Lymphocytic Hypophysitis and Infundibuloneurohypophysitis; Clinical and Pathological Evaluations

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Abstract. This report describes the clinical and pathological characteristics of two patients with lymphocytic hypophysitis (LHy) and two with infundibuloneurohypophysitis (INHy). Two of the patients were women and two were men, and their ages were between 27 and 38 years old. This disease was not associated with either pregnancy or the postpartum period in the female patients. Two of the patients presented with diabetes insipidus, one with panhypopituitarism and right abducens paralysis and one with headache and galactorrhea. At presentation three of the patients had mild to moderate hyperprolactinemia and one had low prolactin levels. All four had abnormal magnetic resonance imaging (MRI): focal nodular enlarging of the infundibulum and normal hypophysis in one, expanding sellar masses in two, and diffusely thickened stalk with slightly enlarged pituitary gland in one. Three cases showed no sign of adenohypophysial deficiency with stimulation tests. One patient had associated chronic lymphocytic thyroiditis. Of the first three patients, one patient underwent transcranial and two underwent transnasal transsphenoidal (TNTS) surgery for mass excisions since they were thought to have pituitary tumors. Endoscopic endonasal transsphenoidal biopsy was performed in the last one with a suspicion of LHy. The pathological and immunohistochemical examinations revealed lymphocytic infiltration. Hyperprolactinemia resolved with surgery in two patients and one developed diabetes insipidus as a complication. We conclude that LHy and infundibuloneurohypophysitis should be considered in the differential diagnosis of the mass lesions of the sellar region and also should be kept in the mind for the etiopathogenesis of cases of hyperprolactinemia, galactorrhea and diabetes insipidus. In suspected cases endoscopic endonasal biopsy for the histopathological diagnosis can be a safe approach.

Key words: Lymphocytic hypophysitis, Infundibuloneurohypophysitis

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LYMPHOCYTIC hypophysitis (LHy), which is a rare inflammatory lesion of the pituitary gland, was first described in 1962 by Goudie and Pinkerton [1] and more than 100 cases have been documented since then. Although LHy has been reported to be a disease of females related to pregnancy or the postpartum period [2–12], it can occur in nonpregnant women and even in men [13–24]. The disease can cause complete or partial hypopituitarism and visual disorders and can mimic nonfunctioning pituitary adenomas.

Infundibuloneurohypophysitis (INHy), which was first described by Imura et al. [25], is a different entity and involvement of the posterior pituitary and/or pituitary stalk involvement may result in diabetes insipidus (DI) [20, 26, 27]. The etiology of LHy and INHy remains obscure but some evidence exists for an autoimmune pathogenesis because of its association with other autoimmune diseases including thyroiditis, adrenalitis, pernicious anemia, lymphocytic parathyroiditis, atrophic gastritis, retroperitoneal fibrosis and the existence of circulating antipituitary antibodies [1, 10, 14, 15, 21, 22, 24, 28−31].

In this report we describe four distinct cases with
either LHY or INHy. All the patients were diagnosed histopathologically. Because three of them were suspected of having tumors, they all underwent surgical explorations with initial diagnoses of pituitary neoplasms, but the fourth patient biopsied had a preoperative diagnosis of LHY. The clinical, radiological and histological features of the patients are described.

**Case 1**

A 27-year-old man was admitted with a two month history of polydipsia, polyuria and fatigue. He had had a diagnosis of major depression three years previously. He had used amitriptyline and lithium for two years but stopped the medication over six months before the presenting complaints. He denied head trauma or operation.

His vital signs were normal. There was no restriction of his visual field and his systemic examination was normal.

His white blood cell count, hematocrit and erythrocyte sedimentation rate were normal. Other acute phase reactants were also found to be negative. Apart from hypernatremia (158 mEq/L), all biochemical tests were normal. Daily urine volume was 10.5 L and urine osmolality was 52.7 mOsm/kg. Water deprivation and desmopressin tests indicated a partial central DI. His serum prolactin levels were found to be high (on two measurements 22.3 ng/ml, and 48.0 ng/ml). He had normal serum free T3, free T4 and TSH levels and he was negative for thyroid antibodies (Anti-microsomal antibody and antithyroglobulin antibody).

The plasma ACTH, serum cortisol, FSH, LH, free and total testosterone levels were normal (Table 1). Partial hypopituitarism was excluded by means of insulin induced hypoglycemia testing with adequate plasma cortisol and growth hormone responses. Thyrotropin releasing hormone stimulation test responses were also normal.

His plain lateral sella turcica film was normal. T1-weighted magnetic resonance imaging (MRI) revealed a focal nodular thickening of the infundibulum and a normal hypophysis (Fig. 1). The nodular lesion was enhanced after iv gadolinium administration. Since the patient was thought to have a tumor of this region, right pterional craniotomy was performed. At operation the pituitary stalk was observed to be thicker than normal. An incision was made on the stalk. A gray-white mass was detected in the stalk and normal stalk structures were dissected from this mass and the lesion was removed while protecting the pituitary stalk. No complication occurred during and after the operation. By light microscopy, hematoxylin and eosin stained sections exhibited a diffuse lymphoplasmacytic (mainly lymphocytic) infiltration (Fig. 2). There was no evidence of granulomas, giant cells or neoplastic tissue. On immunohistochemical evaluation, the inflammatory

| Table 1. Preoperative and postoperative hormonal findings of the patients. |
|-------------------------------|------------------------------|------------------------------|------------------------------|------------------------------|------------------------------|------------------------------|
|                              | Case 1 | Male | Case 2 | Female | Case 3 | Male | Case 4 | Female | Normal Ranges        |
| Free T3 (pmol/L)              | 3.7     | 5.0  | 6.2    | 3.8    | 3.0    | *4.0 | 4.1    | 4.5    | 3.4-7.2           |
| Free T4 (pmol/L)              | 12.4    | 10.8 | 12.5   | 1.43   | 7.1    | *14.8 | 17.8   | 19.2   | 9.5-26            |
| TSH (mIU/ml)                  | 0.84    | 0.58 | 1.5    | 2.8    | 0.23   | 0.2  | 1.1    | 1.4    | 0.2-5.1           |
| Anti TPO (IU/ml)              | 1.6     | 14.0 | 23.9   | 20.9   | 16.0   | 21.0 | 139    | 207    | 0-50              |
| Anti Tg (IU/ml)               | 2.0     | 17.0 | 13.8   | 7.8    | 14.0   | 15.0 | 324    | 470    | 0-50              |
| ACTH (pg/ml)                  | 16.2    | 45.0 | 35.0   | 19.9   | 48.0   | 26.7 | 56.7   | 60.4   | 10-100            |
| Cortisol (pg/dl)              | 21.0    | 11.2 | 11.1   | 21.0   | 5.0    | *5.4 | 18.2   | 15.7   | 7.0-25.0          |
| PRL (ng/ml)                   | 22.3 & 48| 4.0  | 84.0   | 14.0   | 1.1    | 1.7  | 52     | 48     | 3.0-17.0          |
| Total Testosterone (ng/dl)    | 312.0   | 363.0| —      | —      | 89.0   | 79.0 | —      | —      | 280-880          |
| Free Testosterone (pg/ml)     | 16.0    | 24.0 | —      | —      | 0.1    | 0.6  | 3.5    | 3.8    | 1.0-9.0           |
| FSH (mIU/ml)                  | 2.3     | 1.2  | 4.5    | 12.9   | 0.8    | 1.2  | 3.5    | 3.8    | 1.0-9.0           |
| LH (mIU/ml)                   | 4.3     | 1.5  | 3.2    | 2.3    | 1.6    | 0.9  | 7.1    | 5.6    | 3.0-13.5          |

The clinical, radiological and histological features of the patients are described.
cells were found to be a polyclonal population of T and B cells with positivity for CD45 (pan leukocyte antigen, 80–85%) and CD20 (B-cell antigen, 15–20%) respectively. The diagnosis was lymphocytic infundibuloneurohypophysitis.

The patient’s prolactin levels returned to normal and no additional hormonal deficiency occurred (Table 1) after the operation, but his diabetes insipidus continued. The patient is now receiving replacement doses of desmopressin acetate (20 μg/day, bid, via the intranasal route) and he has had no symptoms along with the treatment. This case was reported before [32].

Case 2

A 42-year-old woman, sought medical attention six months before she was referred to us for galactorrhea and chronic headache. She had regular menses and she was not pregnant or in the postpartum period.

On physical examination no abnormality could be detected apart from bilateral galactorrhea. Her visual field evaluation was normal. Laboratory evaluation demonstrated a normal white blood cell count, hematocrit and erythrocyte sedimentation rate. Her biochemical tests were in the normal ranges. She had normal urinary output and normal urine specific gravity. Her serum prolactin level was found to be slightly high (84.0 ng/ml). Both basal (Table 1) and stimulated adenohypophysial and target tissue hormones were normal.

Her plain sella film revealed an enlarged sella turcica and MRI showed an enlarged pituitary with suprasellar extension (Fig. 3) which was enhanced diffusely after contrast injection. She was operated on by transnasal transsphenoidal (TNTS) surgery. After opening the dura a gray-white non-bleeding mass was detected. A normal pituitary gland was not detected in the sellar region. It did not seem to be a pituitary adenoma. A frozen section of the mass was reported to be lymphocytic hypophysitis, and sellar decompression was achieved.

The specimens were stained with hematoxylin and eosin. Light microscopy showed a generalized lymphocytic infiltration. On immunohistochemical evaluation the inflammatory cells were positive for CD45 (100%), CD20 (10%) and negative for CD3 (T-cell antigen).

After the operation the patient’s prolactin levels returned to normal and her galactorrhea disappeared and no new hormonal deficiency occurred, but she
developed DI. After replacement therapy with desmopressin (20 µg/day, bid, via the intranasal route) her urinary output returned to normal.

Case 3

A 35-year-old man with an approximately 15 year history of panhypopituitarism was admitted to our hospital with fatigue, headache, diplopia and loss of libido. He had been receiving replacement therapy with L-thyroxine (100 µg, daily, po), prednisolone (7.5 mg, daily, po) and testosterone (depot testosterone 250 mg, monthly, IM) since 1993 and discontinued to use testosterone three months before admission.

On physical examination he had a eunuchoid habitus and a dry-pale skin with diminished body hair. His visual field evaluation showed bilateral concentric narrowing and he had right abducens paralysis.

He had normal urine output and urine specific gravity. All of his biochemical tests and complete blood count were normal. In addition to the low levels of adenohypophyseal and target tissue hormones, hypoprolactinemia was also found (Table 1).

His plain sella film showed an enlarged and distorted sella turcica. MRI revealed a pituitary mass, showing hyper- and isointensive areas and expanding to half of the clivus, with thickening of the dura on the upper and bottom sides indicating dura infiltration (Fig. 4). He was suspected of having nonfunctioning pituitary adenoma and for surgery the TNTS route was used. The dura was very hard and thick and was so infiltrated by the mass so it could not be separated from the mass. Half of the clivus was removed with a high speed drill. The mass was removed until adequate surgical decompression was achieved.

On light microscopy predominant lymphocytic infiltration was noted. Immunohistochemical examination showed diffuse CD45, focal CD20 and minimal CD3 positivity.

His diplopia and panhypopituitarism continued after the operation. No surgical complication was observed. He is on replacement therapy with L-thyroxine (150 µg/day, po), prednisolone (7.5 mg/day, po) and testosterone (depot testosterone 250 mg, monthly, IM).

Case 4

A 38-year-old woman was admitted for two months with polyuria and polydipsia. Her past medical history revealed no abnormality and she was not taking any medication. She had regular menses and had her last pregnancy 13 years previously.

Her vital signs were normal and physical examination revealed no abnormality apart from grade Ib diffuse hyperplasia of the thyroid gland.

The blood count, erythrocyte sedimentation rate and routine biochemical tests were found to be normal. Her daily urine output was 8 to 10 liters with a urinary osmolality of 103 mosm per liter, and the plasma osmolality was 301–310 mosm per liter. Serum basal anterior pituitary and target tissue hormones were all within the normal range. Prolactin
levels were found to be high on two measurements (29 and 52 ng/ml) (Table 1). Insulin hypoglycemia and thyrotropin releasing hormone tests revealed no anterior pituitary deficiency. Her thyroid autoantibodies were found to be high (anti-M 139 IU/ml; normal <50, anti-Tg 324 IU/ml; normal <50). Water deprivation and desmopressin tests indicated central diabetes insipidus.

Her plain lateral sella film was normal but the MRI showed diffuse thickening of the stalk with a slightly enlarged pituitary gland (increased convexity, Fig. 5). As lymphocytic hypophysitis was suspected, endoscopic endonasal transsphenoidal biopsy was performed from the posterior pituitary. On pathological examination apparent lymphocytic infiltration was observed. The lymphocytes were positive for CD45 (100%), CD20 (25%) and CD9 (5%) on immunohistochemical staining.

She is under medical supervision with desmopressin nasal solution for one year and her anterior pituitary hormone levels have all remained within the normal range.

Discussion

LHy is classically considered to be an autoimmune reaction in the anterior pituitary and is predominantly a disease of females and frequently associated with pregnancy or presenting during the postpartum period, but its occurrence in nonpregnant women has also been reported [1–9, 11, 12, 14, 16, 17, 19]. The case (case 2) with LHy presented in this paper was a nonpregnant woman who was also not in the postpartum period. Observation of LHy in men is rare and about 15 male patients have been reported [10, 13–15, 17, 18, 23, 24, 26, 33, 34]. Our third patient was a male patient with LHy.

Adenohypophysial hypofunction characterized by total or partial hypopituitarism and a pituitary mass are the most common clinical presentations in patients with LHy [2–19, 21–24, 28, 33–44]. Several endocrine deficiencies including those of ACTH, TSH, LH, FSH and growth hormone, alone or in combination have been reported. Pituitary insufficiency was present in one patient of ours as panhypopituitarism (case 3). This case also showed signs of cavernous sinus involvement presenting as lateral rectus palsy. Cavernous sinus involvement is a rare feature of the disease and has been reported in only six cases up to the present time [4, 10, 24, 34, 37, 38].

INHy was reported to be an entity distinct from LHy. This disease is confined to the hypothalamus and/or stalk and/or posterior pituitary [20, 25–27]. Diabetes insipidus is the major clinical presentation of this disorder. Our two cases (cases 1 and 4) were regarded as having INHy since they had the evidence of stalk and posterior pituitary involvement on MRI and diabetes insipidus. Growth hormone deficiency was suggested as a feature of INHy by some authors but we could not observe this condition in our patients on provocative tests.

Mild to moderate hyperprolactinemia, which was observed in three of the presented cases, was reported in most of the patients with LHy and INHy [19, 22, 24, 34, 45–47]. In a review article by Hashimoto et al. [48] hyperprolactinemia was found to be reported in 32.4% of the cases. The hyperprolactinemia in our cases was attributed to stalk involvement and/or compression. On the other hand, hypoprolactinemia was reported in 36.1% of the cases [48]. Hypoprolactinemia in our case 3 probably occurred as a result of extensive destruction of the pituitary gland, including lactotrophs, by lymphocytic infiltration, since he had panhypopituitarism and cavernous sinus involvement.

One of the MRI findings in lymphocytic hypophysitis is an enhancing pituitary mass with or without suprasellar extension and was observed in two of our cases. Stalk enlargement, which was present in two cases (cases 2 and 4), has been reported to be characteristic of LHy and INHy [17, 18, 25, 34]. Marked contrast enhancement in images is a sign of inflammatory lesions of the pituitary gland, including lactotrophs, by lymphocytic infiltration, since he had panhypopituitarism and cavernous sinus involvement.

A diffusely enlarged pituitary gland with enhancement can be a clue in diagnosing. In addition, a nodular lesion in the stalk with a normal pituitary image in MRI as in case 1 should be kept in mind [32].

Several findings suggest that autoimmunity is involved in the pathogenesis of LHy and probably also in the pathogenesis of INHy. Circulating antipituitary antibodies have been reported but the exact relationship to the pathogenesis still remains obscure. A 20–50% incidence of coexistent autoimmune disorders is also found in the literature in patients with LHy [1, 10, 14, 15, 21, 28–30, 37, 42]. As one
patient with INHy (case 4) in the present report had Hashimoto thyroiditis, although accepted as a different disorder, we suggest that patients with INHy should also be examined for the existence of other autoimmune diseases.

Pituitary surgery is both diagnostic and in some instances therapeutic in cases of LHy. Amelioration of the symptoms of sellar mass, hyperprolactinemia and pituitary dysfunction have been reported with surgery [3, 4, 7, 9, 11, 12, 29, 34, 37, 41, 46, 47, 50-52]. Among our patients hyperprolactinemia was resolved in two cases (cases 1 and 2) with surgery. The procedure remained diagnostic for case 3 since his clinical status, panhypopituitarism and sixth cranial nerve palsy, did not improve with the operation. Although the procedure is accepted to be safe, diabetes insipidus, which was developed after the operation in one of our cases, may occur as a complication of surgery [9, 14]. In addition development of hypopituitarism and worsening of the existing clinical status were reported after extensive surgery [9-11], so such aggressive procedures should be avoided in patients with LHy and INHy.

The correct preoperative diagnosis of INHy was suspected in only one of our patients (case 4). In our review of the literature we observed that preoperative consideration of the diagnosis was very rare [4, 11, 21, 24, 52] and that most of the patients underwent surgery with a preoperative diagnosis of tumoral involvement as in our first three cases. But because of the extent of our experience of the disorders, a preoperative diagnosis of lymphocytic hypophysitis was suspected in the fourth case and an endoscopic endonasal transsphenoidal biopsy was performed. This procedure has been performed for lesions of the sellar region, especially for the treatment of pituitary adenomas [53-55]. This approach facilitates faster postoperative recovery, shortens the hospital stay, and avoids traditional incision and postoperative nasal packing. This technique was preferred for these reasons in our patient since she was suspected of having LHy before operation. Since it has minimal morbidity we suggest this approach for the diagnosis of both LHy and INHy. With the increasing number of reports and with the awareness of the different clinical presentations of disorders, the number of such cases may increase. Although the diagnosis of LHy and INHy mainly depends on histological findings, unnecessary major resections can be avoided in this way.

Histologic examination represents the basis for confirming the diagnosis of LHy and INHy. Evaluation of all four affected pituitaries examined in the present series revealed a typical polyclonal inflammatory infiltrate with a mixed T and B cell population as reported by other investigators [19, 24, 47]. Care must be taken to distinguish LHy from a rare but similar condition, granulomatous hypophysitis. Although the clinical presentation is usually pituitary insufficiency associated with a pituitary mass, this condition is characterized by nodular collection of epithelioid histiocytes and multinucleated giant cells but no lymphoid follicles [17, 31]. The pathological and immunohistochemical evaluations in all of our four cases revealed polyclonal lymphoplasmacytic infiltrate and some showed lymphoid follicles, and since no granulomatous formations were detected in any of the specimens, the diagnosis of granulomatous hypophysitis was excluded.

In conclusion, LHy and INHy should be considered in the differential diagnosis of lesions of the sellar region both in nonpregnant women and men. Clinical presentations of the disorders vary. Pituitary hypofunction with growing pituitary masses and compressive symptoms, diabetes insipidus and hyperprolactinemia with galactorrhea must be included in this spectrum of the diseases. Although the diagnosis can only be established by histological examinations, suspicion alone may avoid aggressive pituitary surgery, and endoscopic transnasal transsphenoidal pituitary biopsy can be a safe and alternative way for the histopathological diagnosis of such cases.

References

LYMPHOCYTIC HYPOPHYSITIS


