Hypothalamic-pituitary Langerhans cell histiocytosis : a diagnostic challenge

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Four cases of hypothalamic-pituitary Langerhans cell histiocytosis (LCH) are reported, highlighting the expanding spectrum of clinical and magnetic resonance imaging (MRI) features in adults. The diagnostic challenge of hypothalamic-pituitary LCH is emphasized in cases revealed as supra-sellar tumors with panhypopituitarism or as isolated central diabetes insipidus. Diagnosis is confirmed by histological examination showing infiltration with CD1a positive histiocytes. General guidelines for diagnosis procedure are drawn out, including the neurosurgical biopsy in particular cases.

Key words : Langerhans cell histiocytosis, diabetes insipidus, hypopituitarism.

INTRODUCTION

Langerhans cell histiocytosis (LCH), or granulomatosis with Langerhans cells, formerly called Histiocytosis X, includes a cluster of symptoms sharing the common characteristic of granular or infiltrating lesions based on the same pathological support : the Langerhans cell. Degree of involvement in LCH ranges from localized forms such as solitary bone lesions, to disseminated disease involving the lung, skin, bone and central nervous system. Likewise, it is well known that LCH can involve the hypothalamic-pituitary region [2, 7]. However, the largest series concern children or adolescents in whom diabetes insipidus (DI) is a common complication [5, 6, 8]. Only few cases have been reported in adulthood with variable presentation and course [1, 14, 15, 18]. We report 4 cases of hypothalamic-pituitary LCH highlighting the expanding spectrum of clinical and magnetic resonance imaging (MRI) features in adults. They illustrate the diagnostic challenge and provide support to draw out general guidelines for the diagnostic procedure. In some cases, diagnosis can be especially difficult ; therefore physicians...
involved in the management of patients with hypothalamic-pituitary disorders must be aware of this rare entity.

**CASE REPORTS**

**Case 1**

A 20-year-old man with a childhood history of malar bone histiocytosis was referred to our department because of progressive polydipsia with concomitant polyuria and nocturia. Diagnosis of DI was established after a water deprivation test. Resolution of symptoms upon administration of intranasal 1-desamino-8-D arginine vasopressin (DDAVP) confirmed the diagnosis of DI. Dynamic testing showed normal anterior pituitary function. Pituitary MRI revealed a gadolinium-enhanced thickening of the pituitary stalk and the disappearance of the normal hyperintense signal in the neurohypophysis on T1-weighted image. No abnormalities were observed in the hypothalamus or pituitary anterior lobe. Four years later, clinical features and laboratory findings were unchanged. Pituitary stalk remained enlarged and DI was still treated with DDAVP.

**Case 2**

A 21-year-old woman was referred for secondary amenorrhea. She had been treated for seven years with DDAVP for DI. Details of the initial investigation were not available. Physical examination was suggestive of ante-hypophyseal failure and ulcerated vulvar lesions were present. Endocrine assessment was consistent with DI and anterior panhypopituitarism resulting from multiple releasing-hormone secretory defects. Pituitary MRI showed a hyperintense (T1/T2) suprasellar mass (diameter = 2 cm) which was enhanced with gadolinium. The tumor was located within the base of the third ventricle, suggesting a glioma of the optic chiasma. Two years earlier, investigation of impotence had shown mild hyperprolactinemia [prolactin 30 ng/ml (normal range = 5-15)] and hypogonadism [total plasma testosterone 2 µg/l (normal range = 3-10)]. At that time, bone survey, chest X-ray and pituitary MRI were normal. This patient had no evidence of skin LCH. Dynamic testing confirmed anterior pituitary failure. Because of the severe eye sight loss and the unusual aspect of the suprasellar mass, the patient underwent a frontal craniotomy with retro-chiasmatic biopsy. Histologic findings were consistent with the diagnosis of LCH showing infiltration with CD1a positive histiocytes. Initial treatment included a 10 Gy megavoltage radiation therapy on the hypothalamic tumor and hormonal substitution therapy. However, there was no visual improvement and a chemotherapy was initiated (vinblastine 10 mg IV/week). DI appeared later on, when combined treatment with radiotherapy and chemotherapy had already been initiated. Unfortunately, the patient suddenly died secondary to agranulocytosis developing after the second course of chemotherapy.

**Case 3**

A 44-year-old man was referred for anterior hypopituitarism and eye sight loss. Visual fields were normal. MRI showed a large hypo/hyperintense (T1/T2) tumor (diameter = 2.5 cm) enhanced with gadolinium. The tumor was located within the base of the third ventricle, suggesting a glioma of the optic chiasma. Two years earlier, investigation of impotence had shown mild hyperprolactinemia [prolactin 30 ng/ml (normal range = 5-15)] and hypogonadism [total plasma testosterone 2 µg/l (normal range = 3-10)]. At that time, bone survey, chest X-ray and pituitary MRI were normal. This patient had no evidence of skin LCH. Dynamic testing confirmed anterior pituitary failure. Because of the severe eye sight loss and the unusual aspect of the suprasellar mass, the patient underwent a frontal craniotomy with retro-chiasmatic biopsy. Histologic findings were consistent with the diagnosis of LCH showing infiltration with CD1a positive histiocytes. Initial treatment included a 10 Gy megavoltage radiation therapy on the hypothalamic tumor and hormonal substitution therapy. However, there was no visual improvement and a chemotherapy was initiated (vinblastine 10 mg IV/week). DI appeared later on, when combined treatment with radiotherapy and chemotherapy had already been initiated. Unfortunately, the patient suddenly died secondary to agranulocytosis developing after the second course of chemotherapy.

**Figure 1:** Sagittal (right) and coronal (left) T1-weighted MR imaging of the hypothalamic pituitary area after gadolinium: note the hyperintense supra-sellar mass and the empty sella turcica.

**Figure 1:** IRM hypophysaire en séquence T1. Coupe sagittale (droite) et coronale (gauche) : notez la tumeur supra-sellaire hyperintense après injection de gadolinium et la selle turcique vide.
Case 4

A 62-year-old man with new-onset central DI was shown to have a posterior pituitary mass (diameter = 0.5 cm) discovered on MRI. It was hypointense on the T1-weighted image enhanced with gadolinium (fig. 2) and shifted the stalk forward. Chest radiography and CT scan of the thorax revealed a diffuse infiltrating pneumopathy with incipient fibrosis in this heavy-smoker patient. Respiratory function tests suggested an obstructive syndrome and measurement of pulmonary carbon monoxide diffusing capacity showed a 40% deficiency. A new MRI, performed 3 months later, no longer found the initial posterior pituitary mass but showed a moderate thickening of the pituitary stem as well as a partially empty sella turcica.

This association of diabetes insipidus and infiltrating fibrous pneumopathy was compatible with several diagnoses including sarcoidosis, LCH or another granulomatosis. A surgical pulmonary biopsy was performed which showed lymphoid infiltration with fibrosis lesions. Positive immunostaining for surface antigen CD1a and protein S100 led to the diagnosis of LCH. Corticosteroid treatment indicated because of the progressive pulmonary damage was refused by the patient. Two years later, the patient presented with a mandibular localization of LCH. Even though pituitary MRI was unchanged, results of endocrine evaluation were consistent with hypogonadotropic hypogonadism resulting from LH releasing-hormone secretory failure. Sudden death occurred at age 64, likely due to myocardial infarction.

**DISCUSSION**

LCH’s first presentation is not commonly linked to hypothalamo-pituitary localization. Furthermore, this is a rare disorder in adulthood. We report here a spectrum of four cases of hypothalamic-pituitary LCH lesions occurring in adults.

**Clinical features**

Case 1, with initial monofocal bone damage appearing in childhood and followed by delayed post-hypophyseal damage resulting in central DI, illustrates the most frequent sequence described in the literature. In the absence of a biopsy we cannot be sure that this patient has hypothalamic-pituitary LCH but it is very likely given the childhood history and the clinical course. Bone eosinophilic granuloma is usually the first manifestation in childhood (50 to 60% of the cases) and incidence of DI in the course of the progressive multisystem disease varies according to different authors from 10 to 50% [6, 8].

If DI is the prominent endocrine manifestation of LCH, partial hypopituitarism has also been described [2, 8] and can occurred, as in case 4, several years after [9, 12]. Panhypopituitarism, as observed in cases 2 and 3, is rarely associated with LCH. To our knowledge, very few cases have been published (review in 9). Results of detailed endocrine evaluation, when performed, are usually consistent with anterior panhypopituitarism resulting from multiple releasing-hormone secretory defect [15]. This hypothalamic dysfunction is likely to be due to histiocytic infiltration and/or to tumorous compression when hypothalamic involvement occurred as a tumor.

**Neuroimaging features**

MRI of the pituitary hypothalamic area provides relevant information for diagnosis. Thickening of the pituitary stalk enhanced with gadolinium is particularly suggestive [11, 14, 17] all the more when associated with a disappearance of the posterior pituitary « bright spot » usually observed in patients with neurohypophyseal dia-
Diagnostic procedure

We would like to draw the attention of clinicians to the diagnostic challenge in the case of a single hypothalamo-hypophyseal site disease presenting as a tumor or an idiopathic central DI.

Careful clinical examination, including skin and oral and genital mucosae, is essential. Chest X-ray is mandatory in search of diffuse infiltrative pneumopathy. Nevertheless, granulomatous diseases, such as sarcoidosis, can also infiltrate the neurohypophysis or pituitary stalk and cause DI [10]. In this case, diagnosis of pulmonary histiocytosis will be established by typical findings on a bronchoalveolar lavage showing positive staining of Langerhans cells for CD1a at a significant rate (> 5 %). In difficult cases, a surgical pulmonary biopsy should be discussed.

In order to screen for possible typical bone LCH localizations (cranial, mandibular, costal, pelvic, scapula) a complete bone survey is required.

In every case, histological proof of LCH infiltration is mandatory. According to the « confidence levels » of the writing Group of the Histiocyte Society [5], a « definite » diagnosis of LCH requires the demonstration either of CD1a antigenic determinants on the surface of Langerhans cells by immunohistochemistry or of Birbeck granules in lesional cells by electron microscopy. Pathologists have to be warned that diagnosis of LCH is entertained, because these tests are not routinely performed. Cutaneous-mucous membrane, bone or hepatic lesions are easily accessible to biopsy. Otherwise, more « invasive » procedures could be performed. In case of pulmonary localization and when bronchoalveolar lavage is not contributive, as previously shown, a surgical pulmonary biopsy is useful. In unusual cases of isolated hypothalamo-hypophyseal localizations occurring as a supra-sellar tumor, only neuro-surgical biopsy may provide the diagnosis [13, 15]. Conversely, in isolated DI, there is no benefit to perform a biopsy on a thickened pituitary stalk because of surgical hazards and lack of specific treatment.

Finally, as other authors [4], we would like to stress the importance of a long-term follow-up in patients with initial diagnosis of idiopathic central DI.

REFERENCES