Radiological remission and recovery of thirst appreciation after infliximab therapy in adipsic diabetes insipidus secondary to neurosarcoidosis

M.W. O’REILLY1, D.J. SEXTON2, M.C. DENNEDY1, T.J. COUNIHAN3, F.M. FINUCANE1, T. O’BRIEN1 and A.W. O’REGAN2

From the 1Department of Endocrinology, 2Department of Respiratory Medicine and 3Department of Neurology, University College Hospital/National University of Ireland, Galway, Republic of Ireland

Address correspondence to Dr M. O’Reilly, Department of Endocrinology, University College Hospital, Galway, Republic of Ireland. email: m.oreilly@bham.ac.uk

Summary

Background: Neurosarcoidosis is a rare and aggressive variant of systemic sarcoidosis which may result in hypothalamic-pituitary dysfunction. We report a case of hypothalamic hypopituitarism secondary to neurosarcoidosis complicated by adipsic diabetes insipidus (ADI). Initiation of anti-tumour necrosis factor-α (TNF-α) therapy resulted in both radiological disease remission and recovery of osmoregulated thirst appreciation after 3 months.

Case summary: A 22-year-old man was referred to the endocrinology service with profound weight gain, polyuria and lethargy. Biochemical testing confirmed anterior hypopituitarism while posterior pituitary failure was confirmed by hypotonic polyuria responding to desmopressin. Magnetic resonance imaging (MRI) demonstrated extensive hypothalamic infiltration; neurosarcoidosis was confirmed histologically after excisional cervical lymph node biopsy. Osmoregulated thirst appreciation was normal early in the disease course despite severe hypotonic polyuria. However, subsequent subjective loss of thirst appreciation and development of severe hypernatraemia in the setting of normal cognitive function indicated onset of ADI.

Management: Clinical management involved daily weighing, regular plasma sodium measurement, fixed daily fluid intake and oral desmopressin. We initiated immunosuppressive therapy with pulsed intravenous anti-TNF-α therapy (infliximab) after multidisciplinary team consultation.

Outcome: Infliximab therapy resulted in successful radiological disease remission and complete recovery of osmoregulated thirst appreciation. This was confirmed by subjective return of thirst response and maintenance of plasma sodium in the normal range in the absence of close biochemical monitoring.
Learning Point for Clinicians

Hypothalamic neurosarcoidosis is an aggressive disease which may respond to anti-TNF-α immunosuppression in refractory cases. The development of hypernatraemia in alert patients with diabetes insipidus (DI) always raises the clinical suspicion of adipsia. This case demonstrates the complexity of management of both ADI and neurosarcoïdosis.

Introduction

Sarcoidosis is a chronic idiopathic multisystem disease characterized by granulomatous inflammation of affected organs. Neurological involvement is observed in 5% of cases, occasionally resulting in hypothalamic hypopituitarism. Central DI occurs with lesions of the pituitary and hypothalamus, including neurosarcoïdosis, and is characterized by hypotonic polyuria and thirst. The vast majority of patients with DI have normal osmoregulated thirst appreciation; water consumption allows maintenance of plasma sodium in the normal range. ADI is a rare form of central DI in which the thirst response to hyperosmolality is lost. It has been reported predominantly after anterior communicating artery aneurysm clipping. We report a case of ADI secondary to neurosarcoïdosis in which anti-TNF-α therapy induced radiological remission and recovery of thirst response to hyperosmolality.

Case

A 22-year-old Caucasian male was referred to our institution with polyuria. On examination, body mass index was measured at 35.1 kg/m². Enlarged cervical lymph nodes were palpated in the anterior chain. Testicular volume was reduced at 5 ml. Anterior hypopituitarism was confirmed on baseline biochemistry and synacthen testing demonstrated severe secondary adrenal insufficiency. 24-hour urine volume was 14.3 l. Water deprivation testing was deemed unsafe due to severe polyuria; plasma and urine osmolalities of 291 and 76 mOsm/kg, respectively, and subsequent response to desmopressin, secured a diagnosis of central DI. MRI brain demonstrated enhancing hypothalamic infiltrates.

Histology after excisional cervical lymph node biopsy revealed non-caseating granulomatous infiltration and a diagnosis of neurosarcoïdosis was made. Pituitary hormone replacement was instituted with desmopressin, thyroxine and testosterone, and immunosuppressive prednisolone (1 mg/kg) was commenced. The patient reported significant clinical improvement; 6-month interval imaging showed disease regression. However, he subsequently represented with headache, loss of thirst sensation and reduction in compulsion to drink. Clinical examination revealed hypovolaemic dehydration and tachycardia. Plasma sodium (162 mmol/l) and urea (11.2 mmol/l) were significantly elevated. Repeat imaging showed new hypothalamic infiltration (Figure 1a). ADI was diagnosed based on subjective loss of thirst, hypernatraemic dehydration and polyuria. The gold standard diagnostic test for adipsia was deemed both unsafe and unnecessary in view of severe hypernatraemia and the overall clinical picture.

Intravenous anti-TNF-α therapy with infliximab was commenced. The patient was discharged, with

Figure 1. (a) MRI (April 2011, flair sequence) after weaning of immunosuppressive glucocorticoids and presentation with hypernatraemia and adipsia. (b) MRI (October 2011) after 6 months of therapy with pulsed intravenous infliximab. This has coincided with resolution of adipsia and recovery of osmoregulated thirst appreciation.
repeat infusion scheduled after 4 weeks. ADI was managed as an outpatient with desmopressin, daily weights, fixed daily fluid intake and electrolyte measurement every other day. There were no further hospital admissions with hypernatraemia. The patient reported complete return of thirst appreciation after 3 months of treatment. Resolution of adipsia was confirmed by subjective improvement in thirst appreciation and maintenance of normonatraemia despite discontinuation of fixed fluid quotas and twice-weekly electrolyte measurement. Repeat MRI on 6-month follow-up showed significant radiological improvement (Figure 1b).

Discussion

Neurosarcoidosis may affect any component of the central nervous system. Corticosteroids are first-line therapy and may be combined with immunosuppressants such as methotrexate or hydroxychloroquine. In our patient, glucocorticoids were initiated with immunosuppressive doses of prednisolone. Despite initial improvement, clinical/radiological benefits plateaued without inducing full disease remission. Infliximab is a chimeric monoclonal antibody that inactivates the pro-inflammatory cytokine, TNF-α. Experience of its use in neurosarcoidosis is limited to case reports, with the largest series consisting of 23 patients, but a growing body of evidence supports its utility in refractory disease.

ADI is a rare complication of hypothalamic disease. Coexistence of AVP deficiency and adipsia places the site of the lesion at the osmoreceptors in the anterior hypothalamus. Fenestrations in the blood-brain barrier allow the osmoreceptors to sense fluctuations in plasma osmolality, sending a neuronal signal to the supraoptic/paraventricular nuclei to synthesize AVP, which is then carried to the posterior pituitary and secreted. Dysfunction of the osmostat in ADI means that patients do not sense thirst and hence do not drink water.

ADI and neurosarcoidosis are rare conditions in whom the natural history is uncertain. Spontaneous remission is common in systemic sarcoidosis but clinical experience suggests that remission is rare without aggressive treatment in neurosarcoidosis. This case highlights the complexity of clinical management of ADI and the aggressive nature of neurosarcoidosis. Here, infliximab successfully induced disease remission, with recovery of osmoregulated thirst appreciation. It may be a useful therapeutic strategy in hypothalamic neurosarcoidosis refractory to conventional treatment.

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References