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CASE REPORT

Lymphocytic hypophysitis with associated thyroiditis in a man with aseptic meningitis

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Abstract *Objective* Lymphocytic hypophysitis (LH) is a rare chronic inflammatory disorder characterized by lymphocytic infiltration of the pituitary gland commonly affecting women during pregnancy or post-partum period. The pathogenesis remains uncertain, however an autoimmune process is frequently implicated. There is limited data on the occurrence of LH outside the setting of autoimmunity. *Case* We describe a 37-year-old man presenting with diarrhoea, nausea, weight loss, low-grade fever, headache and cerebrospinal fluid analysis consistent with aseptic meningitis. Magnetic resonance imaging (MRI) demonstrated a homogenously enlarged pituitary gland with biochemical testing revealing partial hypopituitarism with adenocorticotrophic hormone and gonadotrophin deficiency. Notably, his free thyroid hormone levels were elevated with a suppressed thyroid-stimulating hormone and a suppressed thyroid technetium scan consistent with thyroiditis. Tissue antibodies including thyroid antibodies were negative. Following introduction of hydrocortisone, he developed transient diabetes insipidus which spontaneously resolved after 4 months. Thyrotoxicosis resolved after 5 weeks and thyroxine was commenced as he developed secondary hypothyroidism. Repeat MRI 3 months later showed a reduction in the size of the pituitary gland which by 6 months had returned to normal size. He remains well on hydrocortisone, thyroxine and testosterone replacement. *Conclusions* Based on clinical and radiological grounds, the diagnosis was consistent with lymphocytic hypophysitis associated with subacute thyroiditis. This is only the second report of this combination in the absence of autoimmunity and the first report of LH and thyroiditis with associated aseptic meningitis in the absence of tissue autoantibodies. We propose a possible viral illness as the unifying aetiological cause

Keywords Lymphocytic hypophysitis · Thyroiditis · Aseptic meningitis

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Introduction

Lymphocytic hypophysitis (LH) also referred to as autoimmune hypophysitis is a rare chronic inflammatory disorder involving the pituitary gland. The pathogenesis of LH is unknown, but an autoimmune process is commonly implicated. We report an unusual case of LH occurred in a man with concomitant thyroiditis and no evidence of autoimmunity.

Case study

A 37-year-old Caucasian man was admitted to hospital following a collapse at home. He had a 1 month history of general malaise and 20 kg weight loss following a 4 day history of diarrhoeal illness associated with abdominal pain, headache, dizziness, nausea and vomiting. He was previously well with no past medical history and was on no

medications. Capillary glucose performed by ambulance staff was 1.2 mmol/l. Intravenous dextrose was given with recovery of consciousness. Despite a repeat glucose of 9.8 mmol/l, he remained vague and confused. He was afebrile, blood pressure was normal before and after fluid resuscitation. General examination was reported as normal, with no meningism, focal neurological deficits or signs suggestive of chronic illness. Computed tomography of his brain was reported as normal. Cerebrospinal fluid (CSF) analysis was consistent with lymphocytic meningitis [white cell count 288 $\times$ 10^6/l (98% lymphocytes), CSF protein 1.11 g/l (0.15–0.45) and CSF glucose 2.3 mmol/l].

A presumptive diagnosis of viral meningitis was made but intravenous ceftriaxone and acyclovir were commenced while awaiting CSF cultures. His headache persisted along with development of a low grade fever. Magnetic resonance imaging (MRI) of his brain was normal, except for an enlarged, homogenously enhancing pituitary gland (15 mm $\times$ 12 mm $\times$ 12 mm) (Fig. 1a, b). Pituitary hormone testing demonstrated partial hypopituitarism with ACTH and gonadotrophin deficiency. Notably, he also had elevated free thyroxine (FT4) and triiodothyronine (FT3) levels (Table 1). He was referred for an endocrine opinion.

He gave no history of polyuria, polydipsia, or nocturia and no visual disturbances. There was no personal or family history of diabetes, thyroid or other autoimmune disorders and no tuberculosis exposure. He reported normal sexual desire and erectile function. Additional examination confirmed euvolaemia without postural hypotension, mild thyrotoxicosis with tremor and restlessness, and a non-tender normal thyroid gland. He was eugonadal with normal body hair distribution and no galactorrhoea. Visual field evaluation was normal. Hydrocortisone replacement was commenced with discontinuation of antiviral and antibiotic therapy.

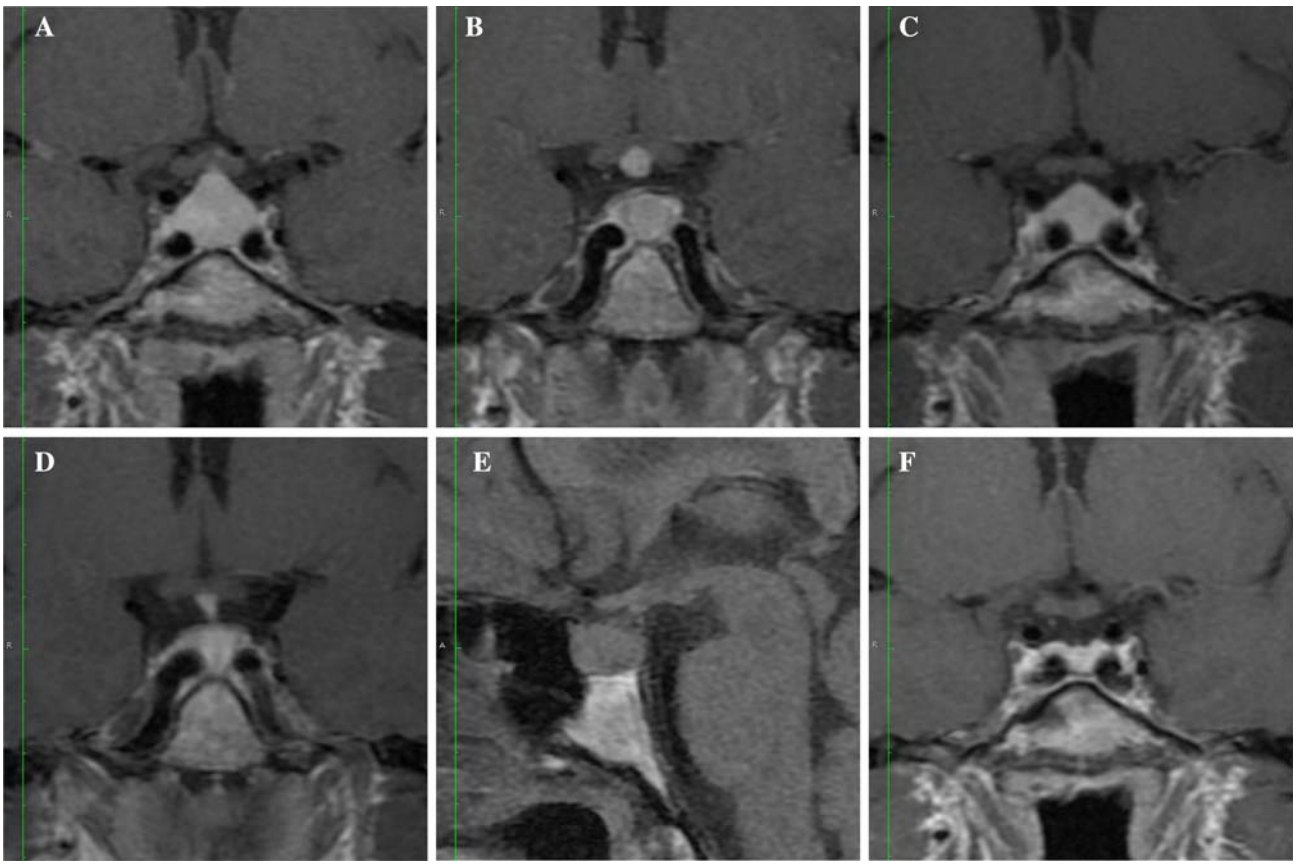

Fig. 1 (**a**) Gadolinium-enhanced T1-weighted MRI coronal images through the pituitary at presentation. A homogeneously enhancing diffusely enlarged pituitary gland abutting the optic chiasm is demonstrated. (**b**) Gadolinium-enhanced T1-weighted MRI coronal images through the pituitary at presentation. Enlargement of the pituitary stalk (infundibulum) is present. (**c**) Gadolinium-enhanced coronal T1-weighted images through the pituitary at 3 month follow up. A reduction in the size of the pituitary gland is seen. (**d**) Gadolinium-enhanced coronal T1 weighted images through the pituitary at 3 month follow up. A reduction in the size of the infundibulum is evident. (**e**) Unenhanced sagittal T1-weighted MRI at three month follow up. Loss of the normal posterior pituitary bright spot is seen. [Note that this was also evident at the time of the patient's initial presentation (image not shown)]. (**f**) Complete resolution of the pituitary gland enlargement at 6 months

Table 1 Serial pituitary hormones

Date (time)	Reference range	13/12/06[a] (11.00 h)	20/12/06 (06.50 h)	30/01/07 (09.30 h)	05/03/07[b] (09.40 h)	10/04/07[c] (09.15 h)	08/05/07 (08.00 h)
FT4	10–20 pmol/l	**38**	47	6	4	12	13
FT3	3.8–6.5 pmol/l		15.3	3.1	1.9	4.2	4.9
TSH	0.3–4.0 mU/L	**0.01**	0.01	<0.1	<0.1	<0.1	0.01
Cortisol	nmol/l	**<10**	<10		11	<10	<10
ACTH	2–11 pmol/l	**<1**	<1	<5	<1	<1	<1
LH	1–10 IU/I	**<0.2**	<0.2	<0.1	<0.1	<0.1	<0.2
FSH	1–14 IU/I	**0.5**	0.4	0.2	<0.2	<0.2	<0.2
Testosterone	9–30 nmol/l	**<0.4**	<0.4	<0.4	<0.4	<0.4	16.4
HGH	0–4.1 ug/l	**1.4**				<0.5	<0.1
IGF-1	14.2–36.9 nmol/l	**17.3**				15.1	12.4
Prolactin	0–360 mIU/I	**<50**		<20	<20	<20	<50
24 hr urine volume	ml	**2040**	1684	6800	5370	4025	2725
24 hr urine creatinine	7–18 mmol/24 h	**10.2**		14.3	13.4	12.5	12.5

Biochemistry from the day of admission is shown in bold. [a] Hydrocortisone commenced on 13/12/06, [b] Thyroxine commenced on 05/03/07, [c] Testosterone commenced on 10/04/07

A thyroid pertechnetate scan confirmed generalised reduced uptake of 0.19% (reference range 0.45–1.7%) consistent with thyroiditis. Inflammatory markers were raised [C-reactive protein 47 mg/l (0–5) and erythrocyte sedimentation rate 47 mm/h (2–25)]. Tissue autoantibodies were negative except for a weakly positive anti-nuclear antibody of uncertain significance. Chest X-ray was unremarkable. General virology screening was negative (Table 2).

Rapid symptomatic improvement was evident with hydrocortisone replacement. One month after commencing steroid replacement, he developed polydipsia and polyuria up to 6800 ml/day. Urinary osmolality showed failure to adequately concentrate urine after 12 h fluid deprivation consistent with partial diabetes insipidus. At this time, there was a gradual reduction in FT4 and FT3 levels consistent with the development of secondary hypothyroidism and thyroxine replacement was introduced.

Four months following his initial presentation, he reported reduced sexual desire and loss of morning erections. Testosterone levels remained <0.4 nmol/l with low gonadotrophin levels and testosterone replacement was commenced. A formal water deprivation test at 5 months demonstrated resolution of his diabetes insipidus.

At last review 6 months after his initial presentation, he remained well on thyroxine, hydrocortisone and testosterone replacement. An MRI brain at 3 months showed a reduction in pituitary size (Fig. 1c–e), and by 6 months the pituitary gland enlargement had shown complete resolution (Fig. 1f).

Discussion

Lymphocytic hypophysitis is a rare cause of pituitary insufficiency with 379 cases reported between January 1962 and October 2004 [1]. Among this, only 87 were men. An additional 81 cases of LH have been identified since then through the John Hopkins Hypophysitis Research Centre [2].

The definitive diagnosis of LH is made based on histological evidence of lymphoplasmacytic infiltration of the pituitary gland. However, it is now recognised that the diagnosis can be made, in an appropriate clinical context, with the classical MRI findings, which include an enlarged pituitary gland which enhances homogenously following gadolinium, a thickened undisplaced stalk and loss of the posterior pituitary 'bright spot' [1, 3]. We did not biopsy the pituitary in this patient as the clinical and radiological features were consistent with LH, and there were no compressive symptoms. An interesting observation in this case was the severe hypoglycaemia at initial presentation. Although subsequent glucose values were normal (prior to steroid commencement), LH has been reported as a cause of hypoglycaemia, presumably as a result of the cortisol and possibly growth hormone deficiency [4].

Two other forms of primary hypophysitis, granulomatous (GrH) and xanthomatous (XnH) hypophysitis were also considered. A clinical–pathological correlation between these three subtypes has recently been published [5]. The severity of hormonal dysfunction, the involvement of neurohypophysis and improvement with glucocorticoids make

Table 2 Immunological Investigations

	Results
Tissues autoantibodies	
Anti-TPO/anti-thyroglobulin	Negative
Thyroid stimulating immunoglobulin	Negative
Anti-adrenal	Negative
Anti-parietal cells	Negative
Anti-smooth muscle, anti-mitochondria	Negative
Anti-GAD, anti-IA2	Negative
Coeliac screen	Negative
Anti-pituitary	Not performed
Antinuclear antibody	Weak positive (1:40 diffuse pattern)
Serum angiotensin-converting enzyme	8 U/L (8-52)
Serology	
Serum immunoglobulin	Normal
HIV 1 and 2	Negative
Treponemal screen	Negative
Leptospirosis	Negative
Typhus fever	Negative
Hepatitis B and C	Negative
Virology	
CSF culture	Negative for CMV, HSV, enteroviruses
Respiratory culture	No growth
Faecal culture	No growth
Microbiology	
Blood culture	No growth
Mid stream urine	No growth
Throat swab	No growth
CSF culture	No growth

XnH very unlikely in this case. GrH resembles LH with controversies existing as to the relationship between LH and idiopathic GrH. It has been suggested that these disorders may represent an autoimmune spectrum from a purely lymphocytic form to a granulomatous form at the end stage of the inflammatory process [6]. The significantly elevated lymphocytes in the CSF of this patient support the diagnosis of LH rather than GrH.

The vast majority of cases of LH occurs in women and is associated temporally with pregnancy [1, 7]. Moreover, it has been reported to have an underlying autoimmune aetiology and a strong association with other autoimmune disorders particularly Hashimoto's thyroiditis or Graves' Disease and adrenalitis [8–10]. The current case is unique in that the classical clinical and radiological features consistent with LH occurred in a male with associated thyroiditis in the absence of any identifiable autoimmune disease. Anti-pituitary antibodies (APAs) may have been useful, particularly if these were absent, but were not measured in this case due to the unavailability of a local assay. In addition, the diagnostic role of APAs remains unclear particularly with the different assay methods currently in use and APAs have been reported to be more useful in the setting of selective hypopituitarism (particularly growth hormone deficiency) with a normal or inconclusive MRI or MRI findings suspicious or overlap with a pituitary adenoma [10], which is not the case in our patient.

On literature review we have identified a total of 51 patients with a combination of suspected OR biopsy (or autopsy) confirmed LH and primary thyroid dysfunction (hypo or hyperthyroidism) but only one case unrelated to pregnancy or tissues autoantibodies. In that report a 45-year-old man presented with anorexia, diarrhoea, confusion and weight loss and was subsequently found to have severe hypercalcaemia, isolated ACTH deficiency, primary hyperthyroidism with rapid development of hypothyroidism on carbimazole and absence of anti-thyroid antibodies which, similar to our case, was suggestive of an episode of silent or subacute thyroiditis with associated LH [11]. Possible explanations for the association of hypophysitis and thyroiditis include a common cellular mechanism acting simultaneously on pituitary secretory cells and thyroid follicular cells or an exacerbation of autoimmune thyroid dysfunction induced by hypoadrenalism as previously described [12]. However the latter is unlikely in this case as there was no evidence of anti-thyroid antibodies.

The relationship between aseptic/lymphocytic meningitis and hypophysitis is intriguing. Six cases have previously been reported [13–18] suggesting that this combination is more than coincidental. More than two-third of cases of aseptic meningitis have an identifiable viral aetiology with enteroviruses the most common agents [19]. Although virology screening was negative in this case, the diarrhoeal illness and prodromal symptoms suggest a possible viral aetiology as a potential disease mechanism. The definitive relationship between these combinations is unknown. One possible mechanism is that a meningitis-inducing virus triggers cytokine induction leading to T-lymphocytes activation causing cellular injury involving the endocrine organs and meninges. Although remains speculative, this mechanism has been described in animal models [20]. This mechanism would also explain the involvement of the thyroid gland. An alternative explanation is merely dissemination of inflammatory cells from the pituitary to the CSF space, however, this does not explain the involvement of subacute thyroiditis. To our knowledge, this is the first case of lymphocytic hypophysitis associated with subacute thyroiditis and aseptic meningitis in the absence of any known tissue autoimmunity.

Conclusion

Lymphocytic hypophysitis is a rare pituitary disorder, however its prevalence may have been underestimated as increasing cases are now being diagnosed without pituitary biopsy, although this remains the gold standard diagnostic tool to date. We report a case with clinical and radiological features consistent with lymphocytic hypophysitis with concomitant thyroiditis and aseptic meningitis in the absence of evidence of autoimmune disease in a man. We hypothesise that a viral aetiology is possible and that this should be considered in patients presenting with LH without the usual clinical risk factors or evidence of underlying autoimmunity.

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