Preoperative Diagnosis of Lymphocytic Hypophysitis (Adenohypophysitis) Unresponsive to Short Course Dexamethasone: Case Report

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Lymphocytic hypophysitis (adenohypophysitis) is a rare lymphocytic infiltration of the pituitary gland that usually occurs during pregnancy. Because of its rarity, it has seldom been diagnosed preoperatively, and no trials of therapeutic treatment have been reported to date. We describe a 29-year-old woman with a pituitary mass and visual-field defects during pregnancy. The patient's pituitary profile revealed an abnormal thyroid axis and relatively low prolactin for her stage of pregnancy. This finding suggested adenohypophysitis, and the patient was given a trial course of dexamethasone. The progression of the visual-field defects, however, indicated that the steroids, both in dosage and duration, were not effective. Thus, the patient underwent a partial hypophysectomy for decompression. The pathology report confirmed adenohypophysitis, and steroids were continued for the remainder of the pregnancy, with slow resolution of the visual-field defects to normal. This report is the first case of adenohypophysitis where the diagnosis was suspected preoperatively, and a trial course of steroids was given. The steroids at the dosage and duration used were not effective. Further evaluation of the use of steroids in this disease is warranted. (Neurosurgery 30:268–272, 1992)

Key words: Adenohypophysitis, Pregnancy, Steroids

Lymphocytic hypophysitis (adenohypophysitis), a rare lymphocytic infiltration of the pituitary cells, which mimics a pituitary adenoma, occurs during pregnancy and the postpartum period (6). Lymphocytic infiltration of the pituitary gland was first noted by Goudie and Pinkerton (16) in a woman who suffered postpartum hypothyroidism and amenorrhea and subsequently died of adrenal crisis after a routine appendectomy. Because the patient in the index case had comitant lymphocytic infiltration of the thyroid and pituitary glands, the disease has been considered part of the spectrum of autoimmune endocrinopathies. Many of the 30 cases in the literature have been diagnosed postoperatively or at autopsy (2, 3, 6, 13, 16–21, 23–25, 29, 31). We describe the history of a 29-year-old woman who developed adenohypophysitis associated with visual-field defects and isolated hypothyroidism during pregnancy. Because the diagnosis was suspected preoperatively, the patient was treated with high doses of dexamethasone for a short trial period. Despite this treatment, she required surgical decompression. She was treated for the remainder of her pregnancy with a moderate dosage of steroids, and her condition was followed closely. In this case, the diagnosis was made preoperatively, allowing suggestions from previous studies to be followed (24) that included operative work up of the thyroid and adrenal functions, performance of a partial pituitary resection only, and treatment with steroids, both preoperatively and postoperatively.

CASE REPORT

A 29-year-old woman (gravida 1, para 0) complaining of frontal headaches was seen by her primary physician at 20-weeks gestation. The headaches did not respond to analgesics and beta-blockers. Subsequently, she developed visual-field complaints. At 27-weeks gestation, she had visual field examinations that showed bitemporal field cuts (Fig. 1A). A magnetic resonance imaging (MRI) scan showed a large pituitary mass (1.9 × 1.3 × 1.1 cm) (Fig. 2A). A pituitary profile was sent, and the patient started receiving bromocriptine empirically (which she tolerated poorly), pending the results of her pituitary hormone levels. She was instructed to take 2.5 mg of bromocriptine daily for 2 weeks, but she often missed the dose because of nausea. In the 27th week of pregnancy, her baseline pituitary profile revealed the following: prolactin (PRL), 94 ng/mL; follicle-stimulating hormone (FSH), <1 mIU/mL; luteinizing hormone (LH), <1; alpha subunit >20 mIU/mL; and growth hormone, 9.9 ng/mL (Table 1). Because the PRL level was low for this stage of pregnancy (normal, 100–200 ng/mL) (9), a prolactinoma was considered unlikely, and the patient was admitted for further evaluation.

At admission to University Hospital, the patient, now in the 29th week of pregnancy, had subsequent visual-field examinations and underwent another MRI scan. The visual-field results showed some mild progression, and the MRI scan was unchanged. The completion of the pituitary profile (Table 1) showed normal adrenal function with a cortisol response of 16 μg/dL. increasing to 33 μg/dL 1 hour after cosyntropin (Cortrosyn, Organon, West Orange, NJ) stimulation and an adrenocorticotrophic hormone (ACTH) of 25 pg/mL. Cortisol-binding globulin elevations in pregnancy can elevate basal cortisol, so it was the normal functional response to cosyntropin (delta > 10 μg/L) that indicated normal adrenal function. Thyroid-function tests uncovered borderline hypothyroidism with thyroxine (T₄) of 6 μg/dL, free T₄ of 0.5 ng/dL, 3.5,3'-triiodothyronine (T₃) RC of 23%, and a thyroid-stimulating hormone (TSH) of 2.7 μU/mL without clinical signs of hypothyroidism.

The diagnoses at this point were glycoprotein-producing pituitary adenoma versus adenohypophysitis. Because the mass had not changed in size, we decided to follow the patient with serial visual-field examinations and not to operate at 29-weeks gestation to avoid risking induction of premature labor under general anesthesia. Over the next few weeks, the patient's visual-field disturbances increased (Fig. 1B), and surgical debulking appeared inevitable. Given the strong consideration of adenohypophysitis in the differential diagnosis, a trial course of 4 mg/d of dexamethasone (Decadron, Merck Sharp & Dohme, West Point, PA) was given for 5 days. At the end of 5 days, at 30-weeks
were performed on multiple tissue blocks. PRL immunostaining was the most frequent and was predominantly of the diffuse, rather than the Golgi-type, typically seen in pregnancy. There was a slight reduction of growth-hormone staining, possibly reflecting physiological diminution during pregnancy (30), but the percentage of ACTH (normal, 15–20%) and TSH (normal, <5%) staining cells compared with the number of remaining pituitary cells seemed normal. Severe parallel reduction of staining for follicle-stimulating and luteinizing hormones and alpha subunit were present, again reflecting physiological diminution during pregnancy (28).

Electron microscopy was performed on small pieces of glutaraldehyde-fixed tissue that were postfixed in OSO₄, dehydrated, and embedded in epoxy resin with ultrathin sections stained with uranyl acetate and lead citrate, and examined with a Phillips 201 electron microscope. Increased collagen was present, and numerous lymphocytes closely interdigitated their membranes with partially degranulated and, in some cases, degenerating anterior pituitary cells. Some anterior pituitary cells showed increased mitochondria (2).

Follow-up thyroid function tests at the time of surgery were the following: TSH, 2.0 µU/mL; T₄, 2 µg/dL; free T₄, 0.5 ng/dL; and T₃;RU, 21% and the patient’s reflexes were delayed. With clear hypothyroidism evident at this time, the patient began receiving 0.1 mg daily of Synthroid (Boots Pharmaceuticals, Lincolnshire, IL). Just before surgery, the patient’s PRL level had decreased dramatically despite the fact she was no longer taking bromocriptine (Table 1). The patient continued to receive 2 mg/d of dexamethasone for the next 8 weeks of pregnancy, and her visual-field disturbances improved gradually.

At 39-weeks gestation, a healthy infant was delivered in an uncomplicated vaginal delivery. The dose of dexamethasone was tapered down to 1 mg/d, and another pituitary profile was sent (Table 1, 5-days postpartum). A postpartum MRI scan showed an intrasellar and suprasellar mass slightly smaller than the initial mass (Fig. 2b). The suprasellar extent of the lesion still displaced the optic nerves. Despite this condition, the patient’s visual-field disturbances had improved dramatically when compared with the preoperative studies (Fig. 1c). Furthermore, the visual-field findings obtained 3-months postpartum were entirely normal (data not shown).

The patient attempted to breast-feed, but she had inadequate milk,
Table 1

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Normal/Pregnancy Values</th>
<th>Preoperative Values</th>
<th>Postoperative Values</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>27-weeks Gestation</td>
<td>29-weeks Gestation</td>
</tr>
<tr>
<td>Prolactin (ng/mL)</td>
<td>1–15/100–300</td>
<td>94</td>
<td>23</td>
</tr>
<tr>
<td>Follicle-stimulating hormone</td>
<td>2–17/&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Luteinizing hormone (mIU/mL)</td>
<td>1–60/&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Alpha subunit (mIU/mL)</td>
<td>0.5–2.1/&lt;1</td>
<td>&gt;20</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Growth hormone (ng/mL)</td>
<td>&lt;5/5–15</td>
<td>9.9</td>
<td>25</td>
</tr>
<tr>
<td>Adrenocorticotropic hormone (pg/mL)</td>
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<td>2.3</td>
<td>2.0</td>
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<td>Cortisol (µg/dL)</td>
<td>9–25/15–30</td>
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<td>2</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone (µU/mL)</td>
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<td>2</td>
<td>2.0</td>
</tr>
<tr>
<td>Thyroxine (µg/dL)</td>
<td>4–12/6–15</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>3,5,3'-triiodothyronine RU (%)</td>
<td>25–35/20–30</td>
<td>23</td>
<td>21</td>
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</table>

*The patient was operated on at 31-weeks gestation. The plasma hormone values are shown during the course of gestation, from 27-weeks gestation to 6-weeks postpartum. Bromocriptine (2.5 mg/d) was administered from 27- to 29-weeks gestation. Dexamethasone (4 mg/d) was given for 5 days before surgery (during the 30th week of gestation). Steroids were continued postpartum as a result of the abnormal cosynipton stimulation test at 6-weeks postpartum. At 1-year postpartum, the patient continued to be treated with 0.05 mg/d of synthroid and 25 mg of cortisol/d, as a result of nausea and hypotension upon withdrawal.

DISCUSSION

Lymphocytic adenohypophysisitis is a rare disorder that occurs primarily in women during pregnancy and the postpartum period, and it appears to be autoimmune in nature (6, 17, 20, 23, 29). Since it was first described in 1962 by Goudie and Pinkerton (16) there have been 30 cases reported (2, 3, 6, 13, 16–21, 23–25, 29, 31). Of the subsequent patients reported, all but one were women (17), and 89% occurred during or after pregnancy (6). The patients usually are seen with a mass effect from a pituitary enlargement, headache, or visual-field disturbances. It is critical to establish a basal endocrine function in these patients because of the 30 patients died of unsuspected adrenal insufficiency (6). The endocrine abnormalities can be either primary or secondary. Autoimmune thyroiditis, adrenalin, ovarian failure, pernicious anemia, and retroperitoneal fibrosis have all been found in association with this disease (6, 16, 21, 23, 24, 29). Because lymphocytic adenohypophysisitis is usually diagnosed postoperatively or postmortem, there are no reported therapeutic trials of steroids in this condition. Surgical debulking to relieve visual symptoms is currently the treatment of choice for adenohypophysisitis, and this procedure was done successfully in our patient.

The differential diagnosis of a pituitary mass seen in pregnancy is fairly limited and difficult, because PRL is elevated during normal pregnancy. Lactotroph stimulation by elevated estrogen in pregnancy causes the mass of the pituitary gland to increase from 30 to 100%, as verified by autopsy studies (14). A recent MRI study of the pituitary gland during pregnancy by Gonzalez et al. (15) showed a 100 to 400% increase in pituitary volume. This increase in the gland size and the number of lactotrophs is paralleled by an increase in PRL to approximately 35, 175, and 210 ng/mL in the first, second, and third trimester, respectively (9). With these physiological elevations of PRL during pregnancy, the presence of a prolactinoma can be masked (27). Nevertheless, prolactinomas remain the most common cause of excessive pituitary enlargement occurring during pregnancy (26).

Given these data, a pituitary mass discovered in pregnancy should be assumed to be a prolactinoma until proven otherwise. Although our patient had an abnormally low PRL of 94 ng/mL during the second trimester (normal, 175 ng/mL or greater in the late second trimester), empiric bromocriptine therapy was a reasonable first choice, because prolactinomas occasionally respond to pregnancy with abnormally low PRL levels (1, 9). Alternative possibilities, however, including adenohypophysisitis and null cell tumors, needed to be considered in the face of the low PRL level. Additionally, the fact that our patient continued to worsen while taking bromocriptine, albeit low, short-term doses, favored one of the latter possibilities. Prolactinomas usually respond rapidly to bromocriptine with improvement in visual-field disturbances (7, 30). The patient...
also had no signs of a prolactinoma before pregnancy. She had regular menses, no galactorrhea, and became pregnant without difficulty. Although null cell tumors are often clinically silent (5), we thought it unlikely that such an adenoma would grow rapidly during pregnancy because these tumors are not usually hormonally responsive. Thus, we were left with adenohypophysitis in the appropriate clinical setting of pregnancy as the most likely diagnosis. Consistent with this diagnosis were the following: 1) visual-field changes out of proportion to the change in size of the mass that might occur with inflammation; and 2) selective defects of TSH and PRL, rather than panhypopituitarism or a hypersecretion syndrome. Finally, it is important to note that MRI scanning is not helpful in distinguishing adenohypophysitis from tumor, as reported recently by Levine et al. (21).

The rapid progression of the patient's visual field defects (Fig. 1, A and B) necessitated therapeutic intervention. To our knowledge, there have been no previous pharmacological trials on patients with adenohypophysitis. Other investigators have suggested the use of a steroid on a trial basis because the disease is suspected to be autoimmune (24). Dexamethasone (4 mg/d) was chosen because it crosses the blood-brain barrier, and it is effective for cerebral edema (11, 12, 22, 32). It also crosses the placenta, and it is an adequate dose to promote fetal lung maturation (8). Because of the worsening of the patient's visual fields, the patient was able to receive only a 5-day trial of steroids before surgical decompression. It is uncertain whether the patient's lack of improvement while receiving steroids was related to the dosage, duration, correct drug choice, or stage of disease at which therapy was initiated, or whether this is not a valid treatment approach. Alternatively, the fibrosis in lymphocytic adenohypophysitis may not respond to steroids. Whatever the reason behind the failure of steroids to effect the outcome in this patient, we think a longer trial period with a similar or higher dosage would be reasonable in a patient with a similar clinical presentation, provided visual-field testing and MRI scans are used to monitor the effectiveness of steroid treatment.

The pathological triad of lymphocytic adenohypophysitis seen in this patient includes lymphocytic infiltration of the pituitary gland, rests of normal tissue, and fibrosis. As seen in our patient, the activated lymphocytes are usually interdigitated with normal pituitary cells. Immunohistochemical stains of surgically removed pituitary cells revealed very few thyrotrorphs, but because thyrotrrophs make up only 3 to 5% of a normal pituitary gland, it is difficult to say if they were selectively lost. Of note, however, there were clearly fewer lactotrophs than would normally be expected during the second trimester of pregnancy (14, 28). Thus, the pathology study supports the serological impression that there was loss of PRL-secreting as well as TSH-secreting cells. This clinical impression was based upon relatively low PRL levels during and after pregnancy. Interestingly, isolated loss of corticotrophs has been previously reported in a patient with adenohypophysitis and ACTH deficiency (19). In the postpartum period, our patient appears to have lost the function of her ACTH axis, as indicated by suboptimal cosyntropin stimulation and clinical symptoms (Table 1).

The pattern of pituitary insufficiency in adenohypophysitis is variable. Isolated TSH deficiency, as seen in our patient, has only been described previously in one patient (6). She may have later developed lactotroph deficiency also, which was clinically manifested by her inability to produce sufficient breast milk to nurse her infant. It is tempting to speculate that an antigen shared by lactotrophs and thyrotrrophs is responsible for their selective destruction in our patient. Of note, both of these cell types contain thyrotropin-releasing hormones and dopamine receptors. Future studies may identify antigenic factors in this disorder and determine whether pregnancy-induced lactotroph hyperplasia and possibly cell lysis are required as the initiating events. In some patients, pituitary antibodies have been noted (4). In this patient, studies for antipituitary antibodies and antithyroid antibodies were negative, suggesting a cell-mediated, rather than a humoral, autoimmune disorder.

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REFERENCES


Congenital External Carotid–Jugular Fistula: Report of Two Cases and a Review of the Literature

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Congenital arteriovenous communications involving the external carotid artery and the jugular vein(s) are exceptionally rare. We report two cases of congenital external carotid-jugular fistulae with clinical, radiological, and surgical features and a review of the literature. The prospects of endovascular treatment and the limits of surgery are discussed. (Neurosurgery 30:272-276, 1992)

Key words: Arteriovenous fistula, External carotid artery, Jugular vein

INTRODUCTION

The majority of arteriovenous communications involving the major vessels of the neck are of traumatic origin, either blunt or penetrating. They may also occur after a surgical procedure or extensive infection of the neck. Congenital arteriovenous fistulae (AVF) between the external carotid artery and jugular vein(s) appear to be relatively rare with only a limited number of cases reported in the literature. Halsted (9) was the first to perform surgery on a patient with this abnormality in 1911 and since then there have been 11 more reports in the literature (1, 3, 5-7, 12, 14, 16, 19-21). We present two patients with congenital AVF between the external carotid artery (ECA) and the external jugular vein (EJV); the case of the first patient was exceptional as it was associated with a congenital patent ductus arteriosus. The literature is reviewed and treatment modalities, with special reference to contemporary embolization techniques, are discussed.

PATIENT 1

A 9-year-old boy's clinical findings included exertional dyspnea and a history of recurrent respiratory infections since the age of 3. There was no history of loss of consciousness or cyanosis, but he frequently experienced tachycardia.

At examination, the child was well and alert. There was a 3-cm