CLINICAL STUDY

Two familial giant pituitary adenomas associated with overweight: clinical, morphological and genetic features

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Abstract

Objective: Pituitary adenomas are usually sporadic, although rare familial cases have been described. Here we report two first degree female cousins with giant pituitary adenoma and overweight. Both presented with secondary amenorrhoea, occasional headache and weight gain.

Materials and methods: In both patients clinical, morphological and genetic studies were performed. Both patients underwent surgery and post-operative medical therapy with somatostatin analogues and dopamine agonist, followed by a conventional radiotherapy course.

Results: Clinical examination at presentation revealed an acromegaloid habitus only in the second patient. Basal and dynamic hormonal evaluation showed high serum GH and serum IGF-I values, higher in the second than in the first patient, and a mild hyperprolactinaemia only in the first patient. On optical and electron microscopy, both tumours were oncocytic adenomas, immunopositive for GH in the first patient and GH/prolactin in the second. The genetic analysis for germ-line mutations of the multiple endocrine neoplasia type 1 gene was negative. Two years after radiotherapy a remarkable shrinkage of both tumours was observed, whereas the overweight worsened in both patients, accompanied by high plasma leptin values.

Conclusion: To our knowledge, this is the first report of familial pituitary adenomas including one case of a clinically silent GH-secreting adenoma. In addition, it provides further evidence that familial pituitary tumours can occur as a multiple endocrine neoplasia type 1 unrelated disease.

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Introduction

Pituitary adenomas are usually sporadic tumours. Most of them are monoclonal proliferations, with some well-recognised abnormalities of oncogene or tumour suppressor gene structure or expression, and endogenous and exogenous factors such as growth factors, neuropeptides and steroids contributing to their progression (1, 2). In about 4% of cases, pituitary tumours are part of multiple endocrine neoplasia type 1 (MEN-1), with a higher incidence in patients with prolactinomas (3). A familial susceptibility, mainly based on inherited mutations of tumour suppressor genes, has been well recognised in some human cancers (4). Similarly, a small number of pituitary tumours occur in McCune–Albright disease or with a familial aggregation, as a component of MEN-1 syndrome or Carney complex, but some of them may present as apparently isolated familial

pituitary adenomas (2). Until now, 72 cases of familial growth hormone (GH)-secreting pituitary adenomas have been reported in 25 families (5–18). In addition, seven cases of prolactinomas in four families (19, 20) and two cases of familial non-functioning pituitary adenoma in a family (21) have been described. To our knowledge, no familial gonadotroph, thyrotroph, corticotroph or clinically silent GH-secreting adenomas have been reported yet. Recently, six families with GH-secreting pituitary adenomas have been negatively screened for genetic abnormalities of the MEN-1 gene, three for loss of heterozygosity and six for mutations (11–18), suggesting that familial acromegaly is a distinct entity. Although a linkage to chromosome 11q13.1 and a potential second locus at chromosome 2p16-12 have been recently proposed (22), the pathogenesis of familial pituitary adenomas remains largely unknown. In particular, no somatic point mutation in the Gs α gene,

Figure 1 Diagrammatic representation of the patients' history. Solid line: IGF-I; ●: weight.

which is the most common abnormality observed in GH-secreting adenomas, was found in such tumours (8, 18). In the present paper, we describe the clinical, morphological and genetic features of two cases of isolated familial GH-secreting adenomas, including for the first time a case of clinically silent GH-secreting adenoma. To our knowledge, they are also the first two cases of familial giant pituitary tumours associated with severe progressive obesity.

Patients and methods

Case I

This 19-year-old girl was referred to the Neurosurgery Unit in 1994 because of recent neurological symptoms

of raised intracranial pressure (see Fig. 1A for schematic history). She had a 2-year history of odd headaches, amenorrhoea, galactorrhoea and weight gain (13 kg) with recent visual field defects. She had been for a few months on dopamine-agonist (DA) therapy because of a mild hyperprolactinaemia (99 µg/l), but the neurological symptoms progressively worsened. On clinical examination, her height was 172 cm, her weight 90 kg (body mass index (BMI) 30.4 kg/m²), and her blood pressure 120/80 mmHg. No stigmata of acromegaly were observed. Bilateral papillary oedema was present. Goldman visual fields testing showed a bitemporal hemianopsia and visual acuity was 3/10 and 6/10 in her right and left eye respectively. A magnetic resonance imaging (MRI) scan revealed the presence of a large mass with infra- and suprasellar extensions causing compression of the optic chiasm

Figure 2 Case I. (A, B) MRI at diagnosis. Contrast enhanced T1-weighted coronal and sagittal images. A giant lesion is evident with intra- and suprasellar localisation, which compresses the III ventricle and Monroe's foramen and mild bilateral ventricular dilatation. (C, D) MRI after surgery: After transcranial surgery, the mass appears grossly debulked. The intrasellar portion is almost unchanged while a residual tumour of approximately 50% of the initial mass is still evident in the suprasellar location. The coronal image (C) also shows an ependymal enhancement compatible with an inflammatory process. (E, F) MRI 2 years after radiotherapy: A dramatic reduction in size of the residual tumour is evident. Coronal (E) and sagittal (F) scans show residual sellar enlargement. The mass has a low intensity, non-enhancing core with peripheral residual enhancement and central necrotic changes.

and of the III ventricle (Fig. 2A and B). A trans-frontal surgical approach was performed with a partial resection of the tumour. Twenty days later, a marked hyperglycaemia (19.98 mmol/l) with ketoacidosis was observed and was treated by insulin followed by oral

anti-diabetic drugs for about 8 weeks. A partial post-operative hypopituitarism contrasting with mildly elevated prolactin (PRL) (32 µg/l), GH (16 µg/l), insulin-like growth factor-I (IGF-I) (420 µg/l) levels was observed (Table 1). Alpha-subunit levels were low

Table 1 Patients' clinical and laboratory values.

Subject	Age (years)	BMI (kg/m ²)	GH (μg/l)	IGF-I (μg/l)	PRL (μg/l)	Alpha-subunit (μg/l)	Insulin (pmol/l)	Glucagon (ng/l)	Gastrin (ng/l)	PTH (ng/l)	Ca (mmol/l)	P (mmol/l)	TPO-Ab	Leptin (μg/l)
Normal	—	<25	<15	<380	5–25	<1.1	15–180	60–200	<85	10.6–54	2.15–2.65	0.96–1.5	—	4.5–10
Case I	19	30.4	16	420	32	0.04	162	93	66	18	2.40	1.2	+	28
Case II	22	27.5	33	630	5	0.05	189	102	72	24	2.25	1.3	+	22

PTH = parathyroid hormone.

TPO-Ab = thyroid peroxidase autoantibodies.

(0.04 μg/l). GH was not suppressed during an oral glucose tolerance test (OGTT) and did not increase after either thyrotrophin-releasing hormone (TRH) (200 μg i.v.) or gonadotrophin-releasing hormone (GnRH) (100 μg i.v.) stimulation; acute pharmacological responsiveness could also be evaluated before starting medical treatment (Table 2). Medical therapy was started, employing somatostatin analogues (SMS) and oral DA drugs (Fig. 1A), with good tolerance and a normalisation of PRL levels, but a minor reduction in GH/IGF-I levels and no shrinkage of the residual tumour mass, as shown by subsequent MRI scans (Fig. 2C and D). Thus, a second transcranial operation was performed, followed by conventional radiotherapy with a linear accelerator (5000 rads). Partial hypopituitarism progressively worsened and was replaced by cortisone acetate, l-thyroxine and sex steroids. A major reduction of the residual mass was observed by MRI throughout the 2 years following radiotherapy (Fig. 2E and F), paralleled by a reduction of GH/IGF-I levels. An ongoing worsening obesity was observed (last BMI 42.5 kg/m²) accompanied by high serum leptin levels (28 μg/l). Six months after medical therapy discontinuation, GH/IGF-I remained low. Thus a secondary GH deficiency could be documented by a combined GH-releasing hormone (GHRH) (100 μg i.v.) and arginine (30 g) test (peak at 0.5 μg/l).

Case II

In 1996, a 21-year-old female, a first degree cousin of

Case I, was referred to the Endocrinology Unit for a 12-month history of secondary amenorrhoea with rapid weight gain and recent bifrontal headache (see Fig. 1B for schematic history). On clinical examination, her height was 164 cm, her weight 74 kg (BMI 27.5 kg/m²) and her blood pressure 135/85 mmHg. A mild acromegalic habitus was noticed, with acral and tongue enlargement, slight facial modifications and sweating. Basal hormonal evaluation was normal with the exception of high GH and IGF-I levels (Table 1). Serum GH was not suppressed during OGTT and did not respond to TRH or GnRH administration. Pharmacological responsiveness was also evaluated before starting any medical therapy (Table 2). Goldman visual field testing was normal. A cranial MRI scan showed a 4.1 cm mass invading the supra- and retrosellar areas and the left cavernous sinus (Fig. 3A and B). The tumour was partially resected by trans-sphenoidal surgery. Surgery was followed by medical therapy with SMS and oral DA (Table 2), with a good tolerance but a low effect on GH/IGF-I levels and no shrinkage of the residual tumour (Fig. 3C and D). A second surgical resection was performed using a trans-ethmoido-maxillary-sphenoidal approach (23), followed by a post-operative course of conventional radiotherapy with a linear accelerator (4500 rads). Transient post-operative diabetes insipidus was medically treated. Cortisone acetate, l-thyroxine and sex steroid hormones replaced post-operative hypopituitarism, and residual GH/IGF-I hypersecretion was medically treated (Fig. 1B). Two years after radiotherapy, the patient had normal GH

Table 2 Dynamic hormonal evaluation and pharmacological responsiveness.

	Hormone	Case I		Case II	
		Basal	Peak/nadir (P)/(n)	Basal	Peak/nadir (P)/(n)
OGTT	GH (μg/l)	16.0	14.1 (n)	23.0	17.0 (n)
	Insulin (pmol/l)	165	775 (P)	207	660 (P)
TRH-test	GH (μg/l)	14.5	15.2 (P)	20.1	23.7 (P)
	PRL (μg/l)	28.1	31.6 (P)	5.0	8.0 (P)
GnRH-test	GH (μg/l)	13.6	14.7 (P)	22.5	25.4 (P)
	FSH (U/l)	2.6	4.4 (P)	6.9	15.5 (P)
	LH (U/l)	2.0	2.2 (P)	1.4	13.2 (P)
SMS-test (octreotide 100 μg/s.c.)	GH (μg/l)	12.1	10.3 (n)	23.4	19.0 (n)
DA-test (cabergoline 0.5 mg/p.o.)	GH (μg/l)	18.5	17.9 (n)	32.3	30.2 (n)
	PRL (μg/l)	86.5	27.3 (n)	6.2	1.1 (n)

Figure 3 Case II. (A, B) MRI at diagnosis. Contrast-enhanced T1-weighted coronal (A) and sagittal (B) images showing a large tumour with intra-supra-retrosellar extension and invasion of the left cavernous sinus. (C, D) MRI after surgery: After surgery, performed by an 'enlarged' trans-sphenoidal approach, a subtotal removal of the mass is observed. Residual adenomatous tissue is present within the left cavernous sinus and in the supra-retrosellar region. (E, F) MRI 2 years after radiotherapy. The residual tumour is dramatically reduced in size and only a small (4 mm) mass adjacent to the stalk is still evident. A secondary empty sella is evident.

and age-corrected IGF-I levels, and MRI (Fig. 3E and F) documented a remarkable shrinkage of the residual mass. In contrast, the overweight progressively worsened (BMI 39.5 kg/m²), accompanied by high serum leptin levels (22 µg/l). Medical therapy was withdrawn because of low GH/IGF-I values and, 4 months later, GH/IGF-I levels remained below the normal range and

GH failed to respond to combined stimulation by GHRH and arginine (peak at 3.9 µg/l).

Bio-clinical screening for MEN-1

Both patients and nine family members gave their informed consent to clinical and biochemical screening

Table 3 PCR primer pairs for the sequence study of MEN-1 gene from genomic DNA.

Pair no.	Exon	Sequence of forward primer	Sequence of reverse primer	Annealing temperature (°C)	Product size (bp)
1	2	TTGCTTGCAGGCCGCCGCC	TGGTAGGGATGACGCGGTTG	62	203
2	2	GGCTTCGTGGAGCATTTTCT	CTCGAGGATAGAGGGACAGG	62	203
3	2	TTCACCGCCCAGATCCGAGG	TAAGATTCCCACCTACTGGG	58	185
4	3	GGAGTGTGGCCCATCACTA	TGGAGTCCCTTGGGTGGCTTG	60	359
5	4	CCATCACCACCCACATAGGA	TCAAGTCTGGCCTAGCCAG	60	291
6	5–6	CGTGGCTCATAACTCTCTCC	TAGGGTCTCCCTTCTGCACC	56	279
7	7	ATTTGTGCCAGCCAGGGCAGC	CAGTCCTGGACGAGGGTGGTT	60	279
8	8	CCTTCAGACCCTACAGAGAC	CCATGGCCCTGTGGAAGGGA	56	242
9	9	AGAGACTGATCTGTGCCCTC	TCAGTCCCACCGGCACCGAAG	56	320
10	10	CACTGGCCGCAACCTTGCT	ACAGTCCCAGGAGGCTTCCG	66	260
11	10	CGGAAGCCTCCTGGGACTGT	CCCACAAGCGGTCCGAAGTC	66	317

for MEN-1-related tumours. None of them reported clinical symptoms or a previous history of gastroduodenal ulcer, nephrolithiasis or any known endocrine neoplasia. Physical examination revealed no feature of acromegaly and no obesity was noticed among relatives. Results of biochemical screening in the patients (Table 1) and their relatives (data not shown) were negative. With the exception of subclinical autoimmune thyroiditis, which was diagnosed in both patients and in two female relatives, no evidence of other endocrine dysfunction was found.

Morphological studies

Tumour samples were formalin-fixed and paraffin-embedded. Haematoxylin–eosin (H&E) staining was used for light microscopy. Immunohistochemistry (IHC) for pituitary hormones was performed with polyclonal rabbit antibodies (anti-PRL, anti-GH, anti-follicle-stimulating hormone (FSH), anti-luteinising hormone (LH), anti-thyrotrophin, anti-adrenocorticotrophin; Orthodiagnostic Systems, Raritan, NJ, USA), using the streptavidin–biotin–peroxidase complex technique. IHC detection of the Ki-67 antigen was performed using the mouse monoclonal MIB-1 antibody (Diagnostic Brokers Associated, Milan, Italy) after microwave pre-treatment, according to the manufacturer's instructions. MIB-1 immunopositivity was counted on 1000 cells and expressed as percentage of positive cells. In addition, small fragments were fixed in Karnovsky solution for ultrastructural studies.

Genetic screening for MEN-1 gene mutations

Peripheral blood samples were collected from the patients and genomic DNA was isolated by using a standard protocol.

Genomic DNA was used for sequence analysis, after amplification by PCR. Eleven primers pair for exons 2 to 10 of the MEN-1 gene were appropriately selected (Table 3). PCR condition were as follow: 50 µl of reaction containing 150 µg DNA, 1 × PCR buffer with 1.5 mmol/l MgCl₂, 0.2 mmol/l dNTPS, 10 pmol pri-

mers, and 2.5 U Amplitaq (Perkin-Elmer Applied Biosystem, NJ, USA). PCR cycles were 94 °C for 10 min, followed by 35 cycles of 94 °C for 1 min, 56–66 °C for 45 s, and 72 °C for 1 min. Primer pairs, their relative annealing temperature and PCR product sizes are shown in Table 3. Direct sequencing of the double-stranded PCR-fragments was performed by automated method using specific primers (ABI PRISM 310 DNA sequencer; Perkin-Elmer Applied Biosystem).

Results

Morphological studies

Both tumours were mixed oncocyctic chromophobic–eosinophilic showing a solid–papillary architecture on H&E. At IHC, both tumours were immunopositive for GH at first and second surgery, whereas focal positivity for PRL was present in Case II at first surgery only. No other pituitary hormone was detected. The MIB-1 index, determined at second surgery in Case I and at both first and second operations in the Case II second, was 0.5% in Case I, and 6% and 2.7% in Case II. By electron microscopy (EM) both tumours were confirmed to present marked oncocyctic changes with sparsely granulated (SG) cells with numerous giant spherulated mitochondria and fibrous bodies (Fig. 4A–C).

Genetic screening for MEN-1 gene mutations

No germ-line mutation of MEN-1 gene could be observed (data not shown).

Discussion

In this paper we describe two new cases of familial GH-secreting adenomas, which share similarities with previously reported cases of familial pituitary tumours, but also present unreported peculiar characteristics (5–18). It is not clear yet whether familial acromegaly represents a specific unidentified genetic entity or reflects a heterogeneous syndrome based on different physiopathological mechanisms. Many features are

common to previous cases and to the patients described herein, such as (i) an early onset of the disease, which explains the relatively high prevalence of gigantism in such patients, (ii) an unusual prevalence of macroadenomas with suprasellar extension, which explains the high incidence of visual field defects in an unusually high percentage of affected patients, and (iii) an apparently low penetrance of the disease, as suggested by the small numbers of affected patients in each family, generally two to four patients over one or two generations. However, substantial differences should be underlined in the present family: (i) two female cousins are affected, whereas familial acromegaly is more frequent in males, (ii) giant pituitary tumours are unusual, (iii) overweight followed by severe progressive obesity, which appears in these patients as a disease-related abnormality, since its evolution shows the same pattern in both patients has not been described previously. The remarkably parallel evolution of the disease in both patients and the common features of their tumours strongly suggest that both patients suffered from the same pituitary disease. Both pituitary adenomas appeared to be isolated, since no evidence for other endocrine tumour or dysfunction could be observed either in the patients or in their relatives. Only autoimmune thyroiditis was observed in both patients and in two of their relatives, but its high incidence in women makes its significance doubtful. Rare diseases such as Carney's complex or McCune–Albright syndrome could be reasonably excluded on the basis of clinical examination and echocardiography (data not shown) and no MEN-1 gene mutation could be observed, indicating that this familial disease is unrelated to MEN-1. This latter finding is in keeping with recent observations (11–18).

Clinically silent GH hypersecretion by pituitary tumours has already been reported in young women with macroadenomas and suprasellar extension (24). SG GH-producing adenomas, which are less common than their densely granulated (DG) counterpart, have also been reported to occur more frequently in young women, to often present as voluminous and invasive tumours, and to be less responsive to medical therapy. Fibrous bodies have been regarded as markers of SG adenomas, and oncocyctic changes are also more frequent in this subtype (25). Oncocyctic changes are uncommonly observed in GH-secreting tumours, but appear to negatively correlate with basal hormone levels. Thus, the mild acromegalic features observed in

Figure 4 Case II. (A) EM $\times 7800$ section of the adenoma consisting of SG cells exhibiting mild to moderate oncocyctic changes. The adenoma cells contain a large number of giant mitochondria. (B) EM $\times 12\,500$. A neoplastic cell with double nucleus. The secretory granules are small and scarce without signs of degeneration. (C) EM $\times 12\,500$ The picture shows an example of the fibrous bodies (paranuclear aggregates of cytokeratin microfilaments).

the Case II, and the complete lack of clinical acromegaly in the Case I, are in agreement with a rapid progression of the tumours. The absence of gigantism despite the young age of the patients can be ascribed to the same explanation.

From a therapeutic point of view, GH/IGF-I hypersecretion appeared in both patients to be poorly responsive to medical treatment with SMS, and the only effect of the introduction of a DA in a combined therapy (26) was to normalise PRL levels. Accordingly, SG somatotroph adenomas are believed to be less responsive than DG adenomas (27). However, the significant reduction in MIB-1 immunopositivity observed in Case II between the first and the second operation, after a 6 month course of combined medical treatment, does not rule out a possible effect of such treatment on cell proliferation. In contrast, both tumours exhibited a remarkable responsiveness to radiotherapy, with a major reduction of post-operative residual mass and a secondary GH deficiency achieved in only 2 years, a shorter time than commonly observed in GH-secreting tumours (28). Such a high radiosensitivity may be ascribed to the relatively high proliferation index of the tumour in Case II, but remains largely unexplained and represents an additional characteristic of these tumours.

Overweight is becoming a major problem in both patients. The increased leptin serum levels observed in both patients are in keeping with the well-described correlation between BMI and plasma leptin levels (29). No familial obesity was present, but an altered behaviour of food intake was present in both patients. Progressive overweight was already present at diagnosis, in agreement with previous observations in clinically silent GH-secreting adenomas (24). Although the presence of unrecognised common metabolic disorders cannot be ruled out, the giant suprasellar mass and further hypothalamic damage induced by neurosurgery and/or radiotherapy may have promoted a local dysregulation and the development of a 'leptin resistant' condition. The sudden post-operative onset of transient diabetes mellitus in the first patient, associated with neuroradiological evidence for post-operative episellar haemorrhage, further supports the hypothesis of hypothalamic damage.

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