empty sella as an incidental finding.

It is postulated that defects in diaphragm sella along with raised ICT can promote herniation of arachnoid into the sella.⁴ Obesity (hypoventilation and CO₂ retention with resulting raised ICT) and multiparous pregnancies (resulting in transient pituitary hypertrophy) are probable contributory factors, supported by the higher prevalence of PES in obese, multiparous females.^{2 5–7} However, defects in diaphragm sella and raised ICT are not found in all patients.

Most series on PES (table 1) have reported a higher prevalence of the disease among female patients and patients who are obese or overweight.^{2 5–7} In females with PES, multiparity is usually present in 57–83.3% of cases.

Clinical symptoms in PES are usually a combination of endocrinal, neurological or ophthalmological symptoms. Headache (with no specific pattern or character) is the most common neurological presentation.^{2 5} A few patients may have symptoms and signs of raised ICT (papilloedema and visual disturbances). Rarely, such cases can present with CSF rhinorrhoea.^{2 5} Other reported symptoms include dizziness, cranial nerve disorders, depression and seizures. Visual disturbances in the form of decreased visual acuity may be seen in 13–17% of cases (table 1).

GH deficiency (30–60%) is the most common endocrine dysfunction. Isolated pituitary deficiencies are infrequent (hypogonadotropic hypogonadism in 6%, central hypoadrenalism in 1% and central hypothyroidism in 1%). Serum prolactin levels are moderately increased in about 10–12% of patients.^{8 9}

Learning points

- ▶ Pituitary tropic hormones, if found inappropriately low in presence of a low-level of target hormones, may give a clue towards secondary endocrine insufficiency.
- ▶ Pituitary deficiency can be missed if only trophic hormones are used for evaluation of hormone deficiencies.
- ▶ Always use free T4 levels for diagnosis when suspecting pituitary pathology and use the upper half of normal free T4 levels as therapeutic target (not serum thyroid stimulating hormone levels).

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Competing interests None declared.

Patient consent Obtained.

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