A corticotroph pituitary adenoma as the initial presentation of familial glucocorticoid deficiency

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Abstract

Context: Familial glucocorticoid deficiency (FGD) is a rare autosomal recessive ACTH-resistance syndrome characterized by glucocorticoid deficiency in the absence of mineralocorticoid deficiency. Here, we report the case of a young woman with a corticotroph pituitary adenoma as the initial presentation of FGD.

Case report: A 15-year-old girl was referred to our institution for a 16 mm pituitary adenoma associated with glucocorticoid deficiency. Clinical and biological features were evocative of FGD. DNA sequencing did not identify mutations in either the melanocortin 2 receptor (MC2R) or the MC2R accessory protein genes, indicating type 3 FGD. Despite adequate glucocorticoid replacement, plasma ACTH levels remained increased and pituitary magnetic resonance imaging (MRI) showed a progression of the tumour size resulting in optic chiasm compression with intra-tumoural haemorrhaging. When the patient was 26 years old, it was decided that she would undergo transsphenoidal surgery. The histomorphological analysis identified a well-individualized pituitary adenoma immunoreactive for ACTH. The proband’s sister also exhibited type 3 FGD associated with pituitary hyperplasia upon MRI.

Conclusion: This case highlights the relationship between FGD and hyperplasia of ACTH-producing cells, potentially leading to histologically proven pituitary corticotroph adenomas. This observation raises the question of the pituitary MRI’s significance in the follow-up of FGD.

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Introduction

The ACTH receptor or melanocortin 2 receptor (MC2R) is mainly expressed in the adrenal gland and exhibits an exclusive affinity for ACTH (1). The functional expression of MC2R requires the MC2R accessory protein (MRAP), a protein involved in the trafficking of MC2R (2, 3). Mutations in MC2R or MRAP cause familial glucocorticoid deficiency (FGD). FGD is a rare autosomal recessive disease and three types of FGD were identified (4). While type 1 is caused by mutations in the MC2R (5–7), type 2 is produced by mutations of MRAP (2, 8). In more than 50% of FGD patients, there is no mutation identified and these patients are classified as type 3 (9). FGD is usually diagnosed during the neonatal period or early childhood. Plasma cortisol levels are undetectable in the majority of cases and are unresponsive to exogenous ACTH stimulation. ACTH concentrations are very high, often over 220 pmol/l (n: 4–22), while plasma renin and aldosterone levels remain in the normal ranges (7). The treatment is usually based on glucocorticoid replacement with hydrocortisone.

Here, we describe an unusual case of a young woman with type 3 FGD in whom the initial clinical presentation was linked to the discovery of a histologically proven corticotroph pituitary adenoma.

Case history

A 15-year-old girl was initially referred to our centre in 1992 for secondary amenorrhoea and galactorrhoea. Serum prolactin concentration was moderately increased to 90 μg/l (n < 30). Pituitary magnetic resonance imaging (MRI) showed a 16 mm-adenoma with suprasellar extension; there was no visual defect. Physical examination revealed a generalized skin hyperpigmentation. A complete hormonal evaluation (Table 1) identified a peripheral glucocorticoid deficiency with low plasma cortisol and increased plasma...
ACTH levels. Plasma cortisol levels were unresponsive to the administration of both 250 μg and 1 mg of synacthen. A high dose dexamethasone suppression test only resulted in a partial suppression of ACTH levels. The combination of the elevated plasma ACTH levels with low plasma cortisol concentrations and a normal renin–aldosterone axis was strongly evocative of an FGD. Molecular analyses were performed and revealed no mutation in MC2R or MRAP, suggesting type 3 FGD. The pituitary MRI did not show any progression of the macroadenoma (16 × 15 × 10 mm; Fig. 1A). Other pituitary hormones, including the prolactin, were in the normal ranges (Table 1).

Dexamethasone treatment (2 mg/day) reduced both the plasma ACTH levels from 880 to 66 pmol/l and the size of the pituitary macroadenoma (12 × 10 × 6 mm). Due to the development of an iatrogenic hypercorticism, dexamethasone was stopped and replaced by hydrocortisone (20 mg/day in two divided doses). During the follow-up, the patient continued to exhibit elevated levels of circulating ACTH, around 66 pmol/l (Fig. 2), but the size of the pituitary adenoma remained stable.

Ten years later, a pituitary MRI indicated a progression of the tumour size (15 mm) resulting in optic chiasm compression with intra-tumoural haemorrhaging (Fig. 1B) leading to a transphenoidal surgery. On gross examination, the histological study demonstrated a well-individualized pituitary adenoma uniformly constituted of cells immunoreactive to ACTH (Fig. 3A and B), with a trabecular pattern underlined by reticular strain; some adenomatous cells were vacuolized. Mitoses were rare (~1 mitose per high magnification field (×400)) with only a few Crooke’s cells (10) scattered throughout the tumour (Fig. 3C). Immunostaining for

### Table 1: Laboratory results at the admission.

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cortisol</strong></td>
<td>Basal</td>
<td>220–660 nmol/l</td>
</tr>
<tr>
<td>(0800 h): 108</td>
<td>Synacthen: 250 μg</td>
<td>30 min: 154</td>
</tr>
<tr>
<td></td>
<td>60 min: 152</td>
<td>Synacthen: 1 mg</td>
</tr>
<tr>
<td></td>
<td>6 h: 215</td>
<td>24 h: 168</td>
</tr>
<tr>
<td></td>
<td>33 h: 220</td>
<td>Synacthen suppression test</td>
</tr>
<tr>
<td></td>
<td>(8 mg/day during 4 days): 26</td>
<td></td>
</tr>
<tr>
<td><strong>ACTH</strong></td>
<td>Basal: 814</td>
<td>4–22 pmol/l</td>
</tr>
<tr>
<td>Dexamethasone suppression test</td>
<td></td>
<td></td>
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<tr>
<td><strong>Aldosterone</strong></td>
<td>Supine: 444</td>
<td>30–250 pmol/l</td>
</tr>
<tr>
<td></td>
<td>Standing: 693</td>
<td>200–800 pmol/l</td>
</tr>
<tr>
<td><strong>Renin activity</strong></td>
<td>Supine: 3.1</td>
<td>0.2–2.7 μg/l per h</td>
</tr>
<tr>
<td></td>
<td>Standing: 6</td>
<td>1.5–5.6 μg/l per h</td>
</tr>
<tr>
<td><strong>Prolactin</strong></td>
<td>3.4</td>
<td>&lt;30 μg/l</td>
</tr>
<tr>
<td><strong>Free T₄</strong></td>
<td>140</td>
<td>51–142 nmol/l</td>
</tr>
<tr>
<td><strong>IGF1</strong></td>
<td>159</td>
<td>70–1085 ng/ml</td>
</tr>
<tr>
<td><strong>Oestradiol</strong></td>
<td>95</td>
<td>70–220 pmol/l</td>
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<tr>
<td><strong>LH</strong></td>
<td>7.8</td>
<td>5–25 IU/l</td>
</tr>
<tr>
<td><strong>FSH</strong></td>
<td>4.4</td>
<td>5–20 IU/l</td>
</tr>
<tr>
<td><strong>SDHEA</strong></td>
<td>&lt;0.2</td>
<td>0.6–7 nmol/l</td>
</tr>
<tr>
<td><strong>Delta(4)androstenedione</strong></td>
<td>3.5</td>
<td>3.5–7 nmol/l</td>
</tr>
<tr>
<td><strong>17 Hydroxyprogesterone</strong></td>
<td>1</td>
<td>1–13 nmol/l</td>
</tr>
<tr>
<td><strong>Adrenal antibody</strong></td>
<td>&lt;0</td>
<td></td>
</tr>
<tr>
<td>(21 hydroxylase)</td>
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</table>

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**Figure 1** Pituitary MRI (sagittal T1-weighted image). Pituitary is indicated by arrow. (A) In 1993, a 16 mm-adenoma with suprasellar extension was visible. (B) In 2002, a progression of the tumour size was identified with optic chiasm compression and intra-tumoural haemorrhaging. (C) Pituitary MRI after transphenoidal surgery in 2004.
human glycoprotein hormone alpha-subunit, LH, FSH, prolactin, GH and TSH were all negative (data not shown). Post-operative pituitary MRI showed partial empty sella with residual pituitary tissue (5 × 3 mm; Fig. 1C). Hormonal assessments revealed lower ACTH levels (15 pmol/l; Fig. 2). Lactotroph, thyrotroph and somatotroph axes were all normal. However, the gonadotroph axis could not be tested due to the patient’s use of an oral contraceptive pill.

We also investigated the corticotroph axis of the proband’s sister when she was 14 years old. Upon first laboratory testing, basal plasma cortisol levels were normal (276 nmol/l) but did not rise in response to 250 μg of synacthen (303 nmol/l). On the other hand, plasma ACTH was increased (around 88 pmol/l) under basal conditions, but became undetectable after a dexamethasone suppression test (2 mg/day for 2 days); mineralocorticoid function was preserved. Pituitary MRI revealed a homogenous pituitary hyperplasia (8 mm), without an individualized tumour. Ten years later, biological investigations showed low serum cortisol (39 nmol/l) with persistent elevated ACTH (52 pmol/l), so a treatment with hydrocortisone (20 mg/day) was started. The last pituitary MRI in 2008 showed a stable pituitary hyperplasia (9 mm). Recently, hormonal dosages have been performed in the parents of the proband. They exhibited both normal plasma cortisol and ACTH levels (mother: cortisol = 309 nmol/l and ACTH = 12 pmol/l; father: cortisol = 469 nmol/l and ACTH = 14 pmol/l) with normal response following the administration of 250 μg of synacthen (mother: cortisol 734 nmol/l at 60 min and father: cortisol 634 nmol/l at 60 min).

**Discussion**

The diagnosis of FGD is based on clinical findings, and a specific hormonal profile, characterized by the association of glucocorticoid deficiency, highly elevated ACTH levels reflecting a defect in ACTH receptor signalling, and absence of mineralocorticoid deficiency. As summarized in Table 1, the hormonal findings of our patient were very similar to those described in the literature. In addition, there were neither clinical nor biological evidences for other causes of primary adrenal insufficiency such as triple A syndrome, adrenoleucodystrophy, congenital adrenal hyperplasia or autoimmune Addison’s disease. Genetic testing failed to identify mutations in MC2R or MRAP in our patient, as observed for the majority (≈ 50%) of FGD patients (i.e. FGD type 3).
One of the primary clinical particularities of this case was the late onset of FGD, since the patient was 15 years old at diagnosis. In the literature, FGD is usually diagnosed during the neonatal period or early childhood (<10 years). It should be underlined that the patient’s sister, who also exhibited hormonal features of FGD, was clinically asymptomatic when she was evaluated at 14 years old.

The most striking observation, described here for the first time, is the occurrence of a histologically proven corticotroph pituitary adenoma in a patient with FGD. The pituitary MRI had identified the tumour earlier in the course of the disease, although it was difficult to distinguish between a simple corticotroph hyperplasia and a true individualized corticotroph adenoma at the time. Histological analysis following transsphenoidal surgery clearly identified a well-differentiated corticotroph adenoma, without staining for the other pituitary hormones. Interestingly, the size of the ‘adenoma’ slowly decreased under hormonal substitution by dexamethasone and hydrocortisone before the surgery, suggesting that it was initially sensitive to the feedback inhibition by glucocorticoids (Fig. 2). Later, the raising of plasma ACTH levels under hydrocortisone substitution was associated with the autonomous development of a corticotroph adenoma, which progressively increased in size. In accordance with this pathophysiological scenario, the circulating levels of ACTH were drastically reduced following transsphenoidal surgery, thereby confirming that such corticotroph adenoma was responsible for the uncontrolled ACTH secretion. In this context, the phenotype of the sister’s patient, who also had type 3 FGD, is very informative since she also had a similar pituitary hyperplasia at the onset of diagnosis.

ACTH-producing hyperplasia or adenoma secondary to Addison’s disease is a very rare feature. Only few cases are described in literature, and histological analyses are rarely available (11–18). One study reports the analysis of 18 pituitary glands of patients with untreated Addison’s disease and reveals that nodular corticotroph hyperplasia is common, whereas adenoma formation seems to be rare (19). This complication could at least be partly compared to Nelson’s syndrome, which is defined by the association between an expanding pituitary tumour and highly elevated plasma ACTH levels after an adrenalectomy in Cushing’s disease. High plasma ACTH levels after an adrenalectomy is the best predictive factor of Nelson’s syndrome, but the pathophysiology remains unclear (20, 21). Pathogenesis could be explained by the lack of a feedback suppression of ACTH-producing cells in response to severe glucocorticoid deficiency. It could be hypothesized that the prolonged stimulation of ACTH-producing cells might lead to a pituitary hyperplasia and, in some cases, to an autonomous corticotroph adenoma. Alternatively, it was suggested that ACTH could exert a feedback inhibition on its own secretion (22). MC2R mRNA was found to be expressed in ACTH-staining cells in normal pituitary. However, a loss of MC2R mRNA expression was retrieved in corticotroph adenomas of patients with Cushing’s disease (23). Therefore, one might say that this feedback is ineffective in patients with FGD due to the defect in ACTH signalling, a phenomenon that may contribute to the development of ACTH secreting adenomas.

Frequently, patients with FGD persistently have high ACTH levels, despite adequate glucocorticoid replacement. In our patient, unsuppressed ACTH levels are explained by an autonomous corticotroph pituitary adenoma. This observation raises the problem of the management of high ACTH levels in FGD. Should we perform a pituitary MRI on FGD patients with excessive ACTH levels despite a correct substitution? Additional studies with pituitary imaging in FGD will help to answer this question.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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