CASE REPORT

A case of acute confusion: Cushing's syndrome presenting with primary hyperparathyroidism

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SUMMARY

Cushing's syndrome is a rare disease. Cushing's syndrome presenting as acute psychosis is an exceptional occurrence. We present the case of a 37-year-old woman who was admitted with acute confusion associated with mild hypercalcaemia and was subsequently diagnosed with parathyroid and adrenal adenomas. Our hospital sees approximately 6000 endocrine patients per year, with an incidence of around four Cushing's cases annually. This is the first such case to occur in our hospital and one of few described in the literature.

BACKGROUND

Cushing's syndrome is a rare endocrine disease caused by hypercortisolaemia. The incidence of endogenous Cushing's syndrome is between 0.7 and 4 cases per million annually and is adrenocorticotrophic hormone (ACTH) dependent in 80%–85% of cases; causes include pituitary corticotrophic adenomas (Cushing's disease) and less frequently ectopic ACTH secreting malignancy's and corticotrophin-releasing hormone tumours.^{1–5} About 15%–20% of cases are ACTH independent; this may be due to adrenocortical tumours or adrenal hyperplasia. Cushing's syndrome can present with a wide range of symptoms, many of which are non-specific. The classic signs of Cushing's syndrome include the dorsocervical fat pad, 'moon face', striae, easy bruising and weight gain.

CASE PRESENTATION

A 37-year-old woman presented to the acute medical assessment unit (AMU) following referral by her general practitioner. She had become acutely confused on returning home from a night shift where she worked as a carer for vulnerable adults. She was anxious and 'muddled'. She did not recall driving home and was unable to form coherent sentences. During her night shift, she reported that she had been caring for an individual who was on several psychiatric medications and she believed that her drink may have been spiked. She was orientated to time, place and person. Physical examination and baseline investigations were unremarkable. She was encouraged to increase her oral fluid intake and subsequently discharged home.

Three days later, the patient re-presented to AMU with exacerbated confusion, agitation and paranoia and was subsequently admitted to hospital. She was disorientated to place and person and unable

to recognise her sister. She repetitively talked about her 'baby' although she had no children; she answered questions inappropriately and was unable to complete sentences. She stated she felt physically 'puffy and swollen'.

During hospital admission, the patient's confusion worsened and her behaviour became more and more erratic. Three weeks into her admission, the patient started to report paraesthesia, polyuria and polydipsia and noticed easy bruising. Her family reported 'funny episodes' whereby her pupils would dilate and she appeared vacant; she had amnesia of these events afterwards.

The patient became increasingly unmanageable on the ward and required antipsychotic medication. On assessment by the mental health liaison team, she appeared distracted and paranoid with a poor attention span and poor short-term memory. She was unable to perform simple tasks and there was evidence of disorganised thinking. She did not appear to be having any visual or auditory hallucinations at that time but reported paranoid ideation.

A collateral history from family members confirmed the inability to perform tasks; for example, they described an occasion whereby she did not know how to have shower. The patient had told her family she thought she or family members were going to be killed. Throughout the admission, the patient responded better to family members; her family made the decision to stay with her 24 hours a day.

There were no recent stressors identified as potential causative factors to her presentation. She had a history of depression and anxiety for which she had been treated with a selective serotonin reuptake inhibitor 3 to 4 years previously, but was otherwise normally fit and well. She had not previously been treated with medications known to cause hypercalcaemia. The patient denied excessive alcohol intake, was an ex-smoker of 10 pack-years and was living independently. Her family described her as an organised, active and family-orientated individual prior to her first admission. The patient had attended her general practitioner's 1 week previously with a vasculitic rash for which she was awaiting a biopsy.

On clinical examination, the patient's baseline physiological observations were normal. Blood pressure on admission to hospital was 132/81, weight 69 kg and height 175 cm with a normal body mass index of 22.5. Examinations of the respiratory, cardiovascular, gastrointestinal and neurological systems were unremarkable. Thorough clinical

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Table 1 Results of dexamethasone suppression tests

Overnight dexamethasone suppression test		
Time (hours)	ACTH	Cortisol
0	<0.3	596
9	<0.3	466
Low-dose dexamethasone suppression test		
Time (hours)	ACTH	Cortisol
0	<0.3	501
48	<0.3	563

ACTH, adrenocorticotrophic hormone.

examination later revealed facial fullness, facial hair, bruising and a stria on the right side of her abdomen.

INVESTIGATIONS

Routine blood, urine and toxicology tests were normal besides a raised adjusted serum calcium level of 2.94 mmol/L (normal range 2.2–2.66 mmol/L) and an elevated parathyroid hormone level of 9.6 pmol/L (normal range 1.1–6.9 pmol/L). Preliminary ultrasound scan of the parathyroid was normal, although a sestamibi scan of the parathyroid gland revealed a right lower parathyroid adenoma. Brain imaging and a lumbar puncture were also performed, both of which were normal. Further investigations are listed in online supplementary appendix 1.

Given the patients physical examination findings, an overnight dexamethasone suppression test was performed to screen for Cushing's syndrome which showed a raised cortisol of 466 nmol (normal level <50 nmol). Subsequently, a low dose 48 hours dexamethasone suppression test was carried out which demonstrated a failure of suppression of cortisol confirming Cushing's syndrome. Aldosterone levels were normal. Table 1 demonstrates the results of the dexamethasone suppression tests.

A CT scan of the chest, abdomen and pelvis was performed which revealed a right adrenal mass. An MRI of the adrenal gland further characterised the mass as a lipid rich adrenal adenoma measuring 2.4×1.8 cm in size.

Based on the clinical findings, positive endocrine investigations and imaging, the patient was diagnosed with ACTH-independent Cushing's syndrome secondary to adrenal adenoma.

Subsequently, investigations for other endocrine disorders associated with parathyroid and adrenal adenomas were performed, predominantly those associated with multiple endocrine neoplasia type 1 (MEN1) and neuroendocrine tumours.

TREATMENT

The patient's hypercalcaemia was treated with intravenous fluids and zoledronic acid.

Correction of the hypercortisolaemia preoperatively was with the 11-beta-monooxygenase inhibitor metyrapone at a dose of 250 mg once daily. Olanzapine 10 mg once daily was prescribed for her psychotic symptoms. Definitive management involved a right transabdominal laparoscopic adrenalectomy and the patient required hydrocortisone replacement following this. She underwent a focused right inferior parathyroidectomy 1 month after the adrenalectomy.

OUTCOME AND FOLLOW-UP

Histological analysis confirmed the adrenal mass to be a cortical adenoma measuring 2.6×2.6×2.1 cm in size. The excised parathyroid adenoma measured 15×12×3 mm in size.

During the first week postadrenalectomy, the patient reported feeling restless with some short-term amnesia. She was polydipsic and serum calcium remained raised at 2.8 mmol/L. After the first week, her confusion gradually improved and her cortisol normalised. She was discharged home 10 days postoperatively. Serum calcium and parathyroid hormone normalised from day 1 postparathyroidectomy and have remained normal since.

The patient continues to be monitored by the endocrine surgeons and remains on long-term hydrocortisone. She reports episodes of dizziness, palpitations and collapse; a recent table tilt test revealed neurogenic syncope for which she has been started on fludrocortisone. She has ongoing mild memory loss and is not yet living independently. A repeat head MRI 6 months' postdischarge was normal. The results of genetic testing for MEN1 are still awaited.

DISCUSSION

This case report demonstrates an atypical presentation of Cushing's syndrome. This was a diagnostically challenging case and required the involvement of several specialities, including endocrine surgery, endocrinology and mental health teams. There are many differential diagnoses for causes of acute confusion. These includes fluid and electrolyte imbalances, infections, drug or alcohol toxicity or withdrawal, metabolic, endocrine, autoimmune and malignant conditions and low perfusion states such as shock or heart failure.⁶ Neurological causes were high on the list of differential diagnoses despite the absence of focal neurology.

Hypercalcaemia is well known to cause neuropsychiatric symptoms, although this is uncommon below serum adjusted calcium levels of <3.0 mmol/L.⁷ Hypercalcaemia was initially thought to be the cause of this patient's symptoms and further investigations into her confusion were not carried out as a presumed diagnosis had been made. It was only when the patient's symptoms persisted and worsened despite the correction of serum calcium levels that we were prompted to look for alternative causes.

There are two case reports of Cushing's syndrome secondary to adrenal adenoma being associated with concurrent primary hyperparathyroidism.^{8,9} Both of these case reports were patients who presented with uncontrolled hypertension for several years and were later found to have hypertension secondary to adrenal Cushing's syndrome. In both cases, the patients did not have any symptoms of psychosis or confusion. Other reported endocrine associations include primary hyperparathyroidism presenting with Conn's syndrome (hyperaldosteronism) and adrenal adenomas cosecreting mineralocorticoids and glucocorticoids.^{10,11}

Hypertension is reported to occur in up to 85% of patients with Cushing's and up to 70% of patients with primary hyperparathyroidism, interestingly our patient was not hypertensive at any point.^{12,13} Cardiovascular risk is increased in both conditions; in Cushing's mainly via increased metabolic complications such as metabolic syndrome and in hyperparathyroidism through activation of the renin-angiotensin-aldosterone system and cardiac arrhythmias.¹⁴ May this remind clinicians not only of potential endocrine associations but also of the morbidity and mortality of undiagnosed disease.

Psychiatric symptoms have been documented in Cushing's syndrome since Harvey Cushing first described the existence of the syndrome in 1912, with its features including 'fits of unnatural irritability alternated with periods of depression' and 'sleeplessness, inability to concentrate and visual disturbances'.¹⁵ According to current literature, the psychiatric symptoms are most likely to be mood disorders; major depression disorder

is seen in 50%–70% of cases, anxiety in 12%–79% and hypomania 3%–27%.¹⁵ Features of psychosis and mania are far less common.¹⁶

Exogenous corticosteroids are well known to induce neuropsychiatric symptoms, the reported incidence of which varies widely from 1.8% to 57%.¹⁷ Severe psychiatric reactions occur in 6% of patients and mild to moderate reactions occur in around 28% of patients according to two large meta-analyses of patients treated with exogenous systemic corticosteroid therapy.¹⁷ The most common effects of short-term corticosteroids are elated mood and hypomania, conversely the use of long-term steroid tends to induce depressive symptoms. The dose of steroid directly correlates to the incidence of psychiatric disturbance, but not to onset, severity or duration of symptoms, although onset is usually in the first 1–2 weeks of treatment commencing.¹⁷ A study of 676 hospitalised patients who received prednisolone therapy reported a dose of greater than 80 mg/day was associated with a high risk (18.4%) of psychiatric adverse effects. The dose of 41–80 mg/day was associated with moderate risk (4.6%), and ≤ 40 mg/day was found to have minimal risk (1.3%).¹⁸ Symptoms usually resolve with cessation or reduction of steroid use.¹⁹

The incidence of neuropsychiatric symptoms secondary to endogenous Cushing's syndrome is far less common and not widely reported. Psychiatric symptoms may be the presenting complaint and precede the onset of physical signs and symptoms, creating a diagnostic challenge; case reports of Cushing's induced psychosis have reported occasions where patients have been admitted to psychiatric inpatient units before a diagnosis is made.^{20–22} McCallum *et al* describe the case of a 38-year-old woman admitted to an acute psychiatric unit with delusional, disorganised and paranoid ideation who was subsequently noted to have hypertension and central obesity and diagnosed with Cushing's disease. Following trans-sphenoidal hypophysectomy, cortisol normalised and her psychotic symptoms resolved.²⁰ Another case describes a 51-year-old Afro-Caribbean woman, who presented with severe refractory hypertension and severe psychosis secondary to ectopic Cushing's syndrome from a carcinoid tumour of the lung; once more, symptoms only resolved after resection of the tumour.²¹ Cushing's induced psychosis secondary to an adrenal cortical adenoma was described in a 46-year-old woman who presented to hospital with major depression and psychotic features. She had a cushingoid appearance and was hypertensive. By 6 weeks postadrenalectomy, her psychosis had resolved and cushingoid features were reduced.¹⁵ The random cortisol of these patients' ranged from 858 to 1058 nmol/L, significantly higher than our patient's cortisol level. The mean time to diagnosis for patients presenting with psychiatric symptoms is reported as high as 6 years.²³ Symptoms may persist in the first year after surgery despite the correction of cortisol; a longitudinal study found an inverse correlation between the resolution of baseline morning cortisol and psychological recovery.^{8,24} In our patient, antipsychotics did not significantly improve the patient's symptoms, in keeping with current evidence that corticosteroid inhibitors are more effective than antipsychotics in this group of patients at controlling psychiatric symptoms.²⁵

MEN1 most commonly involves the parathyroid gland, pancreas and pituitary gland, but can include adrenal tumours, carcinoid tumours and rarely pheochromocytomas. MEN1 is associated with multiple parathyroid gland involvement, making MEN1 in our patient more unlikely, however as independent events must occur in each parathyroid gland over time, it could not be excluded at this stage without genetic testing.²⁶ Cushing's syndrome is infrequently associated with MEN1: in a

retrospective review of 19 patients over a 40-year period with MEN1 with Cushing's syndrome, 79% of these were secondary to Cushing's disease and 21% of these were secondary to an adrenal adenoma.²⁷

The initial finding of hypercalcaemia in our patient was assumed to be the cause her confusion and psychosis. Had further tests and differential diagnoses not been considered, the patient may have been admitted to a psychiatric inpatient unit for control of her acute psychosis. Long-term endogenous glucocorticoid exposure can lead to high rates of morbidity and mortality as a result of the associated metabolic, cardiovascular, rheumatological, immunological and neuropsychiatric complications, emphasising the importance of prompt diagnosis and treatment. Patients presenting with acute confusion or psychiatric symptoms should therefore be thoroughly investigated for endocrine causes and differential diagnoses such as hypercalcaemia and hypercortisolaemia should be considered.

Learning points

- Organic endocrine causes of acute confusion should always be in the differential diagnosis and investigated appropriately.
- Endocrine disorders may present with psychiatric symptoms alone.
- New or refractory psychopathology with features suggestive of hypercortisolaemia should raise the possibility of Cushing's syndrome.
- Beware of red herring diagnoses: there may be more than one cause for symptoms.

Contributors EI and YWY were part of the medical team and wrote and co-edited the transcript. TP was senior clinician and coedited the transcript.

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