Diabetes Insipidus as a Primary Clinical Manifestation of Lymphocytic Hypophysitis in a Postmenopausal Woman

Pedro Iglesias, M.D., & Juan J. Diez, M.D.

Lymphocytic hypophysitis is a rare inflammatory disease of the pituitary gland that is characterized by a chronic lymphocytic infiltration of the anterior and/or posterior pituitary gland. Inflammatory lesions of the adenohypophysis occur predominantly in young women and usually are accompanied by some degree of hypopituitarism. The coexistence of diabetes insipidus with this disorder is very uncommon. We report a case of lymphocytic hypophysitis in a menopausal woman presenting with diabetes insipidus as a primary manifestation in which the endocrinologic evaluation of the anterior pituitary showed only a blunted response of growth hormone to hypoglycemic stress and slight hyperprolactinemia. The radiologic study by means of MRI revealed an enlargement of the anterior pituitary with a loss of hyperintense posterior lobe signal and a thickened pituitary stalk. We comment on the different pathologic mechanisms of the development of diabetes insipidus in lymphocytic hypophysitis.

The Endocrinologist 2000; 10: 127–130

Introduction

Lymphocytic hypophysitis is a rare inflammatory disorder of the pituitary gland. It was first reported in 1962 by Goudie and Pinkerton [1] at autopsy and by Queener in 1980 in a living patient [2]. Since the first description, fewer than 200 cases have been reported. This inflammatory process usually affects the anterior pituitary, although neurohypophysis and/or stalk involvement also is reported. In the classical lymphocytic adenohypophysitis (LAH) form, the inflammatory lesion is limited to the adenohypophysis. LAH commonly occurs in young women and is predominantly related to pregnancy or delivery. One or more adenohypophyseal hormone deficiencies are the rule, but diabetes insipidus is very uncommon. However, when the inflammatory lesion extends to the posterior lobe and/or pituitary stalk, diabetes insipidus is usually present. This clinical entity, recently called lymphocytic infundibulohypophysitis (LIH) with diabetes insipidus [3], is not usually related to pregnancy or delivery, and adenohypophyseal function is less frequently affected. In this report, we describe a menopausal woman with lymphocytic hypophysitis presenting with diabetes insipidus as a primary clinical manifestation. We also discuss the different etiopathogenic mechanisms of diabetes insipidus associated with this rare disorder.

Case Report

A 53-year-old woman was referred to us because of frontal headaches, polyuria, nocturia, and polydipsia of 6 months of duration. She had not noticed visual disturbances. Her medical history was unremarkable. There was no family history of endocrinopathies. Physical examination was normal. Blood pressure was 145/85 mmHg. Her weight and height were 70.7 kg and 151 cm, respectively. Neurologic examination also was normal. No visual field defects were observed. Routine laboratory evaluation including liver and kidney function was normal. The urine volume collected during a 24-hour period was 3000 mL, and specific gravity was <1005. Serum sodium (Na, 144 mmol/L) and potassium (K, 4.1 mmol/L) levels were normal. Urine Na was 32 mmol/L, and urine K was 7 mmol/L. The presence of high plasma osmolality (303 mmol/kg, N: 285–295), low
urinary osmolality (206 mmol/kg), and polyuria suggested the diagnosis of diabetes insipidus, which was confirmed with the water deprivation test and subsequent arginine vasopressin administration. Endocrine evaluation revealed normal function of the anterior pituitary: thyrotropin, TSH 0.41 mU/L (N: 0.1-5.0); free thyroxine, FT4 1.01 ng/dL (N: 0.75-2.10); follicle stimulating hormone, FSH 51 U/L (menopausal range: 40-150); luteinizing hormone, LH 18 U/L (menopausal range: 20-55); corticotropin, ACTH 18 pmol/L (N: 2-13); urinary free cortisol 110 nmol/24h (N: 55-275); prolactin (PRL) 23 µg/L (N: 7-26); growth hormone (GH), 1 µg/L (N: 0-5); insulin-like growth factor type 1 (IGF-1), 196 µg/L (N: 54-389). Provocative tests of anterior pituitary function by means of insulin (0.1 U/kg) and TSH-releasing hormone (400 µg) administered intravenously as a bolus injection resulted in a normal responses of TSH, FSH, LH, and cortisol with blunted GH response and high PRL response (Table 1). Serum β-human chorionic gonadotropin and α-fetoprotein were negative. Skull x-ray film showed no abnormalities. Computed tomographic study demonstrated an enlarged anterior-posterior diameter of the pituitary gland. Gadolinium-enhanced MRI study showed homogenous enlargement of the whole pituitary gland (Fig. 1). The patient was treated with intranasal desmopressin (DDAVP, 10 µg/12h) therapy, and the polyuria and polydipsia were controlled (serum osmolality 293 mmol/kg and urinary osmolality 632 mmol/kg). At that point, the clinical diagnosis was nonfunctioning pituitary macroadenoma or lymphocytic hypophysitis with normal anterior pituitary function, except for GH secretion, associated with diabetes insipidus. To establish a histologic diagnosis, transphenoidal exploration of the pituitary fossa was performed. Histologic study revealed anterior pituitary cells with diffuse infiltration of lymphocytes with no evidence of granulomatous or giant cell disease (Fig. 2). Antinuclear antibodies, anti-DNA antibodies, antithyroglobulin and antithyroid microsomal antibodies, rheumatoid factor, and autoantibodies to the pituitary gland, adrenal cortex, and gastric parietal cells were not found. Serum immunoglobulin levels (IgG, IgA, and IgM) were also in the normal range. Repeated endocrinologic examination after surgery showed no changes in adenohypophysal function except for normalization of the PRL response to TSH-releasing hormone (Table 1). These findings were diagnostic of lymphocytic hypophysitis with GH deficiency and diabetes insipidus with normal residual pituitary function. Following the 3 years, serum concentrations of the all anterior pituitary hormones were in the normal range and her diabetes insipidus was controlled with DDAVP (10 µg/12h intranasally). The last MRI of the pituitary gland, performed 3 years after surgery, was normal.

Table 1

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<th>Evaluation of the anterior pituitary function (insulin 0.1 U/kg iv and TRH 400 µg iv) before and after surgery</th>
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<td>Preoperative basal peak</td>
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*Menopausal range.

Figure 1. T1-weighted MRI of the pituitary gland in coronal (A) and sagittal (B) views. Figure A shows a diffusely enlarged pituitary gland without signal intensity defects, measuring 12 mm in height and 15 mm in sagittal diameter. Height is 2 mm higher in the right side of the gland, and there is a slight displacement of the infundibulum to the left. There is no evidence of suprasellar or parasellar extension. Figure B shows an absence of hypertense signal of the posterior lobe and a thickened pituitary stalk.
Discussion

This case report shows the presence of central diabetes insipidus as the primary clinical manifestation of lymphocytic hypophysisis in a menopausal woman. In addition, the endocrinologic evaluation of the anterior hypophyseal function showed only a GH deficiency and modest hyperprolactinemia. This case represents an unusual clinical form of lymphocytic hypophysisis for these reasons: first, the age of the patient at diagnosis and the absence of relation with pregnancy or postpartum period; second, the coexistence with diabetes insipidus, reflecting a posterior pituitary or hypothalamic dysfunction.

Lymphocytic hypophysisis is a chronic inflammation that usually affects the adenohypophysis. It develops mainly in women during pregnancy or the postpartum period [4]. In recent years, however, it has been described with increasing frequency in both postmenopausal women [5, 6] and men [7, 8]. Clinically, it is characterized by headaches, visual disturbances, hypopituitarism, and the presence of a large intrasellar mass with or without suprasellar extension. Endocrinologic function usually varies from normal to partial or total hypopituitarism. Most patients present with two or more hormone deficiencies, the most frequent abnormality being the combination of central hypothyroidism and hypoadrenalism. Panhypopituitarism is present in 38% of the patients, and pituitary function is normal in 3% [4].

Posterior pituitary involvement is very rare in LAH. Central diabetes insipidus has not been considered a distinctive clinical entity of this disorder. None of the 30 patients reviewed by Cosman et al. [4] had preoperative diabetes insipidus. In recent years, however, the number of patients with both entities has increased [3, 9–11]. The first reported case of lymphocytic hypophysisis causing diabetes insipidus, which was transient, was reported by Vanneste and Kamphorst in 1987 [12]. Four years later, Nusebaum et al. [7] described the two first cases of permanent diabetes insipidus associated with lymphocytic hypophysisis. Since the first description, fewer than 20 cases have been documented, most of them in women [3, 5–9, 13–15], although it has also been described in men [7, 8, 10, 16].

Several mechanisms have been proposed in the pathogenesis of diabetes insipidus associated with lymphocytic hypophysisis. Among them are immunologic, compressive, inflammatory, and infiltrative processes of the hypothalamic neurohypophysis region.

Although the etiology of lymphocytic hypophysisis is unknown, it is thought that the disease has an autoimmune basis. Therefore, it is possible that an autoimmune process could affect both the anterior and posterior pituitary gland, the stalk, and/or magnocellular neurons of the hypothalamus. The absence of hyperprolactinemia and the normal morphologic study of the hypothalamus and neurohypophysis found in some patients [8] suggest that diabetes insipidus might be secondary to an autoimmune process in our patient, all autoantibodies studied were negative.

Some authors suggest that the neurohypophysis or hypothalamus might be compressed by the sellar mass secondary to LAH, producing a decrease in vasopressin secretion [7, 9]. This possibility in our patient seems remote due to the absence of the suprasellar extension of the sellar mass.

Finally, diabetes insipidus might be caused directly by lymphocytic inflammation of the posterior lobe, pituitary stalk, and/or hypothalamus with destruction of these tissues. Iruma et al. [17] described in 1993 lymphocytic infundibuloneurohypophysisis as a common cause of what was previously considered to be idiopathic diabetes insipidus. This disorder is characterized by lymphocytic inflammation confined to the hypothalamic-neurohypophyseal system. MRI study shows thickening of the pituitary stalk, enlargement of the neurohypophysis, and/or loss of the normal hyperintense signal of the neurohypophysis on T1-weighted image, whereas the adenohypophysis and hypothalamus appear to be normal. It seems to be a self-limiting disease [18]. One year later, Koshiyama et al. [9] reported a 50-year-old woman with lymphocytic hypophyseis presenting with diabetes insipidus in which MRI study revealed homogeneous swelling of the whole pituitary gland, absence of the normal high intensity of the posterior pituitary, and thickening of the pituitary stalk. These authors suggested that this case might represent a variant of LAH and/or lymphocytic infundibuloneurohypophysisis. More recently, Nishikawa et al. [11] described two postmenopausal women with lymphocytic hypophysisis causing diabetes insipidus with normal adenohypophyseal function. The radiologic findings were...
sellar mass lesion mimicking pituitary adenoma, with loss of
the hyperintense signal of the posterior pituitary in both
cases and thickening of the stalk in one case. These patients
were thought to be variants of lymphocytic infundibuloneu-
rohypophysitis. In 1997, Miyagi et al. described LIH with di-
abetes insipidus as a new clinical entity [3]. This process is
characterized by lymphocytic infiltration in both the ante-
rior and posterior pituitary and extends to the pituitary stalk
and, sometimes, to the hypothalamus. In LIH, all patients
reported had diabetes insipidus. It is seen not only in
menopausal women but in men as well.

Our patient shares several common features with the
patients described by Koshiyama et al. [9] and Nishioka et
al. [11]. First, the age of the patient and the perimenopausal
state; second, the clinical manifestations at diagnosis;
third, the normal adenosynphysisal function, except for
the blunted GH response to hypoglycemia, indicating a
possible hypothalamic lesion; and fourth, the morphologic
and histologic findings of the anterior and posterior pitu-
itary gland. The present case report illustrates a new case of
LIH with permanent diabetes insipidus.

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