

SHORT REPORT

Infundibulohypophysitis in a man presenting with diabetes insipidus and cavernous sinus involvement

N Tubridy, D Saunders, M Thom, S L Asa, M Powell, G T Plant, R Howard

Abstract

Infundibulohypophysitis is an unusual inflammatory condition that affects the infundibulum, the pituitary stalk, and the neurohypophysis and may be part of a range that includes lymphocytic hypophysitis. Lymphocytic hypophysitis occurs mainly in women and most often presents in the later stages of pregnancy. Infundibulohypophysitis usually presents with diabetes insipidus and the cause remains unclear. The case of a 46 year old man with a 12 week history of polyuria and polydipsia is reported. Cranial diabetes insipidus was diagnosed on the basis of a water deprivation test. Initial cranial and pituitary imaging studies were normal. He subsequently developed symptoms of panhypopituitarism over a period of 6-9 months and then, more acutely, developed diplopia secondary to a fourth nerve palsy. Further brain imaging studies disclosed an enhancing pituitary stalk and a left cavernous sinus lesion. An initial trial of immunosuppressive treatment did not help symptoms significantly. The diagnosis of infundibulohypophysitis was made on histological evidence. The patient was

treated with prednisolone and methotrexate. At 9 months he is well, without symptoms, and the radiological abnormalities have resolved.

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Lymphocytic infundibulohypophysitis is an inflammatory condition affecting the posterior pituitary gland and often presenting clinically with cranial diabetes insipidus.¹ It is distinct from lymphocytic hypophysitis, which affects the anterior pituitary and usually presents at the end of pregnancy with visual disturbances.² Differentiating between the conditions may be difficult and requires detailed pituitary function testing and MRI.³ A definitive diagnosis, however, requires histology. We describe the unusual case of a man with lymphocytic infundibulohypophysitis who presented with diabetes insipidus but, over the period of a year and despite immunosuppressive therapy, the condition progressed to involve most of the pituitary gland and the cavernous sinus. Treatment of both conditions remains controversial

National Hospital for
Neurology and
Neurosurgery, Queen
Square, London
WC1N 3BG, UK
N Tubridy
D Saunders
M Thom
M Powell
G T Plant
R Howard

Department of
Endocrine Pathology,
Mount Sinai Hospital,
Toronto, Ontario,
Canada
S L Asa

Correspondence to:
Dr R Howard
ntubridy@hotmail.com

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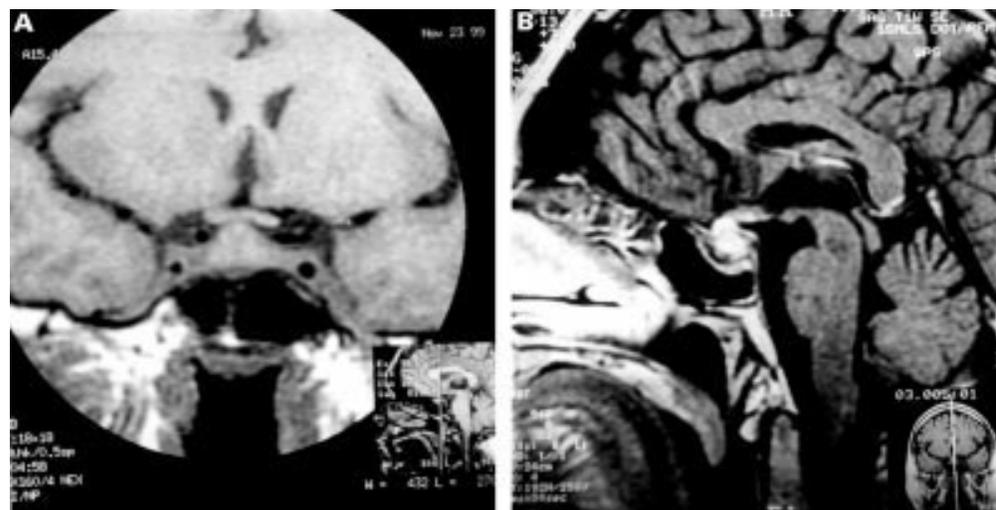


Figure 1 (A) Coronal T1 weighted image. The pituitary gland is enlarged and the suprasellar extension impinges on the optic chiasm and seems to extend into the cavernous sinuses, more on the right than the left; (B) midline, sagittal postcontrast T1 weighted image. The enlarged pituitary gland and the thickened infundibulum avidly enhance after the administration of gadolinium-DTPA.

with immunosuppression and surgical removal the two approaches most often advocated.

Case report

A 46 year old man presented with a 12 week history of headaches, polyuria, and polydipsia. The headaches, mainly frontal, were worse in the morning and had begun to wake him at night. He was a heavy smoker and alcohol consumption was moderate. He had no relevant medical history but there was a strong family history (sister and mother) of autoimmune dysthyroid disease. Clinical examination was normal including blood pressure. Investigations disclosed a normal full blood count, urea and electrolytes, bone profile, thyroid function, and plasma cortisol. Plasma osmolality was 293 mmol/kg (normal 285–295); urinary osmolality was 235 mmol/kg (normal 300–1200) and urinary sodium was 55 mmol/l. His 24 hour urinary output was 0.7 litres with an intake of over 7 litres. During a water deprivation test, the plasma osmolality remained between 292 and 299 mmol/kg but the urinary osmolality fell to 157 mmol/kg at 3 hours. After 2 µg intramuscular DDAVP the plasma osmolality did not alter significantly but the urinary osmolality rose to 599 mmol/kg. A diagnosis of cranial diabetes insipidus was made and he was prescribed 10 µg intranasal desmopressin once at night. A cranial and pituitary MRI study was normal.

The polyuria and polydipsia were well controlled but the headaches persisted and he was referred to the neurology service 2 months later. The headaches were occurring twice a day—morning and evening—and had changed site to now involve the back of the neck, back of the skull, and forehead. They were relieved with mild analgesics within about 30 minutes. Once again neurological examination was normal and visual acuity was 6/4 bilaterally, with normal visual fields and fundoscopic examination. Further tests of osmolality showed good control of the diabetes insipidus but low testosterone (8.8 nmol/l (normal 9–33)) and an erythrocyte sedimentation rate of 30 mm/h. Luteinising hormone (LH) and follicle stimulating hormone (FSH) were normal but prolactin was slightly raised at 516 mU/l (normal 31–399). Serum angiotensin converting enzyme (ACE), an autoantibody screen, and a chest x ray film were all normal. An HIV test was negative.

The headaches persisted and 6 months later he complained of diplopia on looking up and to the right. The CSF examination showed a protein concentration just above the normal range (0.56 g/dl) but was otherwise normal. Further MRI studies showed a small parasellar mass on the left side and the posterior pituitary was hypointense on T1 weighted images consistent with cranial diabetes insipidus. There was a separate gadolinium enhancing, pituitary mass and an enhancing left cavernous sinus lesion that encased the internal carotid artery (fig 1 A and B). The radiological differential diagnosis of sarcoid, Wegener's granulomatosis and, though less likely, histiocytosis X, prompted

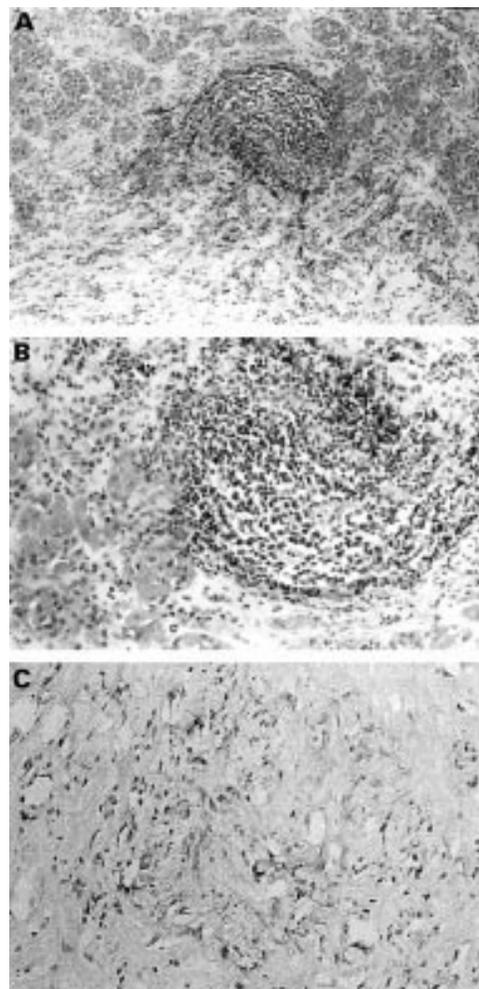


Figure 2 (A and B) The border of the anterior pituitary gland and adjacent fibrous connective tissue with an infiltrate of chronic inflammatory cells showing germinal centre formation. The normal acinar pattern of the anterior pituitary gland is maintained with some fibrosis between acini but little evidence of destruction of this part of the gland (both haematoxylin and eosin (A) $\times 90$ (B) $\times 225$). (C) Immunocytochemistry for vasopressin showed residual positive cells in the inflamed and fibrotic area consistent with residual, scarred neurohypophysial tissue (immunohistochemical localisation of vasopressin using the streptavidin-biotin-peroxidase technique and then stained with haematoxylin nuclear counterstain; $\times 125$).

the start of prednisolone and fludrocortisone therapy. His symptoms disappeared on this regime but returned when the steroid dose was tapered.

He subsequently developed a reduced libido and an increased sensitivity to cold. Six months later he developed increasingly severe headaches, nausea, and vomiting, numbness of the left face, and diplopia on horizontal gaze. There was a reduction in sensation in the distribution of the first division of the trigeminal nerve on the left and there was a left fourth nerve palsy. There was now some mild left proptosis. The rest of the examination was normal.

A trans-sphenoidal biopsy showed a non-infectious, chronic inflammatory process and the possibility of lymphocytic hypophysitis was raised. Histology showed several fragments of pituitary tissue that included adenohypophysitis

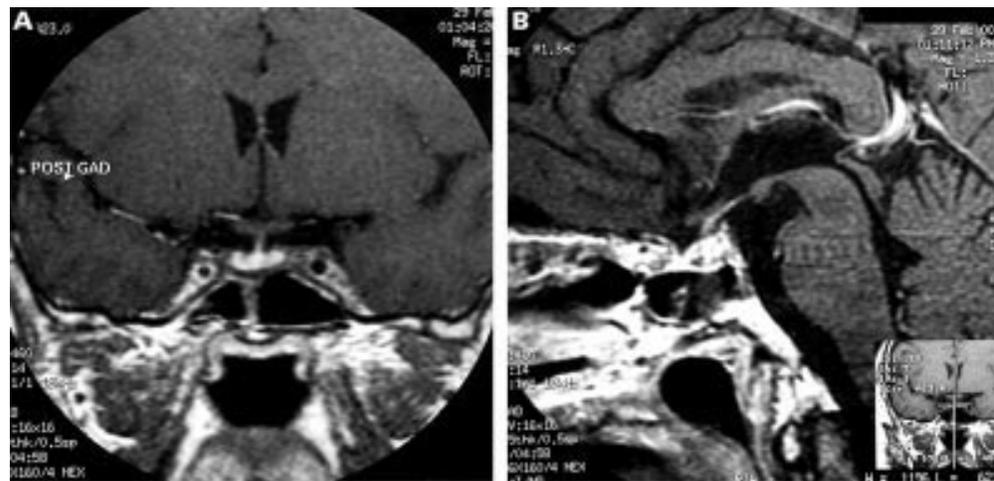


Figure 3 (A) Coronal and (B) sagittal postcontrast T1 weighted images. The pituitary gland and infundibulum have reduced in size and the infundibulum is pulled down into the pituitary fossa. The optic chiasm is no longer compressed and the cavernous sinus appears normal.

and fibrotic inflamed tissue. A chronic lymphoplasmacytic infiltrate was present in fibrous tissue and the adjacent adenohypophysis was intact and apparently spared by this inflammatory process. Immunohistochemical stains showed that this infiltrate was mixed B and T cell polyclonal for κ and λ light chains and contained scattered histiocytes (fig 2 A and B). There were no well defined granulomas, giant cells, or vasculitic features. Stains for vasopressin and neurophysins identified immunoreactive components of the posterior lobe trapped within this tissue (fig 2 C). A diagnosis of lymphocytic infundibuloneurohypophysitis was made. He was discharged on 60 mg daily of prednisolone and 7.5 mg (weekly) of methotrexate. At 9 months he is well without symptoms and with normal eye movements. A further MRI showed that the pituitary and infundibulum had reduced in size and that the optic chiasm was no longer compressed (fig 3 A and B).

Discussion

Cranial or central diabetes insipidus may be idiopathic or it may be inherited as an autosomal dominant trait.¹ In most reported cases, cranial diabetes insipidus is secondary to a disturbance of the hypothalamic-neurohypophysial system and may be due to a wide range of conditions including trauma, infection, tumours, and granulomatous disease, although lymphocytic infundibulohypophysitis has been suggested as the underlying cause in some cases previously labelled "idiopathic" diabetes insipidus.¹ In lymphocytic infundibulohypophysitis the MR imaging may demonstrate a thickened pituitary stalk or an enlarged neurohypophysis.² There may also be a loss of the hyperintense signal of the normal neurohypophysis on contrast enhanced T1 weighted imaging. The anterior pituitary is spared, which distinguishes this condition from lymphocytic hypophysitis radiologically.

Lymphocytic hypophysitis may rarely present with diabetes insipidus³ but the anterior pituitary is the principal site of inflammation and anterior pituitary cells are seen among the plasma cells and lymphocytes. In lymphocytic

hypophysitis, the lymphocytes are mostly CD4+ cells and there is unequivocal evidence of hypopituitarism (especially amenorrhoea, although 60% of the reported cases of lymphocytic hypophysitis in women present during pregnancy³). Brain MR imaging shows an intrasellar mass often extending into the suprasellar region. Most cases demonstrate an isolated or multiple anterior pituitary hormone deficiency (generally in the descending order of frequency adrenocorticotropic hormone>thyroid stimulating hormone>FSH/LH>growth hormone>prolactin). The antigens involved in these two conditions may differ and antibodies to magnicellular neurons have been reported to occur in infundibulohypophysitis.⁴ The two conditions have long been thought of as possibly autoimmune in origin and Levine⁵ induced a pathologically process similar to lymphocytic hypophysitis by injecting a mixture of pituitary tissue and Freund's adjuvant in rats. Indeed, Levine showed that the inflammatory process was more severe in rats that were recently postpartum. The pathogenesis of both conditions remains unclear although associations with other autoimmune disorders are well documented.⁶

The differential diagnosis includes histiocytosis, a condition in which there is thickening of the pituitary stalk with typical Langerhans cells and patients often display hypopituitarism. Histologically these cells show positive staining for S100 protein which was not present in our patient. Primary intracranial plasma cell granuloma of the hypothalamus can produce a similar clinical picture has similar histology but there is associated tumour formation. Occasionally meningiomas may contain plasma cells and lymphocyte components but meningeoepithelial components can also be found.¹ Tuberculosis and sarcoidosis may present in a similar way clinically but granulomas are seen. A plasmacytoma was excluded by the polyclonality of the plasma cells and a lymphoma is unlikely, as they are associated with atypical cells and, in the CNS, lymphomas are nearly always of the B cell type.

Lymphocytic infundibulohypophysitis, as it was first described at necropsy in 1970,⁷ is rare

and characterised by lymphocytic and plasma cell infiltration confined to the hypothalamic-neurohypophysial system. It is a chronic inflammatory process with infiltration by plasma cells and lymphocytes. The natural history of infundibulohypophysitis is that it may regress spontaneously or with the administration of steroids and this suggests a self limiting inflammatory process perhaps of an autoimmune nature. Most patients are female and the infiltration of tissue by T cells favours the autoimmune hypothesis.

Our case is unusual because of the long clinical history, the patient's male sex and the involvement of the cavernous sinus. The diagnosis is further suggested in our case by the strong family history of autoimmune dysthyroid disease. Cavernous sinus involvement has been reported, to our knowledge, only once before with infundibulohypophysitis⁸ and once with lymphocytic adenohypophysitis.⁹ Both cases were in men and in the first the patient developed "permanent diabetes insipidus". It is tempting to speculate that that hypophysitis, whether confined to the anterior or the posterior pituitary, or whether beyond the gland and into the cavernous sinus is all part of a range of the same disease. The clinical severity of this condition may relate to the extent of the inflammatory response,¹⁰ which

may differ in males and postpartum women. It is still unclear from the literature as to the optimum management but both conditions seem to be steroid responsive, they may regress spontaneously, and a conservative (non-operative) approach is often advocated.¹¹

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