Lymphocytic Adenohypophysitis Simulating a Pituitary Adenoma in a Pregnant Woman

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ABSTRACT

The lymphocytic hypophysitis, appearing in women during the third trimester of pregnancy or early post-partum period, is a rare cause of hypopituitarism and pituitary enlargement. A 39 year-old woman presented in the 37th week of pregnancy with bilateral heteronymous quadrantanopsia, CT indicative of tumorous mass and symptoms of hypopituitarism with decreased thyroid hormone and thyrotrophin levels, and low normal level of cortisol. After the birth of a healthy male child the patient breastfed for 10 days, sight disturbances disappeared, but amenorrhea persisted. Upon admittance the visual field showed no abnormalities. MR of the sellar region confirmed previous CT findings. Endocrinological testing confirmed secondary hypothyroidism and cortisol deficiency, normal levels of prolactin with satisfactory reaction to thyrotrophin. Histology showed mononuclear infiltration, and immunohistochemistry revealed T-cells (CD⁵) at the borders, and B-cells (CD₂⁰) in the follicular center. Due to enlargement of the pituitary associated with hypopituitarism, an incorrect diagnosis of a tumor could be made.

Introduction

Lymphocytic adenohypophysitis (LH) was first described in 1962 by Goudie and Pinkerton. Subsequently there have been approximately 130 cases¹ described in literature. It is an uncommon, but increasingly recognized cause of pituitary enlargement, diagnosed primarily in women in the last trimester of pregnancy or in the early postpartum period (about 90% of all cases), and is often associated
with a mild elevation of blood prolactin level. LH may also occur in premenopausal women with no recent history of pregnancy, postmenopausal women, adolescents and even in men.

LH is a rare autoimmune inflammatory process of the pituitary gland causing pituitary expansion with hypopituitarism and closely mimicking features of a pituitary adenoma. The presenting symptoms are typically related to suprasellar extension and partial or panhypopituitarism. The hormonal deficits may be atypical with, most often, selective loss of either adrenocorticotropic (ACTH) or thyroid stimulating hormone (TSH). Acquired isolated deficiencies of any pituitary hormone are not uncommon, and several authors have suggested that LH may cause them. Some of them, like secondary adrenal insufficiency can be fatal without proper treatment. In the early stage, the pituitary gland is enlarged, mimicking tumor, and computed tomography (CT) or magnetic resonance imaging (MRI) cannot be used as procedures for the ultimate diagnosis. As it has been suggested that pregnancy neither initiates formation of prolactinomas nor accelerates their growth, thus the probability that the diagnosis in such circumstances is LH increases.

In the later stages, the gland may atrophy, leaving an empty sella, as occurs in Sheehan's syndrome. Recovery from hypopituitarism has been described, but is uncommon. An autoimmune cause, possibly involving both humoral and cell-mediated mechanisms, has been postulated but has not been proven yet. Supporting data include isolation of antipituitary antibodies, female predominance and association with other autoimmune disorders, but antipituitary antibodies have not been documented in all patients with proven autoimmune hypophysitis.

The natural history and pathogenesis of LH remains poorly understood. The first case of preoperatively suspected and steroid-treated adenohypophysitis was described in 1992. A review of literature suggests that conservative treatment may be given in suspected cases of lymphocytic hypophysitis, if the vision of the patient is not threatened. A transphenoidal stereotactic biopsy of the pituitary may be performed if the patient does not improve or deteriorates, thus avoiding open exploration of the sella in selected cases.

Case Report

In February 1998, a 39-year-old woman was admitted to the University Hospital «Sestre milosrdnice» – 4 months after her second delivery. Her family and personal history revealed no abnormalities, but she had an interesting gynecological history: 1994 she had a missed abortion, and 1997 she delivered by Caesarian section a healthy male child. In the 37th week of her second pregnancy she complained of visual disturbances, mild headaches, exertion intolerance, muscle and joint pain. Due to mentioned disturbances she was admitted to the Gynecological Department in local hospital. She was found to have bilateral heteronymous quadrantanopsia.

Endocrinological evaluation revealed low levels of blood thyroxin (T4) 45 nmol/l (normal values 50–165 nmol/l), blood triiodothyronine (T3) was 0.7 nmol/l (normal values 1.1–2.8 nmol/l), blood TSH level was 0.1 mU/l (normal values 0.1–4 mU/l), normal basal blood PRL level 20 ng/ml (normal values 5–30 ng/ml) and a low level of blood cortisol 95 nmol/l (normal values 188–800 nmol/l). After therapy (ordered by anaesthesiologist) with steroids (hydrocortisone Cortef 2×10 mg) and thyroid hormone (Levothyroxinum a 50 μg), she delivered by Caesarian section a healthy male child. She breastfed for 10 days only, sight disturbances disappear-
ed, and amenorrhea persisted. One month after delivery she felt dizziness and general weakness.

CT of the sellar region showed a suprasellar spreading structure typical for macroadenoma.

Because her physical condition deteriorated, she was admitted to our hospital.

Upon admittance to the hospital (February 1998) the visual field was normal, she suffered from mild hypotension (100/70 mmHg), her skin was pale and dry (mild features of hypothyroidism). Other clinical findings revealed no abnormalities.

Magnetic resonance imaging (MRI) of the sellar region confirmed a homogeneously enhancing structure measuring 16x12 mm with suprasellar extension, atypical but indicative of a macroadenoma (Figure 1a and 1b).

Hormonal tests confirmed secondary hypothyroidism ($T_3=0.7$ nmol/l, $T_4=49$ nmol/l) and cortisol deficiency (24-hour urinary cortisol=75 nmol/l, blood sol=140 nmol/l) with normal basal of PRL and satisfactory response to roilsiberin$^{17}$. Anterior pituitary function was assessed by measurement of ACTH, TSH, growth hormone (GH), follicle stimulating hormone (FSH), $T_4$, estradiol and progesteron. All hormone determined by radioimmunoassay method$^{21}$.

In February 1998, transsphenoidal surgery was performed. The turgeous tissue showed solid consistency as for adenomatous tissue, the mass spreading into sellar and suprasellar structures. Ex tempore histological analysis of the extirpated tissue was not possible at the time.

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In February 1998, transsphenoidal extirpation was performed. The tumorous tissue showed solid consistency atypical for adenomatous tissue, the mass was spreading into sellar and suprasellar structures. Ex tempore histological analysis of the extirpated tissue was not possible at the time.

Histopathological examination of the paraffine sections of the lesion showed extensive mononuclear infiltration of the pituitary tissue. Plasma cells and lymphocytes formed follicles with germinal
Fig. 2. Lymphocytic adenohypophysitis forming follicle and with aviable adenohypophysial cells. Mallory X 200.

Fig. 3. Lymphocytic adenohypophysitis, lymphatic follicle. Immunohistochemical stain CD20. APAP X 400.
centers (Figure 2). The neurohypophysis was uninvolved, morphologically normal. The immunoperoxidase technique of Sternberger showed diffuse presence of immunoreactive prolactin, CD20 positivity was observed in follicular centers (Figure 3), and lutetotropic hormone was shown within remaining pituitary cells. Immunohistochemistry revealed CD3 (Figure 4) and CD8 positive T cells at the periphery of lymphatic follicles and in the interfollicular areas. Diffuse positivity for CD45 was observed in the whole lesion.

Tissue samples were fixed in 10% buffered formalin, embedded in paraffin wax and 5 mm sections were routinely stained with hematoxylin and eosin (H-E), the Mallory trichrome method and periodic-acid Schiff (PAS) reaction. For analysis of CD3, CD8, CD20 and CD45 the alkaline phosphatase anti-alkaline phosphatase (APAAP) method was used (the source of used antibodies is DAKO, Denmark).

Over the next few months, while taking hormonal replacement therapy, all pituitary functions gradually recovered.

Discussion

Although the classic cause of postpartum hypopituitarism is Sheehan's syndrome, with improvements in obstetric care, the most common cause may now be lymphocytic hypophysitis.

Like other endocrine organs, the pituitary may also be affected by autoimmune processes. Inflammation may be present diffusely in the adenohypophysis. This case presents the rare histological form of lymphocytic adenohypophysitis with formation of lymph follicles with germinal centers without any process affecting the neurohypophysis. Lymphocytic hypophysitis may be primarily due to a T-cell-mediated autoimmune inflammation of the pituitary gland, with little or
no humoral immunity being generated, but it also needs to be elucidated. In about 30% of cases lymphocytic hypophysitis coexists with other autoimmune disorders. The autoimmune hypothesis is further supported by experimentally induced lymphocytic hypophysitis in rats. Serologic examination of women one week following normal delivery demonstrated that 18% developed antipituitary antibodies suggesting that pregnancy may induce reactions against the pituitary gland in a potentially large group of women. It is possible that those women with LH diagnosed due to visual defects or hormonal changes represent only the tip of the iceberg. Only individual cases have been reported not to be related to pregnancy, a few cases have been described in men, but the occurrence of lymphocytic hypophysitis without associated pregnancy is more frequent than previously considered. Pestell et al. suggested that some alleles (A2 C4A3 C4B1 Bf1 F1 Bf2 DR4 DRW53 DQW3) may predispose Caucasians to develop thyroiditis, IDDM and less commonly antipituitary antibodies, and rarely the emergence of LH.

In cases of LH not associated with pregnancy, there was a history of antecedent viral illnesses. Possibly an altered immune reaction to viral antigens cross reacted with the pituitary tissue suggesting LH may be the final result of several combinations of genetic background and viral antigens.

Pituitary antibodies have been detected in sera of patients with hypopituitarism or other endocrine diseases. Methodological problems have, however, hampered the characterization of pituitary autoantigens. Recently, immunoblotting with human pituitary proteins allowed detection and characterization of pituitary autoantibodies in sera of patients with biopsy-proven lymphocytic hypophysitis. Moreover, Stromberg et al. have by immunoblotting identified autoantibodies against pituitary cytosolic protein in significantly high frequencies in sera of patients with partial or total hypopituitarism and also in sera of their relatives. The possibility of a hereditary immunological pituitary process causing partial or panhypopituitarism in some patients can not be excluded.

Clinical presentation is typical for a pituitary mass with suprasellar extension and either partial hypopituitarism or panhypopituitarism. Concerning the hormonal status, hyperprolactinemia has been reported in about 50% of patients. Possible causes of elevated PRL include either the disruption of the pituitary transport of prolactin inhibitory factor by a large mass compressing the pituitary stalk, or a direct effect of the inflammatory process on the lactotrophic cells, or a lactotroph-stimulating antibody arising as a consequence of the inflammatory process. However, elevated blood levels of other anterior pituitary hormones are very rarely described. Most patients with lymphocytic hypophysitis have permanent partial hypopituitarism or panhypopituitarism, but elevations of IGF-I and GH levels in the peripartum patient have also been reported. The diagnosis remains difficult when CT scanning shows only non-specific features of a contrast-enhancing pituitary mass, and angiography shows only non-vasculairity. In the study by Ahmadi et al. the MR-imaging appearance of lymphocytic hypophysitis was analyzed. The involved pituitary glands were typically enlarged, and, in some cases, lobulated, without signal abnormalities on precontrast T1-weighted images. The postcontrast images revealed intense enhancement of the entire gland in patients, which was extending into the pituitary stalk in most cases. In some patients, the contrast-enhancement was also spreading along the leptomeninges and dura, adjacent to the hypo-
thalamus, and in the sellar region. In comparison, most cases of pituitary adenoma showed a typical alteration in signal intensity on both pre- and postcontrast MR images but without enhancement of the adjacent dura mater. In a majority of patients with histologically proven LH, surgical reports showed dural changes consisting of conspicuous adhesions to the adjacent abnormally firm pituitary mass. However, in pituitary adenomas complicated by hemorrhage, necrosis or infarction, surgical or pathologic findings were similar to those of adenohypophysisis. Concerning all these facts, an intensely enhancing mass associated with strips of enhancing dura mater adjacent to the mass are valuable clues in the preoperative differentiation of adenohypophysisis from typical pituitary adenoma.

If the clinical findings and MR imaging features are consistent with the diagnosis of lymphocytic adenohypophysitis (and if there is no visual field defect), a therapeutic trial with steroids is justified. Additionally, abnormal gallium-67 uptake in the lesion, a positive response to a steroid therapy, and resolution of symptoms in the acute stage with shrinking of the lesion on neuroimaging could indicate the correct diagnosis had been made. Such conservative management however, should not be extended too long if the pituitary lesion does not respond to this regimen.

The question is, if the diagnosis of lymphocytic hypophysitis can be made with MR imaging, is a biopsy still necessary?

The diagnosis is resting on histological examination, so biopsy may be needed to establish the correct diagnosis if a trial of steroid therapy fails.

Histological examination of the mass usually shows normal pituitary tissue infiltrated with lymphocytes (confirmed by leucocyte common antigen stain) and/or plasma cells with a small number of neutrophils, sometimes germinal center-like lymphoid follicles, and strands of fibrous tissue. Immunohistochemical staining with a panel of anterior pituitary hormones identifies the presence of normal anterior pituitary endocrine cells with or without apparent selective loss of a specific cell type.

A firm diagnosis of LH can be made only histologically, and it may coexist with normal pituitary tissue. Sometimes only a complete removal of a pituitary mass gives an accurate tissue diagnosis.

It is very difficult to rely on a specific immunological test for autoimmune hypophysitis; the results of immunofluorescence on post mortem glands have generally been disappointing. Crock et al.28 described a new approach to the detection of antipituitary autoantibodies by immunoblotting. It was used to identify at least two target autoantigens in LH, cytosolic proteins of 49 and 40 kDa. It is speculated that the 49 kDa autoantigen might be related to ACTH deficiency due to corticotrop destruction. ACTH deficiency, as already mentioned, is the most prominent feature of lymphocytic hypophysitis and may be seen isolated. As mentioned earlier, LH may be associated with other autoimmune disorders: adrenitis, atrophic gastritis, pernicious anemia, lymphocytic parathyroiditis and isolated ACTH deficiency.41-43. In 1962, Goudi and Pinkerton reported a case of a young woman with histologically confirmed Hashimoto's thyroiditis and lymphocytic infiltration of the adenohypophysis. A case of LH is also described in a patient with Graves disease and diabetes mellitus.44,45 Mc Connol et al.46 reported a case of sparsely granulated growth hormone cell adenoma associated with lymphocytic adenohypophysitis.

The majority of authors agreed that hormone replacement is necessary although there is increasing evidence of
some spontaneous pituitary function recovery in the short-to-medium term. The pituitary function may ultimately normalize in any case after corticosteroid treatment.

However, the recommendations have been to avoid major resection whenever possible, because of the self-limited course\(^4\) or to delay surgery if vision is not compromised. If firm adhesions are encountered during surgery, and examination of frozen sections reveals only lymphocytes without any evidence of tumor (assuming there is no extensive hemorrhage or necrosis), surgery should be limited to biopsy only or, if needed, decompression of the optic chiasm\(^47\). To perform a limited surgical biopsy for obtaining a histological diagnosis and to follow the evolution of the mass with MRI or CT scan may be the reasonable approach.

The course of the disease can sometimes be insidious, and recurrence can precipitate severe pituitary and hypothalamic damage\(^48,49\).

**Conclusion**

1. Inflammatory lesions of the pituitary gland have been increasingly recognized in the past decade and several indicators suggest that this rarely diagnosed condition is probably more common than previously suspected.

2. The entity should be suspected in young females either during pregnancy or immediately post partum with persistent malaise in whom hypocortisolism and/or hypothyroidism may be found.

3. In persons at greater risk for LH (those with other autoimmune endocrine diseases or postpartum women) who develop a severe, unexplained illness, conservative, supportive treatment with or without surgical decompression is generally favored over aggressive and extensive surgical resection resulting in hypopituitarism.

4. Glucocorticoids have a diagnostic, as well as a therapeutic role (prolactinoma will not change after steroid therapy), so this will allow further differentiation of these two entities.

5. The long-term endocrinological and radiological follow-up may be necessary in all suspected, as well as in proven cases of LH. Recurrent cases should be promptly treated with steroids when a definitive histological diagnosis has been confirmed.

**REFERENCES**

LASZETAK

Limfocitni hipofizitis, koji se primarno javlja kod žena u trećem trimestru trudnoće i poslije partalno, rijedak je uzrok hipopituitarizma i uvećanja hipofize. 39-godišnjica bolesnica, u 37-tom tijeku trudnoće prezentirala se simptomima bilateralne heterominne kvadranbansije te simptomima hipopituitarizma, a CT-om selarnog područja vizualizirala se tumorska masa. Nakon poroda zdravog muškog novorođenčeta i perioda dojenja od 10 dana, nestalo je smanjenje vasa, no amenoreja je i dalje postojala. Primitku u našu ustanovu nisu utvrdili ispadati u vidnom polju, no na MR-u selarnog...
područja vizualiziran je makroadenom sa supraselarnim širenjem. Rezultati endokri-
nološkog testiranja upućivali su na sekundarni hipotiroidizam i insuficijenciju korti-
zola, dok su vrijednosti prolaktina, kao i njegov odgovor na tiroliberin bile uredne. Pa-
thistološkom verifikacijom postavila se dijagnoza limfocitnog adenohipofizita s lim-
fatičnim folikulima građenim od (CD 3) T i (CD 20) B limfocita.