Central diabetes insipidus unmasked by corticosteroid therapy for cerebral metastases: beware the case with pituitary involvement and hypopituitarism

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Abstract

Patients with intra-cerebral metastases often receive glucocorticoids, particularly in the presence of peri-lesional vasogenic cerebral oedema. We present a case of presumptive lung carcinoma with cerebral metastases where central diabetes insipidus was unmasked after glucocorticoid administration and correction of undiagnosed central hypocortisolism.

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Case report

A 71-year-old female presented with a 3-day history of lethargy, poor oral intake, unsteady gait, intermittent nausea and headache, as well as progressive confusion on a background of blurred vision for 3 months. Her past medical history was notable for bronchial asthma, hypertension, type 2 diabetes mellitus, dyslipidaemia, and an incidental small anterior communicating artery aneurysm.

She was afebrile, confused and clinically dehydrated without any localising neurological signs. Fundoscopy was impaired by the presence of bilateral cataracts. Computed tomography of the brain revealed a large suprasellar mass and the patient was admitted to the Neurosurgical Department. Investigations revealed hyponatraemia with serum sodium of 130 mmol/L (reference interval (RI) 134–144 mmol/L) associated with serum osmolality of 288 mOsm/kg (RI 275–305). Paired urine studies were not done on admission. Renal function and other serum electrolytes were normal. A hormonal workup done in view of brain imaging revealed unequivocal evidence of hypopituitarism (Table 1).

Further magnetic resonance imaging of the brain confirmed the presence of a well-defined suprasellar mass measuring 26 mm x 26 mm x 19 mm, and multiple intracerebral hypodensities with perilesional oedema consistent with metastases (Figure 1). These lesions had not been seen on earlier surveillance imaging for the previously indentified intracranial aneurysm approximately a year ago; repeat CT angiography also showed that the aneurysm was largely stable and unlikely to be the cause of the patient's symptoms. While there was no corresponding plasma adrenocorticotropic hormone (ACTH) level, the suprasellar mass, low cortisol level and hyponatraemia on presentation was highly suggestive of pre-existing central hypocortisolism.

Table 1 Endocrine picture consistent with hypopituitarism

Test	Result	Units	Reference interval
fT4	8	pmol/L	8–21
Thyroid-stimulating hormone	1.21	mIU/L	0.34–5/60
8 am cortisol	147	nmol/L	240–618
Luteinising hormone	< 1	IU/L	11–59
Follicle-stimulating hormone	2	IU/L	17–114

Chest radiography performed as part of the diagnostic workup revealed lytic bony erosion of the fourth left rib, raising the suspicion of malignancy. The patient was rehydrated with an isotonic saline infusion. A contrast-enhanced CT thorax, abdomen and pelvis revealed evidence of a right pulmonary mass lesion, likely representing the primary malignant neoplasm; the adrenal glands appeared normal bilaterally. In view of her history of bronchial asthma, intravenous hydrocortisone 100 mg every 8 h was initiated shortly before her contrast-enhanced scans to prevent bronchospasm, and

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Figure 1 MRI brain with contrast studies revealed multiple avidly enhancing lesions in both cerebral and cerebellar hemispheres with the largest in the suprasellar region (marked with arrow, with measurements and scale) with perilesional oedema and local mass effect seen

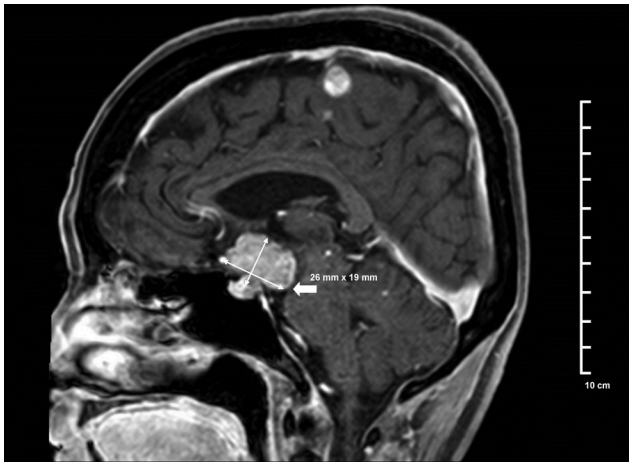
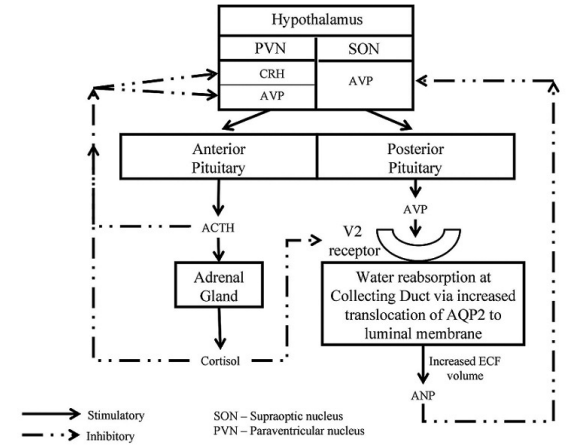


Figure 2 Feedback loops mediating the interactions between CRH-ACTH-cortisol of the hypothalamus-anterior pituitary-adrenal (HPA) axis and AVP of the hypothalamus-neurohypophysis-nephron axis



switched to dexamethasone subsequently for perilesional oedema surrounding the cerebral metastases. However, soon after glucocorticoid administration, polyuria ensued with urine output exceeding 3 litres in 24 h. Serum sodium and osmolality rose to 163 mmol/L and 355 mmol/kg, respectively, by the third day of admission. The paired urine osmolality was also inappropriately dilute at 392 mOsm/kg despite the high serum osmolality.

The Endocrinology service was consulted and diagnosed partial central diabetes insipidus (CDI), initially obscured by concomitant central hypocortisolism and possibly masked by bronchogenic carcinoma-associated ectopic antidiuretic hormone secretion, only becoming overt after steroid replacement. Prompt treatment with DDAVP and hypotonic fluids normalised her serum sodium levels, and urine output fell accordingly to 594 ml over 24 h, with urine osmolality rising to 719 mmol/kg. Due to her guarded prognosis, a biopsy was not performed, and the patient was eventually transferred to an inpatient hospice on nasal DDAVP and oral dexamethasone.

Discussion

While the exact mechanism is unclear, glucocorticoid deficiency is believed to impair free water excretion via arginine vasopression (AVP)-dependent and AVP-independent mechanisms. For instance, cortisol induces a state of relative AVP resistance by interfering with AVP signalling at the V2 receptor or post-receptor level which in turn decreases translocation of type 2 aquaporins to the surface membrane of the collecting duct cells of the kidneys for water reabsorption.[1] Hence, this accounts for the well-established diminished free water clearance observed in hypocortisolism. Hypocortisolism results in renal sodium loss and consequent volume depletion, a potent stimulus of 'appropriate' AVP secretion.

ACTH secretion is mainly controlled by corticotropin-releasing hormone (CRH) – an AVP-secretagogue – and AVP,[2] which works to further potentiate CRH-stimulated ACTH release. ACTH itself also exhibits a short-loop feedback on CRH and AVP secretion by the hypothalamus.[3] Glucocorticoids on the other hand act as a down-regulatory signal on putative glucocorticoid response elements upstream of the AVP and CRH gene promoters to suppress, respectively, AVP[4–6] and CRH[7] secretion via negative feedback loops. Conversely, glucocorticoid deficiency stimulates CRH and therefore AVP release. Glucocorticoid deficiency also leads to decreased stroke volume and cardiac output, resulting in non-osmotic stimulation of AVP secretion (Figure 2).[8]

Several studies have looked at the role of AVP in relation to glucocorticoids in both rat and human models. Mandell et al. demonstrated that hypophysectomised rats demonstrated marked impairment in free water clearance, plasma hypo-osmolality and hyponatraemia, compared to controls; these defects were associated with increased levels of plasma AVP.[9] All these values were normalised following physiologic glucocorticoid replacement. Ahmed et al. compared patients with diabetes insipidus and controls; glucocorticoid deficiency was found to result in abnormally elevated AVP levels while glucocorticoid replacement resulted in a normal diuretic response with normalisation of AVP.[10]

Green et al. studied the response to oral water loads in rats with hereditary diabetes insipidus. A portion of these rats underwent adrenalectomy and it was shown the adrenalectomised rats showed decreased free water excretion, which later corrected with glucocorticoid replacement.[11] It was therefore postulated that mechanisms other than AVP were at play. Others have shown that haemodynamic fluctuations limiting delivery of filtrate for dilution could impair free water excretion, independent of AVP.[12]

As such, glucocorticoid replacement in patients with hypocortisolism can lead to reversal of the above processes and increase free water excretion, unmasking concomitant CDI. The subsequent rapid rise in serum sodium and osmolality from a state of chronic hyponatraemia can

potentially induce serious osmotic demyelination syndrome. Early recognition of this phenomenon is crucial to ensure appropriate and expeditious management.

While the phenomenon of CDI masked by glucocorticoid deficiency has been described in other case reports,[13,14] most of the aetiologies of CDI have been attributed to rarer causes such as empty sella syndrome[15] and neurosarcoidosis.[16] Patients with intra-cerebral metastases present much more commonly, and often receive glucocorticoids to alleviate raised intracranial pressure. Notably, even though we cannot prove that SIADH (syndrome of inappropriate antidiuretic hormone) from bronchogenic carcinoma contributed to the masking of CDI in our patient, it has been reported that paraneoplastic SIADH can paradoxically mask CDI, thereby showing that such diametrically opposing endocrinopathies can co-exist in the same patient and mask the presence of each other.[17] This conflicting and often confusing 'tug-of-war' hormonal situation challenges the classical diagnostic paradigm and ought to be considered in the list of biologically plausible differentials during the clinical workup of fluid-electrolyte perturbations in such patients. In patients with pituitary lesions and hypocortisolism, one should therefore be wary of unmasking CDI after instituting glucocorticoid replacement. Urine output and serum electrolytes should be monitored closely with a high index of suspicion for CDI.

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