CASE REPORT

Neurosarcoidosis-associated central diabetes insipidus masked by adrenal insufficiency

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SUMMARY

Central diabetes insipidus (CDI) is an infrequent complication of neurosarcoidosis (NS). Its presentation may be masked by adrenal insufficiency (AI) and uncovered by subsequent steroid replacement. A 45-year-old woman with a history of NS presented 2 weeks after abrupt cessation of prednisone with nausea, vomiting, decreased oral intake and confusion. She was diagnosed with secondary AI and intravenous hydrocortisone was promptly begun. Over the next few days, however, the patient developed severe thirst and polyuria exceeding 6 L of urine per day, accompanied by hypernatraemia and hypo-osmolar urine. She was presumed to have CDI due to NS, and intranasal desmopressin was administered. This eventually normalised her urine output and serum sodium. The patient was discharged improved on intranasal desmopressin and oral prednisone. AI may mask the manifestation of CDI because low serum cortisol impairs renal-free water clearance. Steroid replacement reverses this process and unmasks an underlying CDI.

BACKGROUND

Sarcoidosis is characterised by immune-mediated, non-caseating granuloma formation in affected organs. Involvement of the central nervous system or neurosarcoidosis (NS) is uncommon, occurring in 5–15% of patients with sarcoidosis.¹ NS can lead to an infiltrative process of the hypothalamic-pituitary axis resulting in neuroendocrinological dysfunction, with central diabetes insipidus (CDI) leading to polyuria and polydipsia as one of its most common manifestations.^{2–3} The full manifestation of diabetes insipidus (DI) can be impeded by the coexistence of adrenal insufficiency (AI) in the same patient. This rare phenomenon is known as masked DI, and is 'unmasked' by glucocorticoid (GC) replacement. Its exact mechanism is unknown, but it is believed to be the result of impaired free water clearance brought about by AI.

We present a patient with NS who presented with AI, and whose CDI was eventually uncovered after GC therapy. The pathophysiological processes resulting to masking of the DI, while putative, are remarkable and noteworthy. In this report, we review the relevant literature on this rarely reported phenomenon.

CASE PRESENTATION

A 45-year-old woman presented with a 2-week history of nausea, vomiting, fatigue and anorexia. One week prior to admission, the patient also developed delirium, described as episodes of confusion,

disorientation, and both visual and auditory hallucinations. Her medical history is significant for asthma, for which she takes inhaled fluticasone combined with salmeterol, and sarcoidosis with pulmonary and cranial involvement. The patient was taking azathioprine and high-dose prednisone for her sarcoidosis, but stopped taking both of them 4 weeks prior to the onset of symptoms. The patient's NS was diagnosed as workup for altered mental status during her last admission a year prior in another hospital. At that time, she did not have any known neuroendocrine complications from her NS, such as hypopituitarism, CDI or hypothyroidism. She had no previous surgeries. Her family medical history is significant for diabetes mellitus and hypertension. She denies actively smoking and drinking, but admits to using marijuana. She has had no travels outside of the city, and denies any history of recent exposure to animals, and insect bites. On physical examination, the patient appeared cushingoid, was awake and alert, but confused with delusions, and auditory and visual hallucinations. The blood pressure on admission was 112/70 mm Hg, pulse was 123 bpm, and temperature was 36.9°C. The patient appeared volume-depleted, with dry mucous membranes. She had no hyperpigmentation or hypopigmentation, and no physical evidence to suggest hyperthyroidism or hypothyroidism. The rest of her physical examination, including neurological findings, was unremarkable.

INVESTIGATIONS

Initial laboratory investigations revealed hypokalaemia with potassium 2.9 mEq/L, and pre-renal acute kidney injury based on an elevated creatinine 2.6 mg/dL, urea nitrogen 11 mg/dL, bland urinalysis, urinary sodium of less than 20 mEq/L, and fractional excretion of sodium of 0.06%. Both were attributed to the patient's dehydration due to vomiting, and the patient was immediately given intravenous fluids. At this time, the patient had a normal sodium of 137 mEq/L, serum osmolality of 277 mOsm/L and a urine osmolality of 329 mOsm/L. Her thyroid-stimulating hormone (TSH) was low to 0.29 mIU/mL and her free T4 level was normal at 0.82 µg/dL, which was interpreted as sick euthyroid syndrome. Morning serum cortisol was less than 0.8 mg/dL, and the patient failed to respond adequately to high-dose cosyntropin stimulation test (see figure 1). This and the fact that she was receiving supraphysiological doses of prednisone indicate that she had secondary AI. The patient was then started on stress-dose intravenous hydrocortisone at 100 mg every 8 h that was rapidly tapered over the next few days. The rest of

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Figure 1 Response of patient to cosyntropin stimulation test.

her laboratory examinations were unremarkable. Evaluation of her head with MRI showed subcortical white matter changes consistent with NS. However, the MRI was performed prior to our suspicion that she had any pituitary involvement, and it was performed to investigate her altered mental status, so a dedicated study for hypothalamic and pituitary lesions was not performed.

TREATMENT

During the next few days while on GC therapy, the patient's symptoms, including delirium, eventually resolved, but she was noted to have extreme thirst, frequent nocturia and polyuria (4–6 L/day). Her serum sodium also increased steadily to a peak of 158 mEq/L (figure 2), accompanied by increased serum osmolality of 313 mOsm/L, despite being able to drink freely, and these were associated with an inappropriately low urine osmolality of 95 mOsm/L. Intranasal desmopressin was started on day 5, which resulted in a 300% increase in her urine osmolality, subsequent normalisation of her serum sodium (figure 2), and resolution of her polydipsia and polyuria. These findings were consistent with CDI.

OUTCOME AND FOLLOW-UP

The patient was eventually restarted on prednisone 20 mg daily with continuation of the intranasal desmopressin, and was transferred to an acute inpatient rehabilitation centre. The patient

required desmopressin for a few weeks, but was eventually discontinued because of hyponatraemia. She was lost to follow-up after discharge from the rehab centre.

DISCUSSION

Our patient is one of the few cases of NS-associated CDI masked by the presence of secondary AI, and eventually uncovered by GC replacement. The prevalence of this phenomenon is unknown, largely because it is uncommon and under-recognised.

NS is rare, with an incidence of 0.2/100 000, and involvement of the central nervous system in sarcoidosis is estimated to occur in 5–15%. Lesions in the brain have been described in the leptomeninges, cranial nerves and the hypothalamic-pituitary axis.^{1 4 5} Its pathological hallmark is the finding of infiltrative non-caseating granuloma, which consists of centrally organised macrophages and epithelioid cells usually circumscribed by lymphocytes. While NS has been reported to cause bulbar palsies, meningeal disease, intraparenchymal lesions, cognitive/behavioral symptoms, seizures, meningitis and peripheral neuropathy, it is well known to cause neuroendocrine dysfunction.^{3 4 6} These neuroendocrine disorders include: CDI, thirst dysregulation, hyperprolactinaemia, secondary amenorrhoea, hypothyroidism, hypoadrenalism, growth hormone deficiency and panhypopituitarism.^{3 4} In a multicentre study of 24 patients with hypothalamo-pituitary sarcoidosis, hypogonadism (87.5%) was the most frequently reported disorder, followed by DI (58%), TSH deficiency (56%), hyperprolactinaemia (55%), secondary AI (37%) and GH deficiency (30%).² In terms of symptoms, polyuria and polydipsia due to either DI or disordered control of thirst are common presenting features of hypothalamic NS.³ Mainstay of treatment of NS is GC, which suppresses the increased CD4-CD8 lymphocyte ratio, cytokine production and collagen synthesis found in sarcoidosis. Other treatments include antimalarials like hydroxychloroquine, and immunosuppressive agents, such as azathioprine, cyclosporine, cyclophosphamide, methotrexate, thalidomide and infliximab.^{3 4}

Our patient's polyuria and polydipsia, which manifested following steroid replacement, was attributed to her NS causing CDI. Given her level of hypernatraemia despite being able to drink freely, it is also possible that she may have thirst dysregulation from involvement of the hypothalamus, which is also a known manifestation of NS. The patient had polyuria, accompanied by severely hypo-osmolar urine (less than 200 mOsm/kg) despite her worsening hypernatraemia. While her MRI did not show infiltration of the hypothalamic-pituitary axis, she had biochemical and clinical findings consistent with a diagnosis of CDI and likely due to her known NS.^{7 8} We suspect that the CDI developed after she discontinued her prednisone and azathioprine, but did not fully manifest because it was masked by a concomitant secondary AI,⁹ which also resulted from the abrupt withdrawal of her prednisone. This phenomenon of CDI masked by AI is well described in literature, but mostly as case reports. The aetiologies of the CDI in these reports are diverse, including empty sella,¹⁰ lymphocytic hypophysitis,¹¹ septo-optic dysplasia¹² and NS,¹³ as in our case. In all of the reports, the CDI was unmasked after administration of steroids. All of the patients, including our case, were managed with cautious correction of the hypernatraemia, and treatment of both AI and DI with GC and desmopressin, respectively.

The exact mechanism of how this phenomenon occurs is unknown but various explanations have been proposed. It is believed that GC deficiency induces impaired free renal water clearance resulting in the masking of the polyuria in DI. Both

Figure 2 Trend of patient's urine output and serum sodium during her hospitalisation.

antidiuretic hormone (ADH)-dependent and ADH-independent mechanisms have been implicated in the phenomenon.¹⁴

The ADH-dependent mechanisms proposed were based on earlier animal models. The study by Ahmed *et al*¹⁵ on rat models and human subjects demonstrated that ADH expression is exaggerated with GC deficiency, leading to marked inhibition of water diuresis. GC replacement lowered plasma ADH levels by inhibiting its secretion from the posterior pituitary and promoted a normal diuresis response.¹⁵ The classic experiment by Boykin *et al*¹⁶ on adrenalectomised, therefore GC-deficient, dogs also demonstrated impaired renal water excretion from persistent secretion of ADH and its non-suppressibility despite water loading.^{12 14} Linas *et al*¹⁴ who studied Brattleboro rats, known to have complete inherited DI, demonstrated that GC-deficient rats have changes in intrarenal and systemic haemodynamics leading to a decreased delivery to diluting sites. It was shown that these rats did not achieve normal urinary response to water loading in the presence of prolonged GC deficiency. GC deficiency resulted in lower stroke volume and cardiac output, which caused ADH-dependent mechanism by non-osmotic stimulation of ADH secretion.¹⁴ In a mouse model by Saito *et al*,¹⁷ they found that mRNA expression of aquaporin-2 (AQP2), protein channels required for water exchange in cells, was more prominent in GC-deficient rats. They demonstrated that the action of non-suppressible ADH was exaggerated by the GC deficiency, and this resulted in the upregulation of AQP2 channels, which contribute to impaired water excretion.

The study by Green *et al*¹⁸ in mouse models demonstrated that inhibition of water diuresis could occur independent of ADH mechanism. The mechanism is unknown, but they observed a decrease in glomerular filtration rate and increase in osmotic water permeability in distal convoluted tubules in adrenalectomised rats, both reversed by GC administration. In their experiment, adrenalectomised mice with hereditary hypothalamic DI were found to have significantly lower urine flow and higher urine osmolality. This was reversed by administration of prednisolone, which restored the response in urine flow.¹⁸ In the same study by Linas *et al* on Brattleboro rats, they found that other than ADH-dependent mechanism, GC deficiency can also lead to ADH-independent impaired water excretion by decreased delivery of filtrate to diluting site. Haemodynamic changes, even without absolute volume depletion, may also contribute to impaired water excretion, independent of ADH, by limiting delivery of tubular fluid to the diluting site. Normally, the final urine tonicity depends on the osmolality of the medullary interstitium and the permeability of the distal nephron to water. In ADH deficiency states, the distal nephron becomes impermeable to water and dilute urine is excreted. Additionally, adequate filtrate must be available at the diluting site to generate sufficient quantities of dilute urine.¹⁹ In vitro data provide further evidence of an ADH-independent increase in permeability of the distal nephron. Isolated renal medullary tubules from adrenalectomised rats were shown to have greater cyclic AMP concentration compared with controls (independent of ADH). cAMP is believed to be the mediator of ADH-induced increased permeability of the distal nephron.²⁰

This case underscores that polyuria and polydipsia after GC replacement in a patient with established AI could be from an underlying masked DI. This 'masking' phenomenon could be due to a multitude of factors, both from ADH-dependent and ADH-independent mechanisms, resulting in impaired renal-free water clearance. Recognition of this phenomenon in patients with adrenal deficiency and risk factors for developing CDI is important in early diagnosis and management of this phenomenon.

Learning points

- ▶ Neurosarcoidosis can present with neuroendocrinological disorders, including central diabetes insipidus (CDI).
- ▶ Adrenal insufficiency (AI) can mask diabetes insipidus by impairing renal-free water clearance.
- ▶ This impaired water clearance can be explained by antidiuretic hormone (ADH)-dependent and ADH-independent mechanisms.
- ▶ Management of this phenomenon is by addressing the two conditions (AI and CDI) simultaneously.

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Competing interests None.

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