Spontaneous pregnancy after trans-sphenoidal surgery in a patient with lymphocytic hypophysitis

Lymphocytic hypophysitis (LH) is a rare but increasingly recognized autoimmune endocrine condition primarily affecting peripartum young women. In the UK, there have been only 28 reported cases so far. The natural history of LH in relation to the incidence and effect of subsequent pregnancies, especially after pituitary surgery, is not known. We report a 37-years-old patient who had a spontaneous and uneventful pregnancy following LH that had been treated with trans-sphenoidal surgery.

A 37-years-old woman developed progressive visual loss and headache at five weeks after the delivery of her second child. Her pregnancy had previously been uneventful and there was no significant past medical history of note. Physical examination showed bilateral quadrantanopic visual field defects. Laboratory investigations revealed a 9am serum cortisol of 77 nmol/l (280–700), free T4 of 6-7 pmol/l (9–25), TSH of 0-13 mU/l (0-1–5-0) and a serum prolactin of 330 mU/l (up to 700). A magnetic resonant imaging (MRI) scan of the pituitary revealed a pituitary tumour with suprasellar extension and optic chiasmal compression. She underwent trans-sphenoidal surgery with thyroxine and steroid cover. Histological examination of the resected specimen was consistent with lymphocytic hypophysitis showing intense infiltration of lymphocytes, plasma cells, eosinophils, neutrophils and macrophages, excess fibrous tissue and occasional lymphoid aggregates (Fig. 1). No adenoma was identified.

Postoperatively, she developed diabetes insipidus (serum sodium 148 mmol/l, spot serum osmolality 307 mOsm/kg, urine osmolality 95 mOsm/kg) that responded to oral desmopressin. Her headache and visual field defect resolved completely. Subsequent endocrine testing 6 weeks after surgery revealed a subnormal cortisol response to glucagon of 531, 349 and 384 nmol/l at 0, 150 and 180 minutes, respectively, and she was therefore advised to take steroids at times of stress. Peak GH response was also inadequate at 4-9 µg/l with a low basal IGF level of 5-1 units (9-5–40). Free T4 spontaneously improved to 13-6 pmol/l (9–25) and TSH to 1-2 mU/l (0-1–5-0). She continued to have regular periods. Her diabetes insipidus persisted and required regular oral desmopressin. A repeat MRI scan 3 months post hypophysectomy was normal.

Three years after her original presentation she got pregnant spontaneously. At 28 weeks of gestation, laboratory investigations revealed that she continued to have adequate thyroid reserve (TSH 1-83) and her morning cortisol was also in the normal range (serum cortisol 544). Her desmopressin requirement did not change throughout this pregnancy. A mid-trimester MRI scan did not show any recurrence of pituitary mass. She delivered spontaneously under steroid cover and a postpartum MRI scan was normal. Her most recent pituitary function tests showed a free T4 of 15 pmol/l, TSH of 0-77 mU/l and an IGF-1 of 14 units. The peak cortisol and GH response to insulin-induced hypoglycaemia were 467 nmol/l and 1-83 respectively, and her morning cortisol was also in the normal range (serum cortisol 13-6). She was therefore advised to take steroids at times of stress. Peak GH response was also inadequate at 4-9 µg/l with a low basal IGF level of 5-1 units (9-5–40). Free T4 spontaneously improved to 13-6 pmol/l (9–25) and TSH to 1-2 mU/l (0-1–5-0). She continued to have regular periods. Her diabetes insipidus persisted and required regular oral desmopressin. A repeat MRI scan 3 months post hypophysectomy was normal.

In summary, we present a 37-years-old lady with a spontaneous and uneventful pregnancy after developing partial hypopituitarism and diabetes insipidus that followed a diagnosis of lymphocytic hypophysitis requiring trans-sphenoidal surgery after delivery of her previous child 3 years earlier.

Hypophysitis can be primary or secondary. Lymphocytic hypophysitis, granulomatous hypophysitis and xanthomatous hypophysitis are the three distinct clinicopathological entities described in primary hypophysitis, while secondary hypophysitis may be caused by infections, or the pituitary inflammatory process may be a part of systemic disease.

The first description of LH was by Goudie and Pinkerton in 1962. Although it can affect both sexes, it is more common in women with a ratio of 8:1 and more than half have been related to pregnancy. The condition can be associated with other autoimmune disorders and HLA DR4 is the frequently described allele. So far, about 379 cases have been reported worldwide, of which, over a third are from Japan. The exact explanation for this geographical distribution remains unclear. Japanese patients with isolated ACTH deficiency, a predominant feature of LH, have been shown to have a high prevalence (70%) of pituitary autoantibodies that also cross-react to a 49-kD protein. This 49-kD protein (alpha-enolase) has been identified as the autoantigen targeted by the immune system in LH. Pituitary autoantibodies from patients with peripartum hypophysitis also recognize enolase in the placenta, potentially explaining its strong association with pregnancy.

**Fig. 1** Histology of the pituitary showing features of lymphocytic hypophysitis.

White thick arrows indicate plasma cells, white dotted arrows indicate histiocytes; white double arrows indicate neutrophils; black thick arrows indicate eosinophils; black dotted arrows indicate lymphocytes.
Compressive symptoms such as headache and visual deterioration may be the initial complaint of LH. It can also cause hormonal dysfunction affecting the anterior pituitary axes, mainly ACTH, TSH, gonadotropins and prolactin; or the posterior pituitary resulting in diabetes insipidus. Magnetic resonance imaging (MRI) is the imaging of choice; however, even with modern techniques, approximately 40% of the cases are preoperatively misdiagnosed as pituitary adenomas, as it was in our patient. Symmetrical and homogenous enlargement of the pituitary gland, undisplaced and thickened stalk and intact sellar floor are some of the features that may differentiate LH from pituitary macroadenoma. The salient histological picture of LH is a diffuse lymphocytic infiltration of the pituitary that forms lymphoid follicles and at later stages, fibrosis and parenchymal atrophy.

The treatment of lymphocytic hypophysitis is controversial as the natural history of the disease varies from spontaneous resolution to progressive hypopituitarism. Surgery is the commonest treatment option used so far, as this provides histological confirmation, reduces tumour mass and relieves symptoms. Glucocorticoid therapy has been shown to reduce the inflammation and improve the MRI appearances; however, its precise role and efficacy in this condition remains unclear.

Literature on the incidence of spontaneous pregnancy following pituitary surgery is sparse. In patients with LH, the data on subsequent pregnancies is even less. There have been reports of successful induction of ovulation with gonadotrophin therapy after pituitary surgery in a patient with LH. Our patient, however, became pregnant spontaneously despite previous pituitary surgery and partial hypopituitarism. A history of LH in a previous pregnancy does not appear to increase the risk of recurrence in subsequent pregnancies as 16 women in other studies became pregnant again after their initial diagnosis without any recurrence.

In summary, lymphocytic hypophysitis should be considered in the differential diagnosis of pituitary mass, especially when presenting during pregnancy or postpartum period. In the absence of progressive visual disturbances, a trial of steroids can be attempted with repeated visual field and radiological assessment; potentially eliminating the need for aggressive pituitary surgery. A high index of suspicion is however required to diagnose this condition.

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doi:10.1111/j.1365-2265.2006.02734.x

References

Importance of secretion pattern in minimally invasive surgery for phaeochromocytoma

We appreciate the paper of Weismann et al. comparing intraoperative haemodynamic stability in patients undergoing phaeochromocytoma removal by the minimally invasive approach vs. the conventional open surgery. The authors demonstrated in a retrospective study that there is no significant difference in haemodynamic stability between minimally invasive approach and conventional open surgery during surgery for phaeochromocytoma. Less surprising is the fact that intraoperative haemodynamic parameters were much more unstable for phaeochromocytoma compared to adrenocortical adenomas. These results are in line with a previous study in which we demonstrated in eight patients the safety and the efficiency of laparoscopic adrenalectomy to remove phaeochromocytomas including even large-sized lesions (more than 10 cm in diameter).

However, we want to stress other important aspects of the complexity of the pre- and intraoperative blood pressure control for phaeochromocytoma surgery. First, the authors unfortunately did not present any information about haemodynamic differences that possibly could have been linked to the choice of the type of minimally invasive approach: either transabdominal (requiring peritoneal insufflation) or retroperitoneal (requiring a prone position of the patient). As far as intraoperative haemodynamic stability is concerned, the preference of the responsible surgeon is not the final word, as inferred by the authors. Indeed, results of intraoperative blood pressure monitoring show that hypertensive peaks during phaeochromocytoma surgery could be induced by patient positioning on the operating table, peritoneal insufflation and/or tumour manipulation and occur concomitantly with a release of catecholamines and other hormones endowed with vasoactive properties.

Second, the predominant preoperative catecholamine secretion pattern is important to know. Indeed, in our previous study, the greatest haemodynamic instability was observed in noradrenaline secreting phaeochromocytomas probably as a result of the more pronounced vasoconstrictor effects of this amine through binding to alpha-receptors. Of note, we could also establish a relationship between tumour size and the type of catecholamine secretion. Tumours smaller than 30 mm in diameter predominantly secreted adrenaline whereas larger ones mainly secreted noradrenaline. This could be explained by the fact that large phaeochromocytomas are devoid of sufficient cortisol supply for phenylethanolamine-N-methyltransferase induction and hence adrenaline synthesis.

Third, because phaeochromocytomas can provoke severe cardiomyopathy as well as myocarditis, one may raise the question of the