Familial isolated pituitary adenomas (FIPA). Case report of four families and review of literature

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Abstract

Background: The majority of pituitary adenomas are sporadic, but about 5% of them occur in a familial setting, predominantly in multiple endocrine neoplasia type 1 and Carney complex. Familial isolated pituitary adenomas (FIPA) have also been described. The clinical course of FIPA differs significantly from sporadic cases and is characterised by a larger tumour size, more aggressive course, and younger patient’s age at the moment of recognition.

The aim of this retrospective study is to present four families in which two closely related people were diagnosed with pituitary adenomas. Probably these cases are clinical manifestations of FIPA.

Material and methods: Eight patients within four families, presenting with anterior pituitary tumours, were described. The authors analysed the medical and family histories of the patients, their imaging pictures (MRI/CT), and hormonal tests.

Results: Family 1: two sisters with acromegaly in the course of macroadenoma. Family 2: two brothers with clinically non-secreting macroadenomas. Family 3: a father and daughter with clinically non-secreting macroadenomas. Family 4: a young man with acromegaly caused by macroadenoma and a daughter of his mother’s sister with microprolactinoma.

Conclusions: Familial isolated pituitary adenomas are more common than was previously thought; therefore, specific questioning regarding family history should be a part of the workup of all patients with pituitary adenomas. (Endokrynol Pol 2017; 68 (6): 697–706)

Key words: familial isolated pituitary adenoma, FIPA, AIP gene, AIP mutations

Introduction

Pituitary adenomas are one of the most common tumours of the central nervous system. There is a wide range of prevalence of pituitary adenomas estimated in individual studies, from 1% to nearly 40% in imaging studies and from approximately 1% to 35% in post-mortem studies. The overall estimated prevalence across both groups of mentioned studies was estimated by Ezzat to be 16.7% [1]. Clinically relevant adenomas, however, occur in about 78–94 cases per 100,000 population [2, 3]. Although the majority of pituitary adenomas are sporadic, a small number of them (about 5%) occur in a familial setting, predominantly in multiple endocrine neoplasia type 1 (MEN-1) and Carney complex (CNC) [2, 4–9].

Rarer hereditary forms of pituitary adenomas may be a component of multiple endocrine neoplasia type 4 (MEN-4), pheochromocytoma/paraganglioma syndrome (3PAs syndrome), and X-linked acrogigantism (X-LAG) [4, 7, 8].

In the late 1990s, several cases of family-bound isolated pituitary adenomas (FIPA), unrelated to the syndromes mentioned above, were described. Patients within the same family could have the same pituitary tumour type (homogenous FIPA), or different types (heterogeneous FIPA) in all affected members [5, 7, 8]. The clinical course of FIPA differs significantly from sporadic cases and is characterised by a larger tumour size and younger patient’s age at the moment of recognition [7, 8, 10].

Isolated familial somatotropinomas (IFS), related only to FIPA patients with acrogigantism, have been also well described. Daly et al. [10] performed a retrospective study of the incidence of FIPA in 22 European reference study centres. Among all FIPA cases, IFS accounted for 18%.

According to the same study, FIPA cases presented 1.9–3.2% of the total patients’ population with pituitary adenomas. Prolactinomas (39.9%) and somatotropinomas (34.1%) were the most prevalent phenotypes within this familial group. Clinically non-secreting adenomas (NS), including gonadotropinomas, accounted for 20.2% and ACTH-secreting for 5.8% of FIPA [10].

Mutations of aryl hydrocarbon receptor-interacting protein (AIP) gene of variable penetrance have been identified as responsible for pituitary adenoma predisposition [5, 7, 8, 11]. They account for 15–20% of...
FIPA families, and they are found in about half of the patients with familial acromegaly, but they are very rare in sporadic cases [5, 7, 8, 12, 13]. AIP-associated somatotropinomas and prolactinomas are larger and more aggressive, occurring at an earlier age than in AIP mutation-negative cases [7, 8].

**Objectives**

The aim of this study is to present four families in which two closely related persons were diagnosed with pituitary adenomas. Probably these cases, in the absence of other components of endocrine syndromes, are clinical manifestations of family isolated pituitary adenomas.

**Material and methods**

The authors retrospectively analysed medical and family histories, the imaging pictures (pituitary MRI/CT), and hormonal tests of the eight patients within four families with anterior pituitary tumours and no evidence of other genetic syndromes.

**Results**

**Family 1.**

*63-year-old sister A.B.* Acromegaly was recognised at the age of 55 years based on typical symptoms (present already 10 years prior to the diagnosis), elevated IGF-1, and lack of GH suppression during OGTT. MRI revealed a pituitary macroadenoma (13 × 10 mm) destroying sella turcica and infiltrating sphenoid sinus. Neither cavernous sinus nor optic chiasm were affected. For the three years after the diagnosis was established, the patient was treated with long-acting somatostatin analogues, which was followed by transsphenoidal adenomectomy. The postoperative immunohistopathology presented: GH (+), PRL (+), ACTH (–). After the surgery, the patient underwent non-radical transsphenoidal tumour resection preceded by three injections of long-acting somatostatin analogue. After transient improvement, the clinical and laboratory acromegaly symptoms relapsed and the MRI confirmed the recurrence/remnant of pituitary tumour (13 × 9 mm). After a few months of somatostatin analogue treatment, the patient underwent a second, non-radical transsphenoidal adenomectomy. The postoperative immunohistopathology presented: chromogranin (+) and GH (+). At present, due to persistent active acromegaly, the patient receives long-acting somatostatin analogue.

**Family 2.**

*Brother S.G.* The pituitary tumour was recognised at the age of 70 years. CT revealed a large pituitary macroadenoma. The patient has undergone transsphenoidal tumour resection, which was followed by hormonal pituitary deficiencies in corticotropin, thyrotrophic, and gonadotropic axes. Therefore, the patient received chronic substitution therapy. The postoperative tumour immunohistopathology presented: chromogranin (+) — strong wide reaction, PRL (+) — strong wide reaction, GH (+) — weak focal reaction, and ACTH (–). The patient died at the age of 72 years due to cardiovascular disease.

*66-year-old brother MG.* Pituitary macroadenoma was diagnosed at the age of 39 years. CT confirmed enlargement and deepening of sella turcica, without the destruction of bone structures, with the presence of a hyperdense area, non-homogeneous after contrast application, corresponding to pituitary adenoma. Preoperative tests did not reveal hormonal abnormalities except gonadotropic hypofunction. After the total transsphenoidal adenomectomy, secondary adrenal and thyroid insufficiencies developed — the patient receives chronic substitution treatment. In postoperative histopathology chromophobic adenoma was confirmed.

**Family 3.**

*80-year-old father J.P.* Pituitary macroadenoma (24 × 32 × 24 mm) was recognised in MRI at the age of 73 years. The tumour was compressing the hypothalamus and the floor of the III ventricle, infiltrated left cavernous sinus, and left internal carotid artery and was causative of bitemporal vision deficit, headaches, and dizziness. No clinically evident hormonal activity of the tumour was stated. The patient underwent non-radical transsphenoidal tumour resection. The postoperative tumour immunohistopathology presented: chromogranin (+), PRL (+), GH (+), and ACTH (–). After the surgery, the hormonal function of the pituitary remained normal.

*54-year-old daughter M.M.* The pituitary tumour was detected at the age of 45 years. Preoperative MRI revealed pituitary macroadenoma (43 × 33 × 28 mm)
infiltrating the right cavernous sinus and compressing the right internal carotid artery, encompassing suprasellar cisterns, compressing the optic chiasm, and protruding towards the sphenoid sinuses. The tumour caused bitemporal vision impairment. The hormonal tests did not reveal hormonal activity of the tumour; however, slight hyperprolactinaemia and hypogonadotropic hypogonadism were stated. The patient underwent transphenoidal adenomectomy — postoperative immunohistopathology revealed the following: chromogranin (+), PRL (+), ACTH (+), and GH (-). After the surgery, thyrotropin and adrenocorticotropin deficiencies developed, and gonadotropin deficiency with hyperprolactinaemia persisted. The patient receives substitution therapy and bromocriptine. The control MRI does not show the tumour recurrence.

**Family 4.**

39-year-old man R.S. Acromegaly was detected at the age of 32 years after only two years of typical symptoms with the diagnosis based on elevated GH and the presence of pituitary macroadenoma (35 × 35 × 30 mm) in MRI. The tumour was protruding towards the sphenoid sinus, infiltrated the cavernous sinuses and internal carotid arteries, proceeded to the III ventricle, and partially encompassed the anterior cerebral arteries. The patient underwent non-radical transphenoidal adenomectomy complicated by liquorrhoea, which required reoperation. The postoperative examination revealed: GH (+), PRL (-), ACTH (-), TSH (-), FSH (-), LH (-), α-subunit (-), MIB1 < 1%, and sstr2A (+) — weak cytoplasmic reaction. Since the surgery, the patient receives hydrocortisone in substitution therapy. Based on postoperative hormonal evaluation, the persistence of active acromegaly (high IGF-1 level and lack of GH suppression in OGTT) was confirmed and secondary hypothyroidism and hypogonadism were detected. The control MRI revealed a tumour remnant (31 × 24 × 10 mm); however, the patient was disqualified from another pituitary surgery. Despite octreotide LAR treatment followed by lanreotide Autogel therapy, disease control was not achieved.

36-year-old A.L. — daughter of his mother’s sister. Pituitary microadenoma with the focus of past bleeding was detected in MRI at the age of 25 years; the examination was performed because of amenorrhea and galactorrhoea. Therefore, the patient was treated effectively with bromocriptine, became pregnant spontaneously two times, and gave birth to two healthy children. Since the second pregnancy, she discontinued dopamine agonist therapy, which resulted in hyperprolactinaemia relapse but with stationary pituitary images in MRI at the same time. Treatment with quinagold was introduced for 1½ years; however, for a few months now the patient has discontinued the therapy. Despite this fact, a recently performed control MRI revealed significant reduction in tumour size. The pituitary hormonal function remains normal.

**Discussion**

Diagnosis of family isolated pituitary adenomas is based on the finding of at least two cases of pituitary adenoma in the same family, after excluding other familial syndromes. At the same time, it is worth emphasising that sporadic pituitary adenomas are common in the general population, so there is the possibility of two sporadic pituitary tumours in one family, also in the presented families.

Patients within the same family can present homogeneous or heterogeneous FIPA types [5, 7, 8]. In the cases described by us, we can talk about the homogeneous type in three families (somatotropinomas in Family 1 and clinically non-secreting tumours in Family 2 and 3). In Family 4 a heterogeneous type was recognised because one patient had somatotropinoma, and his cousin — prolactinoma.

The rank order of frequency of pituitary adenoma subtypes among FIPA patients is approximately: prolactinomas (37.5%) > somatotropinomas (35.0%) > NS (14.5%) > somatolactotropinomas (6.4%) > Cushing disease (2.9%) > gonadotrophinomas (2.0%) > plurihormonal tumours (1.2%) > thyrotropinomas (0.5%) [5, 10, 14].

Comparing the frequency of pituitary adenoma subtypes in the general population to FIPA, the proportion of prolactinomas in FIPA is lower (37.5% vs. 66%), whereas the incidence of somatotropinomas in FIPA is much higher (35% vs. 13%) [2, 5, 10, 14].

Prolactinomas in FIPA are most frequently microadenomas occurring in premenopausal women, whereas males with prolactinomas comprise a minority of cases, but frequently present with macroadenomas (similarly as in sporadic cases). However, FIPA prolactinomas appear to be more aggressive than sporadic adenomas [10].

Somatotropinomas in FIPA are almost equally divided between heterogeneous and homogeneous FIPA, the latter called isolated familial somatotropinomas (IFS). IFS cases present larger diameter and an earlier age of onset of the tumours [10].

FIPA families with Cushing disease, TSH secreting adenomas, and secreting gonadotropinomas are too rare to be compared with sporadic cases [5]. We did not observe such cases, either.

In our study, clinically non-secreting tumours dominated. They were recognised in four members within two families (Family 2 and 3). These patients did not present any clinical nor laboratory markers...
of hormonal activity of the tumour (patient M.G. from Family 2 developed hypogonadotropic hypogonadism, and patient M.M. from Family 3 presented slight hyperprolactinaemia and hypogonadotropic hypogonadism).

However, in one patient from Family 2 and both patients from Family 3 postoperative immunohisto-pathological examination revealed the presence of certain hormones in the tumour cells, so despite the lack of clinical and laboratory signs of activity they were in fact hormonally active adenomas. Unfortunately, despite the performed surgical procedures, the lack of postoperative immunohistopathological evaluation in the second member in Family 2 prevents accurate assessment of the nature of the tumour.

NS FIPA have a significantly younger age at onset and are more frequently invasive than sporadic cases [10]. Three of our NS cases were detected after the age of 40 years (including two cases > 70 years); only one man was diagnosed at the age of 39 years. All four cases were macroadenomas and, with the exception of the youngest patient, showed expansion to neighbouring structures. It is therefore likely that they are also FIPA cases.

Somatotropinomas were second in frequency in the families described. Familial acromegaly present in the two sisters in Family 1, as we have previously discussed in an earlier dissertation [15], is probably the clinical manifestation of IFS. Neither of the sisters nor their relatives developed features of other genetic syndromes. On the other hand, the diagnosis was made later (at age 55 and 59 years) than the median age of recognition of IFS [16]. Furthermore, no AIP mutation was found in the case of sister A.B., in whom the analysis was carried out. But taking into account that the proportion of somatotropinomas in the general population is much lower than in FIPA, it is highly likely that our first family presents IFS despite absence of AIP mutation.

Family 4 presents heterogeneous type FIPA. The young man with macroadenoma secreting growth hormone was diagnosed at the age of 32 years, had expansive macroadenoma, and was refractory to treatment. His cousin was diagnosed with microprolactinoma in his 25-year-old cousin. In addition, in five cases, adenomas were invasive (infiltrating surrounding structures).

The prevalence of AIP mutation in unselected sporadic pituitary adenoma is very low (0–3%) [17, 18]. It appears to have slightly higher frequency in sporadic acromegaly (8%) [17], in sporadic pituitary macroadenomas in children (20%), and in young adults < 30 years old (11.7%) [19].

Because pituitary adenomas associated with AIP mutations occur in a much younger population and are larger and more aggressive than non-mutated sporadic cases, they raise clinical challenges to successful treatment. Therefore, the identification of carriers could permit potentially curative treatment [5, 7, 8].

Currently, searching for mutations in the AIP gene in patients in whom pituitary tumour was detected after the age of 40 years is controversial. In a large group of such patients, either no mutations [13] or only in a few of them (in 10% and 5% for the patients diagnosed after the age of 40 and 50 years, respectively) were diagnosed [5].

Considering the indications for genetic testing in our patients, a relatively late age at the moment of diagnosis of pituitary adenoma speaks against the studies towards AIP mutation in most of them. Besides, five out of seven patients who had been operated were cured after surgery. On the other hand, in three families (1, 2, and 3), the possibility of FIPA may be suggested by the presence of two cases of pituitary adenoma among first-degree relatives, and the large tumour size because in all patients macroadenomas were described. In Family 4, in turn, although in further-degree relatives, heterogeneous pituitary adenomas were diagnosed at the youngest age: acromegaly in a 32-year-old man and microprolactinoma in his 25-year-old cousin. In addition, in five cases, adenomas were invasive (infiltrating surrounding structures).

The strongest indication for testing for AIP gene mutation was for two sisters with acromegaly. In one of them (A.B.), the study was conducted. However, AIP gene deletion or insertion were excluded. The possibility of having a mutation in the remaining families is much lower.

Conclusions

Familial isolated pituitary adenomas are more common than was previously thought; therefore, specific questioning regarding family history should be a part of the workup of all patients with pituitary adenomas.

References


