CASE REPORT

Diabetes insipidus from sarcoidosis confined to the posterior pituitary

Keh-Chuan Loh, Angelique Green, William P Dillon Jr, Paul A Fitzgerald, Noel Weidner and James B Tyrrell
Division of Endocrinology, Department of Medicine and Metabolic Research Unit, Section of Neuroradiology, Department of Radiology and Department of Pathology, University of California–San Francisco, San Francisco, California, USA

(Correspondence should be addressed to K-C Loh who is now at Department of General Medicine, Tan Tock Seng Hospital, Moulmein Road, Singapore 308433, Republic of Singapore)

Abstract
A young white man with new-onset central diabetes insipidus was discovered to have a posterior pituitary mass on magnetic resonance imaging. No other radiological abnormalities were noted in the anterior pituitary, infundibulum or hypothalamus. No other endocrinopathies were present; laboratory investigations showed normal basal concentrations of anterior pituitary hormones, including prolactin. The patient was suspected to have sarcoidosis affecting the posterior pituitary, because of the discovery of pulmonary sarcoidosis during his diagnostic evaluation. His symptoms of polydipsia and polyuria responded promptly to intranasal administration of 1-desamino-8-D-arginine vasopressin (DDA VP). The patient demonstrated complete regression of the posterior pituitary mass after a course of corticosteroid therapy. However, his diabetes insipidus persisted and he continues to need DDA VP treatment, currently at 12 months of follow-up. The resolution of the neurohypophysial mass was compatible with the diagnosis of pituitary sarcoidosis and this precluded the need for a transsphenoidal biopsy or surgery.

European Journal of Endocrinology 137 514–519

Introduction
Endocrinopathy occurring in sarcoidosis is relatively rare, the hypothalamus and pituitary gland being the most commonly affected regions (1–3). Of the numerous symptoms attributed to neuroendocrine sarcoidosis, polyuria and polydipsia are the most frequent, as reported in 33% of patients with sarcoidosis of the central nervous system. However, diabetes insipidus resulting from sarcoidosis remains uncommon, as the central nervous system is involved in only 5% of all cases of sarcoidosis (4). Patients with neuroendocrine sarcoidosis commonly have hypothalamic dysfunction and, to a lesser extent, variable involvement of the infundibulum, the pituitary gland, or both. In addition to diabetes insipidus, they often exhibit hypothalamic disturbances and anterior pituitary hormone deficiency (1–3). We report a patient with pulmonary sarcoidosis and central diabetes insipidus secondary to posterior pituitary involvement, who was notable for normal hypothalamic and anterior pituitary functions, and a complete regression of the neurohypophysial mass after corticosteroid therapy.

Case report
A previously healthy 27-year-old white man presented with a 3-month history of progressive polydipsia, polyuria and nocturia. Each day, he drank 6–7 l water because of excessive thirst; he had concomitant polyuria and nocturia. This resulted in disrupted sleep, which prompted him to seek medical attention. He also had mild headache, but no nausea, vomiting or visual problems. He had no symptoms of hypogonadism, hypothyroidism or adrenal insufficiency. He had lost 4.54 kg over the preceding 3 months, but was otherwise well, with no other constitutional symptoms. He had suffered mild bronchial asthma since childhood, but he did not report recent exacerbations, cough, wheeze or effort dyspnea. There was no family history of endocrinopathy or sarcoidosis.

Physical examination showed a muscular young man with normal clinical findings. He had normal visual field and neurological examinations. Initial laboratory screening excluded the diagnosis of diabetes mellitus, revealing both normal fasting plasma glucose and glycated hemoglobin concentrations. He was then subjected to an outpatient overnight (7-h) fluid restriction, following which his urine osmolality was 296 mmol/kg, serum sodium 146 mmol/l and serum osmolality 299 mmol/kg. He responded promptly to a trial of intranasal 1-desamino-8-D-arginine vasopressin (DDA VP), thus confirming the diagnosis of central diabetes insipidus. Pituitary magnetic resonance (MR)
imaging revealed a rounded 8 mm mass in the posterior pituitary, which enhanced with gadolinium contrast. This was associated with a mild compressive effect on the anterior lobe, indicated by deflection of the pituitary stalk in an anterior–superior direction. The normal hyperintense signal in the neurohypophysis on T1-weighted images was absent. However, no obvious abnormalities were noted in the hypothalamus, pituitary stalk and anterior lobe (Fig. 1). Baseline serum hormone measurements were as follows: prolactin 5 μg/l (normal value (NV) <15 μg/l), follicle stimulating hormone 13 IU/l (NV 2–17 IU/l), luteinizing hormone 9 IU/l (NV 4–18 IU/l), total testosterone 580 ng/dl (NV 280–1100 ng/dl), thyroid stimulating hormone 1.5 mU/l (NV 0.5–4.7 mU/l) and free thyroxine 19 pmol/l (NV 9–24 pmol/l). Serum prolactin concentration was 31 μg/l 30 min after a thyrotropin-releasing hormone (200 μg i.v.) stimulation test.

The patient was scheduled to have a transsphenoidal biopsy of the posterior pituitary mass. In the interim, a chest radiograph performed as part of the diagnostic procedures unexpectedly showed bilateral hilar lymphadenopathy and reticulonodular interstitial infiltrates (Fig. 2). Transsphenoidal surgery was deferred and the patient received further assessment by a pulmonologist. Pulmonary sarcoidosis was established by typical findings on a bronchoalveolar lavage (Table 1), and a transbronchial lung biopsy showing multiple non-caseating granulomas which stained negative for tubercle bacilli and fungi (Fig. 3). The results of his arterial blood-gas measurements, pulmonary function studies and serum calcium concentration (9.1 mg/dl) were normal. Treatment was initiated with prednisone 40 mg daily for probable neurosarcoidosis. After 1 month of corticosteroid therapy, repeat pituitary MR imaging showed a complete resolution of the posterior pituitary mass, but continued absence of the normal hyperintense signal of the neurohypophysis on T1-weighted images (Fig. 4). The patient has recovered from his headache, lethargy and weight loss, but has continued to require DDAVP treatment for diabetes insipidus, currently at 12 months of follow-up.

**Discussion**

In contrast to their occurrence in the anterior pituitary gland, mass lesions that primarily involve the posterior pituitary are rare. The diagnostic approach in this case included imaging, hormonal evaluation, and correlation with clinical features. The presence of bilateral hilar lymphadenopathy and reticulonodular interstitial infiltrates on chest radiography, along with the typical findings on bronchoalveolar lavage, established the diagnosis of pulmonary sarcoidosis. The complete resolution of the posterior pituitary mass after corticosteroid therapy supports the diagnosis of sarcoidosis as the cause of the mass.

**Table 1 Bronchoalveolar lavage findings.**

<table>
<thead>
<tr>
<th>Cell count</th>
<th>WBC</th>
<th>0.132 x 10⁹/l</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RBC</td>
<td>0.053 x 10⁹/l</td>
</tr>
<tr>
<td>Differential count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>61%</td>
<td></td>
</tr>
<tr>
<td>Monocytes/histiocytes</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Eosinophils</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>CD4 T cells</td>
<td>81%</td>
<td>of lymphocytes (NV: 27–66%)</td>
</tr>
<tr>
<td>CD8 T cells</td>
<td>7%</td>
<td>of lymphocytes (NV: 11–37%)</td>
</tr>
<tr>
<td>CD4/CD8 ratio</td>
<td>11.6</td>
<td>(N: 1–4.3)</td>
</tr>
</tbody>
</table>

WBC, RBC, white and red blood cells; NV, normal value.
pituitary are extremely uncommon. The differential
diagnoses of neurohypophysial masses, as in our
patient, include neoplastic, infiltrative or granuloma-
tous diseases (5). Primary neoplasms originating from
the posterior lobe are extremely rare; the most common
are granular cell tumors or choristomas. The majority
of such tumors remain asymptomatic and are found
incidentally at autopsy, although occasionally they may
reach a size sufficient to cause headache, visual
disturbances, anterior pituitary insufficiency or diabetes
insipidus (6). Other neoplasms originate very rarely in
the posterior lobe, with merely a few cases of gliomas
and gangliocytomas reported in the literature (5).
Although secondary carcinomas more commonly
involve the posterior than the anterior pituitary;
metastases usually represent incidental autopsy find-
ings in cases of disseminated carcinomatosis (7). However, infiltrative and granulomatous diseases are
noted to have a predilection for the posterior pituitary.
The neurohypophysis or infundibulum is frequently
involved in Langerhan’s histiocytosis, a disease pre-
dominantly affecting children (8). This may cause
diabetes insipidus by complete destruction of the
posterior lobe and accompanying impairment of the
pituitary stalk. Granulomatous diseases, such as sarco-
dosis, tuberculosis and syphilis, can also infiltrate the
posterior lobe or pituitary stalk to cause diabetes
insipidus (1–3, 5). While it is true that a definitive
diagnosis of neurohypophysial lesions is only possible
with histological confirmation of specimens obtained
via biopsy or autopsy, one can nevertheless reach a
reasonable presumptive diagnosis on the basis of
associated clinical and laboratory findings in these
patients. As illustrated by our patient, routine
exclusion of common systemic conditions known to
involve the neurohypophysis may be rewarding and
eliminate the need for invasive pituitary biopsy or
surgery (9).

From the endocrine standpoint, diabetes insipidus
caused by a deficiency of arginine vasopressin (AVP)
constitutes the only important clinical manifestation of
posterior pituitary pathology. AVP is synthesized in
magnocellular neuronal perikarya located bilaterally in
the supraoptic and paraventricular nuclei of the
hypothalamus. AVP and its carrier protein, neurophysin,
are packaged in neurosecretory granules and trans-
ported along axons in the supraopticohypophysial tract
for storage and release from the nerve endings in the
posterior pituitary (10). Diabetes insipidus may occur
either from diseases of the hypothalamus affecting sites
of AVP synthesis, or from diseases of the pituitary stalk
disrupting hormonal transport. Clinical studies have
demonstrated retrograde degeneration of magnocellular
neurons after stalk section, resulting in eventual cell
death and AVP deficiency (5, 11). Conversely, lesions
involving the distal stalk or the neurohypophysis usually
do not result in permanent axonal degeneration, and
clinical diabetes insipidus may be transient, partial or
absent (12–14). Despite the lack of a formal water
depprivation test (often impractical in the current health-
care setting), the diagnosis of central diabetes insipidus
was unequivocal in our patient, on the basis of his
increased serum osmolality, inability to concentrate
urine after an overnight water restriction, and the

Figure 3 Photomicrograph showing cytoarchitectural details of a non-caseating sarcoid granuloma in the transbronchial lung biopsy. Note
the epithelioid histiocytes and absence of necrosis. Hematoxylin and eosin stain. Original magnification ×100.
resolution of his symptoms after a therapeutic trial of DDAVP. The absence of the normal hyperintense signal of neurohypophysis on T1-weighted MR images is consistent with deficiency of neurosecretory granules in the posterior lobe of our patient, which corroborates the diagnosis of central diabetes insipidus (15).

As our patient showed no improvement in his diabetes insipidus up to 1 year of follow-up, it seems likely that, despite the lack of any radiological evidence of hypothalamic or infundibular disease, he indeed possibly had more extensive microscopic involvement of these areas at some time (14). Nevertheless, this patient illustrates that significant diabetes insipidus may occur in patients with a primary posterior pituitary lesion. The other common causes of polydipsia and polyuria in a patient with sarcoidosis, such as thirst dysregulation, hypercalcemia, nephrocalcinosis or nephrogenic diabetes insipidus of sarcoidosis, were either eliminated or unlikely here, as our patient had normocalcemia and showed complete response to DDAVP treatment.

Autopsy studies have demonstrated that sarcoid granulomas have a predilection for the hypothalamus, and less commonly involve the pituitary stalk or the pituitary gland (1). Thus patients manifesting diabetes insipidus from neurosarcoidosis usually have concomitant anterior pituitary hormone deficiency or panhypopituitarism, consequent upon the loss of hypothalamic releasing hormones (1–3). These patients also commonly manifest hypothalamic dysfunction such as the impairment of thirst, temperature, sleep or weight regulation (16–18). Although there was an infrequency of hypopituitarism in earlier reports of patients with diabetes insipidus from neurosarcoidosis, several investigators concluded that this was due to inadequate laboratory evaluation of anterior pituitary function in those patients (1, 2). Furthermore, symptoms of hypopituitarism caused by a slowly expanding granulomatous lesion are often subtle in the adult compared with the more rapid onset of symptoms of diabetes insipidus. In a literature review of 29 cases of sarcoidosis complicated with hypopituitarism, Vesely et al. (2) found diabetes insipidus in 16 patients, whereas the majority of patients showed evidence of growth hormone deficiency or hypogonadism. Stuart et al. (3) studied 10 patients with hypopituitarism and generalized sarcoidosis, using dynamic testing of each pituitary axis with one or more techniques. They found that all ten patients had deficiencies of two or more anterior pituitary hormones, five had apparent defects in thirst drive, and only two had AVP deficiency as measured by water deprivation testing. Nine of the ten patients demonstrated complete pituitary responsiveness to dynamic testings, and one showed a partial responsiveness, thus implying that hypothalamic insufficiency was the major cause for hypopituitarism in these patients.

Hyperprolactinemia also commonly occurs as a result of the loss of dopaminergic inhibition. Turkington & MacIndae (19) reported that hyperprolactinemia was a sensitive indicator of hypothalamic involvement in their series of 34 patients with sarcoidosis. However, other investigators have found a low incidence of hyperprolactinemia, even when pituitary hypofunction
is apparent, and have doubted the reliability of serum prolactin measurement as a screening for patients with hypothalamic or pituitary disease (20). Our patient was unusual, in that he showed no evidence of hypopituitarism or hyperprolactinemia, and therefore was unlikely to have significant hypothalamic or infundibular impairment. Our case illustrates that patients with sarcoidosis may manifest diabetes insipidus without overt hypothalamic dysfunction or other pituitary hormone deficiencies.

Imaging manifestations of neurosarcoidosis are protean (21). They include periventricular white matter foci of T2 hyperintensity mimicking multiple sclerosis, leptomeningeal enhancement particularly of the suprasellar region and basilar cisterns, hydrocephalus, enhancing masses of brain or cord parenchyma, nerve root enhancement and enlargement of the pituitary stalk. Whereas diabetes insipidus and absence of the normal posterior pituitary ‘bright spot’ on T1-weighted images is common with neurosarcoidosis, a mass lesion of the posterior pituitary without visible stalk involvement, as exhibited in our patient, is a distinctively uncommon appearance.

The therapeutic results of administration of corticosteroids to patients with hypothalamic–pituitary involvement from sarcoidosis have been disappointing, and the improvement of diabetes insipidus associated with sarcoidosis has been uniformly poor (1, 3, 22, 23). Patients frequently show progression of the disease or failure to improve despite steroid therapy. Interestingly, our patient demonstrated a complete resolution of the posterior pituitary mass 1 month after the initiation of corticosteroid therapy, which obviated the need for pituitary biopsy or surgery. However, he is likely to suffer permanent diabetes insipidus, as this problem had not improved at 12 months of follow-up; albeit that prolonged recovery after intervals of a year or longer had been reported in some patients with post-traumatic or post-surgical diabetes insipidus (24). Hidaka et al. (23) reported a case of hypothalamic sarcoidosis with hypogonadism and diabetes insipidus; the patient similarly showed complete resolution of the suprasellar mass after 1 month of corticosteroid therapy. Interestingly, he also had persistent diabetes insipidus, although his hypogonadism unexpectedly resolved on long-term follow-up. Because of the serious consequences of progressive sarcoidosis on the hypothalamic–pituitary axis, it is reasonable that all patients with a presumptive or definite diagnosis of sarcoidosis of these organs should be given the benefit of a therapeutic trial of corticosteroids (1). However, the role of long-term corticosteroid therapy in the absence of significant neurological involvement from sarcoidosis, as in our patient, remains unknown and deserves dedicated clinical studies.

In conclusion, we report a case of diabetes insipidus associated with a posterior pituitary mass and asymptomatic pulmonary sarcoidosis. The tumor regressed completely with corticosteroid therapy, suggesting neurosarcoidosis as the underlying etiology. This patient had no overt clinical or biochemical features of anterior pituitary hormone deficiency, indicating that sarcoidosis can preferentially affect the neurohypophysis.

References
18 Wathen CG, Campbell I & Douglas AC. Hypothalamic malfunctions in cerebral sarcoidosis with abnormalities in temperature regulation and vascular control. Sarcoidosis 1988 8 74–76.


Received 15 April 1997
Accepted 30 June 1997