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## Idiopathic granulomatous hypophysitis: are there reliable, constant radiological and clinical diagnostic criterias?

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**Abstract** Idiopathic granulomatous hypophysitis is a rare inflammatory disease of unknown aetiology; few cases are reported. We review the clinical presentation and radiological characteristics of these cases and our own experience with three new surgical cases, to determine diagnostic criteria. MRI of three cases revealed sellar lesions extending into the chiasmatic cistern. Their shape varied, from dumbbell to spherical and elliptical. All were isointense with the brain on T1-weighted images and gave heterogeneously high signal on T2-

weighted images. Contrast enhancement was homogeneous in one case and heterogeneous in another. The pituitary stalk could not be identified. There was no dural enhancement. The sphenoid sinus mucosa was thickened in two cases and normal in one.

**Key words** Pituitary · Hypophysitis, granulomatous · Magnetic resonance imaging

### Introduction

Idiopathic granulomatous hypophysitis, a rare inflammatory disease of unknown aetiology, is characterised by lymphoplasmocytic infiltration of the pituitary and the presence of epithelioid cells and multinucleate giant cells constituting granulomas [1]. Cases are generally misinterpreted as pituitary adenomas due to their rarity and to the nonspecific radiological features. The diagnosis is made by histological examination if surgical resection is undertaken.

We report three patients with idiopathic granulomatous hypophysitis who were diagnosed postoperatively. Their clinical and radiological findings were compared with those in the literature.

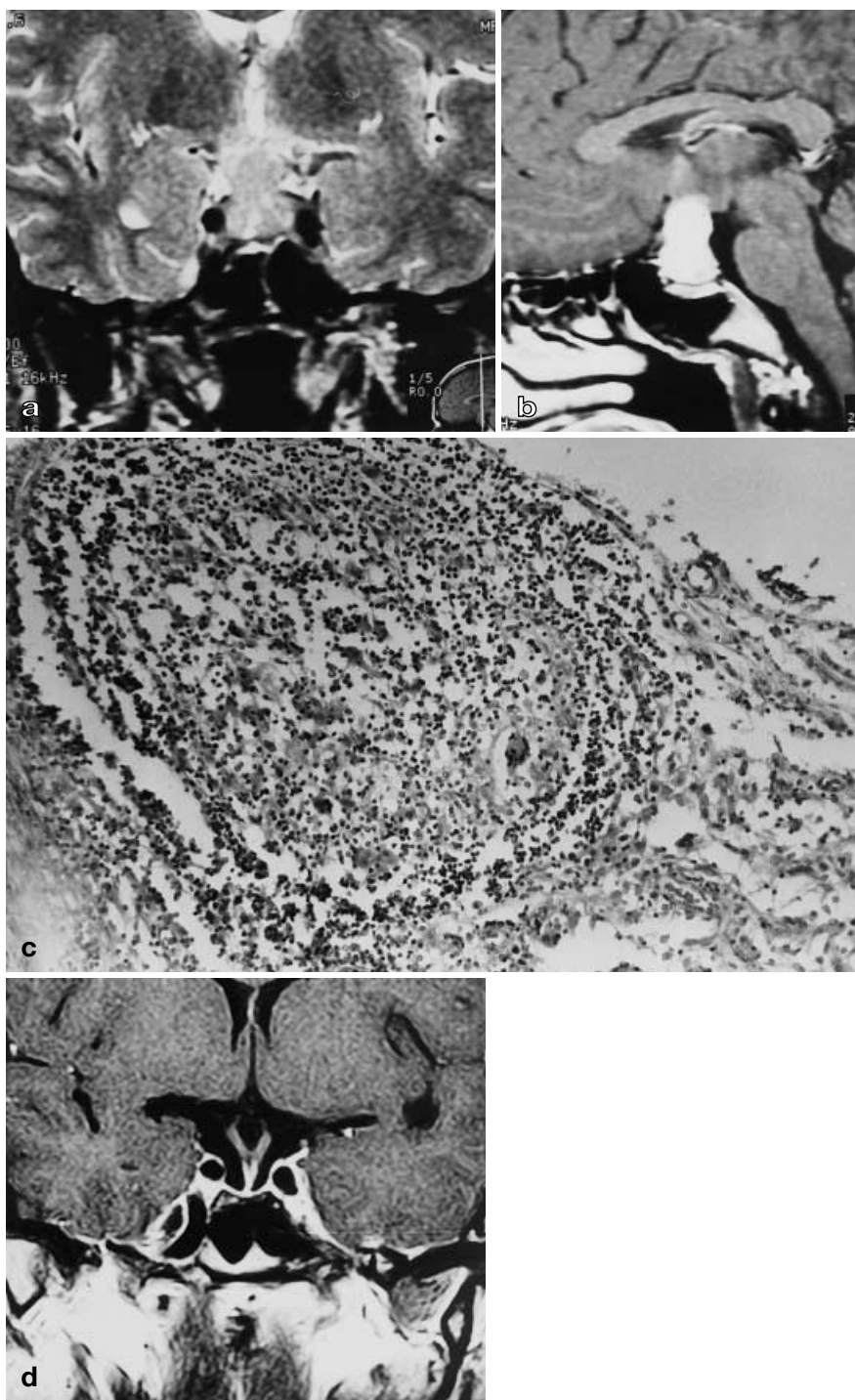
### Case reports

#### Case 1

A 32-year-old woman presented with sudden, severe headache, diabetes insipidus and blurred vision; she had no systemic complaint other than menstrual irregularity for 1 year. Examination

was normal except for decreased visual acuity. The visual evoked potential (VEP) examination revealed long latencies of the N2 and P2 waves with normal amplitudes. CT showed an intrasellar mass extending into the chiasmatic cistern. On MRI there was a 25 × 30 × 25 mm sellar mass with a dumbbell suprasellar extension, compressing the chiasm. The lesion was isointense with brain on T1, gave inhomogeneously high signal on T2-weighted images and enhanced homogeneously (Fig. 1 a, b). The pituitary stalk was unidentifiable. The sphenoid sinus mucosa was thickened. Pituitary hormone levels were normal, but mild hypocortisolaemia (4 µg/dl, normal range 5–25 µg) was noted. The patient was operated upon by the trans-sphenoidal route for a supposed pituitary macroadenoma. The pituitary was found to be firm and only partial resection could be achieved. The postoperative course was uneventful, but the patient required steroid and thyroid replacement therapy. Histological examination revealed granulomatous a non-necrotising lesion (Fig. 1 c). Ziehl-Neelsen staining revealed no acid-fast bacilli. After corticosteroid therapy for three months, the headache and visual disturbance disappeared, as did the lesion on MRI (Fig. 1 d), but the patient remained amenorrhagic. Tests for systemic granulomatous disease were negative. Although the resection was limited, no relapse occurred in 3 years of follow-up.

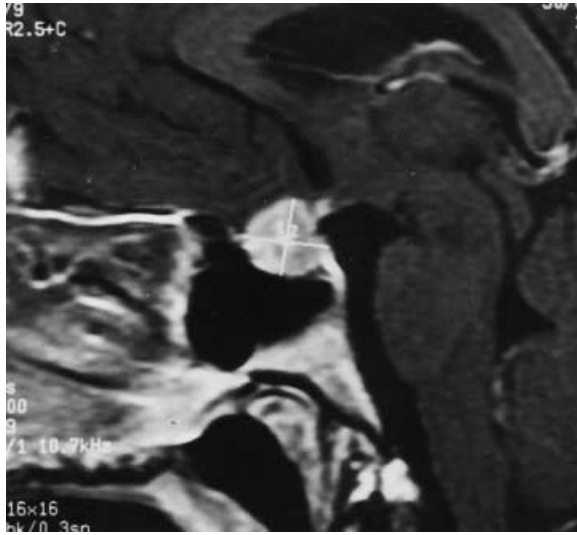
**Fig. 1a-d** Case 1. **a** Coronal T2-weighted MRI shows inhomogeneous high signal from a sellar and suprasellar mass. **b** Contrast-enhanced sagittal T1-weighted image shows an intensely enhancing dumbbell-shaped mass extending up to the floor of the third ventricle. The pituitary stalk cannot be identified. **c** Histological examination (haematoxylin and eosin, original magnification  $\times 200$ ) reveals lymphocyte infiltration and granulomatous change in the anterior lobe of the pituitary, with scattered adenohypophyseal cells. **d** Contrast-enhanced T1-weighted image 15 months after surgery shows shrinkage of the pituitary and an intact infundibulum



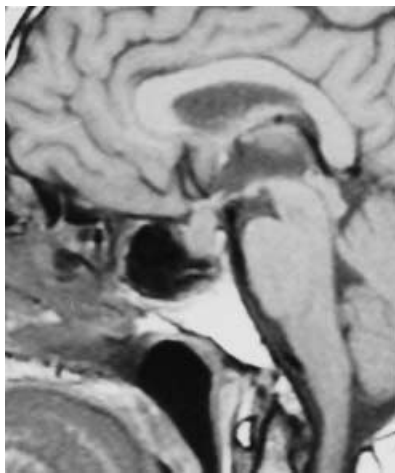
#### Case 2

A 33-year-old woman who had children aged 12 and 8 years had headache for 10 years. Her normally regular menses were delayed twice in the last year. She presented with sudden, severe headache, nausea and vomiting; there was no diabetes insipidus. On MRI there was a  $13 \times 14 \times 14$  mm sellar mass with a suprasellar exten-

sion, isointense with brain on T1, giving inhomogeneous high signal on T2-weighted images, with a nonenhancing centre (Fig. 2). The distal pituitary stalk could not be identified. The sphenoid sinus mucosa was normal. Endocrine investigation revealed no abnormality apart from mild hyperprolactinaemia (34.8 ng/ml). Our diagnosis was nonsecreting pituitary macroadenoma and transphenoidal surgery was performed. A firm lesion, not distinguish-



**Fig. 2** Case 2. Contrast-enhanced T1-weighted image shows an inhomogeneous sellar mass. The distal part of the pituitary stalk cannot be identified



**Fig. 3** Case 3. A sellar and infundibular mass is clearly seen on a T1-weighted image

able from normal pituitary, was removed by total hypophysectomy. Histological examination revealed granulomatous hypophysitis without necrosis; Ziehl-Neelsen staining was negative for acid-fast bacilli. In the postoperative period hormone replacement therapy initiated.

#### Case 3

A 50-year-old man presented with headache, palpitations, dyspnoea on exertion and mild pyrexia (37.3°C). There were no neurological signs; visual acuity and fields were normal. On a chest film, left hilar lymphadenopathy and nodular peribronchial opacities were detected. Tuberculin skin reaction was 14 × 14 mm. Bronchoscopic biopsy diagnosis was nonspecific bronchitis. On

MRI, there was a 18 × 15 × 20 mm sellar lesion extending into the suprasellar area, isointense with the brain on T1- and giving inhomogeneous high signal on T2-weighted images (Fig. 3). The pituitary stalk could not be identified. Endocrine investigation revealed low thyroid-stimulating, hydrocortisol and gonadotropin levels; prolactin was normal. The lesion was interpreted as a non-secretory pituitary macroadenoma causing hypopituitarism and the patient was operated upon by the trans-sphenoidal route. A firm mass was totally resected. In the early postoperative period was transient diabetes insipidus. Anterior pituitary hormones were replaced. Histological examination revealed granulomas and lymphocytic infiltration of the adenohypophysis; no acid-fast bacilli were detected on Ziehl-Neelsen staining. Tests for systemic granulomatous diseases were negative.

#### Discussion

Inflammatory diseases of the pituitary are rare [2]. Honegger et al. [1] reported six cases of idiopathic granulomatous hypophysitis in 2362 operations for pituitary lesions over 13 years.

There are different names for of these lesions, depending on their pathological characteristics. Lymphocytic hypophysitis is characterised by diffuse lymphocyte infiltration of the adeno- and neurohypophysis. Granulomatous hypophysitis is a second form, containing multinucleate giant cells. It can be part of systemic granulomatous diseases such as tuberculosis, sarcoidosis, histiocytosis X and syphilis or an isolated pituitary disease due to a foreign body reaction to a ruptured Rathke's cleft cyst [3, 4], mycotic infection or a pituitary adenoma [5]. If these conditions are excluded by clinical and histological examination, granulomatous hypophysitis is termed "idiopathic".

Lymphocytic is distinguished from granulomatous hypophysitis by the absence of nodular aggregates of epitheloid histiocytes and multinucleate giant cells, but there are ultrastructural similarities between these two pathologies: the presence of inactive, degranulated secretory cells, focal oncocyctic changes in the secretory cells and inflammatory cells within the periacinar membrane, so that it has been suggested that they have the same pathogenetic background or represent different stages of the same lesion [1, 6, 7] and that autoimmunity may play a role [1, 6, 8]. The presence of Hashimoto's thyroiditis in some cases [6] and the presence of growth hormone, adrenocorticotrophic hormone and anti-macrophage immunoreactivity in the cytoplasm of giant cells [8] supports autoimmunity. In our study, on immunohistochemical examination for growth hormone and prolactin, normal pituitary cells had positive reactions we did not encounter a positive reaction within the granulomas.

Clinical presentation of these cases is not always the same: There may be progressive chiasmal compression, amenorrhoea-galactorrhea, fatigue, diabetes insipidus [1, 2, 4, 6, 8, 9] or a sudden onset of aseptic meningitis [1, 10,

11] or blurred vision. Our cases 1 and 2 presented with sudden onset of meningeal irritation and menstrual irregularities; one had visual disturbance. Endocrinologically, two showed mild hyperprolactinaemia and hypopituitarism. Only the first patient had diabetes insipidus preoperatively.

Recent reports have looked for characteristic or pathognomonic MRI findings in inflammatory pituitary diseases [1, 11]. Radiological findings can be studied in two groups: the form, shape and enhancement pattern of the pituitary lesion and changes in parasellar structures. The most detailed study is that of Honegger et al. [1], who reported six cases of lymphocytic and three of granulomatous hypophysitis. In granulomatous hypophysitis a sellar mass with a tongue-like suprasellar extension because of infundibular infiltration was a constant finding. Marked contrast enhancement was seen in two cases, one with central low density. Pamir et al. [2] reported heterogeneous hypertrophy of the pituitary, with irregular high signal on T2-weighted images in their two cases. Higuchi et al. [6] reported five cases, but two had systemic tuberculosis and another two positive tuberculin tests. MRI characteristics of their idiopathic case were an isointense, homogeneously enhancing mass of the pituitary, with a thickened stalk. Vasile et al. [11] reported heterogeneous contrast enhancement and involvement of the cavernous sinus. In our series all the sellar lesions had a suprasellar extension, with considerably different forms. The pituitary stalk was undistinguishable from the lesion in all cases. Contrast enhancement was homogeneous in the first patient and heterogeneous in the second. Pituitary adenomas may also show heterogeneous enhancement so that the contrast enhancement pattern is not a reliable diagnostic criterion.

Dural enhancement, mentioned by Ahmadi et al. [12], was not observed in our patients, and cannot be considered a constant finding. The sphenoid sinus mucosa was normal in one patient and thickened in two, but mucosal thickening or mucocoeles are not rare in the normal population or in patients with pituitary adenomas, so this is not a reliable criterion.

Sato et al. [13] reported nine dynamic MRI studies in five patients. They pointed out that, even if the disease was treated and MRI normal, dynamic MRI might reveal pathology. They concluded that vascular changes

such as destruction and scarring, which occur in hypophysitis, may cause delayed enhancement of the pituitary in dynamic MRI. Dynamic MRI studies were not performed in our cases because the lesions were interpreted as pituitary macroadenomas.

The radiological appearance of granulomatous hypophysitis is thus inconstant and there are no reliable diagnostic signs. The lesion can be dumbbell-shaped, spherical or elliptical. Isointensity with the brain on T1- and heterogeneous high signal on T2-weighted images are the only constant findings in our cases. Enhancement can be homogeneous or heterogeneous. The stalk is always infiltrated in advanced lesions, and this can be tongue-like in typical cases. In our cases the pituitary stalk was indistinguishable from the swollen gland. Anterior and posterior pituitary are usually both involved together. There may be cavernous sinus invasion [11, 13–15]. Enhancement of the basal duramater, absent in our cases, is not specific for hypophysitis, as it can be observed in pituitary adenomas [16]. None of these radiological signs seems sufficient to differentiate hypophysitis from pituitary macroadenoma; in cases of macroadenoma some normal pituitary tissue can be detected on one side of the gland, while in granulomatous hypophysitis this is not possible.

The clinical presentation, on the other hand, is helpful. In macroadenomas presentation is insidious; headache is present in macroadenomas but there are no meningeal irritation signs. Meningeal irritation and sudden onset can be suggestive of pituitary apoplexy or inflammation. The absence of haemorrhage in the gland on CT or MRI makes apoplexy less likely.

Diabetes insipidus rarely accompanies a pituitary adenoma, due to compression of the stalk, but in granulomatous hypophysitis it is one of the most frequent symptoms, due to infiltration of the stalk. Endocrine investigation will usually reveal hypopituitarism, with elevation of only the prolactin level. In chronic cases, hypopituitarism is more prominent than in pituitary adenomas of the same volume [7].

Open or endoscopic biopsy will reveal the pathology. Radical excision of the lesion is not recommended, both because it will adversely affect pituitary function and because these lesions respond well to steroid therapy [6, 7, 9, 10, 15].

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