An Unusual Case of Recurrent Autoimmune Hypophysitis

Abstract

Autoimmune hypophysitis (AH) is an inflammatory disease that can present either as empty sella or as pituitary mass. A 16-years-old girl was admitted at our Unit for primary amenorrhea. A pituitary MRI performed 2 years before for severe headache demonstrated a large sellar and suprasellar lesion. As a craniopharyngioma was suspected, the consultant neurosurgeon suggested the removal of the lesion. Two months later, a preoperative MRI showed the disappearance of the lesion and a residual empty sella, figure consistent with AH. When the patient came at our observation, basal and dynamic testing documented a state of hypopituitarism, high titers of antipituitary antibodies and a partial empty sella at MRI. Hormonal replacement therapy was started, obtaining a good clinical and biochemical control. Four years later, severe headache and a MRI suggestive of pituitary adenoma recurred. A relapse of the autoimmune phenomenon seemed the most feasible hypothesis. A MRI performed 3 months later did not show any pituitary lesion and empty sella was again described. This patient represents one of the few reported cases of recurrent hypophysitis and demonstrates that both pituitary enlargement and empty-sella can be seen in the same patient at different times of his history.

Introduction

The impact of autoimmune process on pituitary size and function is complex. In some patients with autoimmune hypophysitis (AH), magnetic resonance imaging (MRI) may show pituitary gland enlargement or empty sella in combination or not with hypopituitarism. AH is the most common form of chronic inflammations that primarily affects the pituitary gland. The first case was reported by Goudie and Pinkerton (1962). They described a 22-year-old women who died 14 months after her second delivery probably because of adrenal insufficiency. The autopsy revealed an enlarged thyroid gland infiltrated with lymphocytes, atrophic adrenal glands, and a small pituitary. The adenohypophysis was extensively infiltrated by lymphocytes, while the neurohypophysis was normal. Due to the presence of Hashimoto’s thyroiditis, Authors speculated that both diseases could be explained by “the onset of autoimmune reaction to thyroid and pituitary antigens released during the puerperal involution of these glands”. The first antemortem diagnosis of AH, established on transphenoidal biopsy, were reported in 1980 (Mayfield et al., 1980; Quencer et al., 1980). The frequency of case reports of AH recently increased, and the 1 per 9 million per year incidence estimate reported by Buxton and Robertson (2001) may be an underestimate of today’s incidence. Although the disease has been described in men too, the female to male predominance (6/1) remains a peculiar finding (Jenkins et al., 1995; Caturegli et al., 2005). Indeed, it commonly occurs in women during late pregnancy or early postpartum period (Asa et al., 1981). AH usually presents with signs and symptoms of mass compression such as headache and visual impairment, along with variable loss of anterior, and rarely posterior, pituitary function. Clinical and radiological findings may support the diagnosis of AH, usually confirmed by the presence of antipituitary antibodies. However, the diagnosis can be achieved only by microscopic examination of the pituitary tissue obtained by surgery or biopsy, showing lymphocyte infiltration of the pituitary tissue. The clinical history and the long term course of AH is unpredictable, as spontaneous recovery or...
permanent pituitary failure have been described. Here, we report a peculiar case of a young not pregnant girl followed for ten years, affected with an unusual form of recurrent AH.

Case Report

A 14-year-old girl referred in 1996 to a neurological centre for severe headache accompanied by nausea and dizziness. A skull computerized tomography (CT) scan showed a mass involving the pituitary region and extending to the suprasellar cisterns, without calcifications. A magnetic resonance imaging (MRI) of the sella region confirmed the presence of a mass occupying the sella turcica and the suprasellar region. After gadolinium infusion, the lesion showed a homogeneous enhancement involving the pituitary stalk (Fig. 1, panel A). Due to the age of the patient, differential diagnosis was between craniopharyngioma and Rathke's cleft cyst, rather than a pituitary adenoma. It was decided for a surgical approach, but a MRI performed preoperatively, two months after the previous one, surprisingly showed a partial empty sella with no signs of the previously described lesion (Fig. 1, panel B). Given the evolution of the neuroradiological picture, an autoimmune hypophysitis was then suspected. No hormonal evaluations were performed.

Two years later, the girl came to our observation for primary amenorrhea. Physical examination revealed a well-nourished girl, the BMI being 24 kg/m², height 174.5 cm (97th percentile, SDS +2.0), blood pressure 100/60 mmHg and the heart rate 72 beats/min. The girl was at Tanner-stage III (Tanner and Whitehouse, 1976), without presence of pubic and axillary hair. Bone age was slightly delayed (15 vs. 16 years).

Laboratory blood tests showed a normal blood count and a normal liver and kidney function. Total cholesterol levels were slightly high, while serum tryglicerides and HDL-cholesterol were normal. Fasting blood glucose, insulin and glycosilated haemoglobin were normal. As far as basal hormonal evaluation are concerned, ACTH, TSH and PRL serum levels were in the normal range, while serum FT4 and FT3 levels were low and IGF-I levels were below the normal range for age and sex. AbTg and TPO were negative (Table 1).

A short Synachten test showed central hypoadrenalism (serum cortisol peak at 30 min: 335 nmol/L, nv >500). Basal 17beta-estradiol and gonadotropins levels were low. A GnRH test confirmed the diagnosis of central hypogonadism. An appropriate replacement therapy with cortisone acetate (25 mg/day), levo-thyroxine (up to 75 μg/day), estrogen alone and then combined with progesterone was started. According to the clinical context, a concomitant GH deficiency was suspected and confirmed by dynamic testing (arginine +GHRH, serum GH peak 1.7 μg/L, nv >11). After a 3 month-period replacement therapies, recombinant human GH treatment at the initial dose of 0.3 mg/day was started. Pituitary auto-antibodies, performed to strengthen the supposed diagnosis of AH, were positive. The

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TSH (mU/L)</th>
<th>FT4 (pmol/L)</th>
<th>FT3 (pmol/L)</th>
<th>AbTPO (UI/mL)</th>
<th>AbTg (UI/mL)</th>
<th>PRL (mU/L)</th>
<th>IGF-I (nmol/L)</th>
<th>ACTH (ng/L)</th>
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</thead>
<tbody>
<tr>
<td>Result</td>
<td>3.5</td>
<td>6.8</td>
<td>4.0</td>
<td>3.4</td>
<td>6.2</td>
<td>130</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>nv</td>
<td>0.26–4.2</td>
<td>9–20</td>
<td>3.8–8.0</td>
<td>&lt;35</td>
<td>&lt;35</td>
<td>100–500</td>
<td>36–92</td>
<td>3–60</td>
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Final diagnosis was hypopituitarism, characterized by central hypoadrenalism, hypothyroidism, hypogonadism and growth hormone deficiency, in partial empty sella likely secondary to AH. Once replacement therapy was established and optimized, the girl was followed-up twice a year. She was always well and MRI of the pituitary region, performed every 2 years, remained unchanged. Four years later, the patient complained again severe headache and visual impairment. MRI showed an increase in the medium-right portion of the pituitary gland, with convexity of the superior profile, which extended ventrally up to the optic tracts and above up to the suprasellar cisterns. The pituitary stalk was left-deviated. Even though the neuroradiological picture was suggestive of a pituitary adenoma (● Fig. 2, panel A), taking into account the clinical history, a recurrence of the autoimmune phenomenon seemed to be the most feasible hypothesis. Thus, since a computed perimetry evaluation excluded the presence of significant visual field impairment, a “wait and see” behaviour was chosen and a MRI was performed 2 months later. Again, as six years before, this MRI showed a partial empty sella, without signs of the previously described pituitary mass (● Fig. 2, panel B). Headache spontaneously resolved. Six years have passed since the recurrence, the girl is now 26-years old and she is well on replacement therapies. The last MRI, performed few months ago, showed a small pituitary gland with partial empty sella.

Discussion

The present case report represents a novel case of recurrent hypophysitis, occurred in a non-pregnant woman, which caused hypopituitarism after the first manifestation. To our knowledge, only 2 other similar reports are present in the Literature. The first case of recurrent AH was described by Nishioka and coll. (1997). The patient, a 53-year-old woman, presented with central diabetes insipidus and an intrasellar lesion at the pituitary imaging. Regression of the lesion was spontaneous, and pituitary function remained normal. The recurrence, 2 years later, was successfully treated with corticosteroids. In the present case, the young girl came at our observation already in a condition of hypopituitarism. It is difficult to establish whether a prompt corticosteroid therapy, at the onset of symptoms two years before, could have prevented the development of pituitary deficiency. Indeed, the role of corticosteroid therapy in the management of AH is yet to be defined. Another report of relapsing remitting AH described a 45-year-old woman presented with fever, meningeal symptoms and pituitary mass. The patient had also anterior pituitary deficiency, autoimmune thyroiditis and pituitary hypertrophy at MRI. Symptoms disappeared on hydrocortisone replacement therapy, but relapsed two years later. Again, the recurrence was successfully treated with corticosteroids at high doses and the patient, followed-up for about 9 years, had no more relapses (Matta et al., 2002). Similarly, our patient was followed-up for about 10 years and only a “self-remitting” relapse occurred, with a benign outcome. All these reports underline that diagnosis and management of AH may be quite difficult. The main challenge is that the majority of patients with AH presents with clinical, endocrine and radiological features resembling a pituitary adenoma (Bellastella et al., 1980; Thoudou et al., 1995). A correct diagnosis is of crucial importance since, as also demonstrated in the present case, AH may have a spontaneous recovery or be managed with conservative therapies. At present, a sure diagnosis of AH can be achieved only by microscopic examination of the pituitary tissue obtained by surgery or biopsy (Quencer et al., 1980). Histopathological findings include lymphoplasmocytic infiltrates occasionally forming lymphoid follicles and accompanied by varying number of neutrophils, eosinophils and macrophages, associated with focal

Fig. 2 Pituitary MRI performed at recurrence in coronal (left) and sagittal (right) planes. Panel A: intra and suprasellar mass present at the recurrence of symptoms. Panel B: partial empty sella at remission.
and diffuse parenchymal destruction (Thoudou et al., 1980). The clinical course of our patient, along with the detection of antipituitary antibodies (APA), tended to suggest an autoimmune involvement and prevented us from doing either surgery or biopsy. Also the neuroradiological study of pituitary region, along with the clinical presentation may help in the differential diagnosis. Morphological findings on MRI, such as large pituitary mass with symmetrical extension in triangular shape towards the chiasma and homogeneous enlargement with thickened diaphragma sella after Gadolinium infusion, are suggestive of AH (Bellastella et al., 1980; Cohen et al., 1995). However, in some cases, findings from the imaging tend to overlap. An involvement of cavernous sinus and clivus has also been described (Katral et al., 2007). Autoimmune etiology can be suggested by the association with other autoimmune diseases, such as thyroiditis, and less frequently adrenalitis or type I diabetes mellitus, or by the presence, at high titres of APA (Gluck et al., 1990). However, because of several methodological problems, APA are not considered very specific and sensitive markers of autoimmune pituitary disease (Maghnie et al., 1994; De Bellis et al., 2003). In fact, they have been detected not only in some patients with AH, but also in patients with pituitary adenoma or isolated LH/FSH, ACTH or GH deficiency Moreover, hypophysitis superimposed on a non-functioning pituitary adenoma has also been described (Ballian et al., 2007). The treatment of AH is only symptomatic. Two main approaches have been used to treat the symptoms of sellar compression: surgery and glucocorticoids therapy. In the past, surgery has been the commonest form of treatment, with the aim to reduce the pituitary mass and promptly resolve headache and visual defects, as published by Honegger and coll. (Honegger et al., 1997). However, the role of surgery remains controversial and the current literature suggests a restriction in its indication to selective cases with progressive deficit of visual field (Caturegli et al., 2005). Glucocorticoids at high doses can be effective in the treatment of AH, many reports documenting a regression of the pituitary mass (Nishioka et al., 1997; Matta et al., 2002; Caturegli et al., 2005) However, the role of corticosteroids has yet to be clearly defined, since spontaneous recovery of both pituitary function and sellar mass has also been described. Indeed, also in the present case, the pituitary mass spontaneously disappeared, both at the moment of diagnosis and at the recurrence. As far as pituitary function, hypopituitarism may develop after the first manifestation. In conclusion, the present case suggests that even in the presence of a neuroradiological stability, a recurrence of the autoimmune phenomenon can never be excluded. Hence the importance of careful follow-up of these patients.

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Conflict of Interest: None.

References