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Familial acromegaly — case study of two sisters with acromegaly

Rodzinne występowanie akromegalii — opis przypadku dwóch sióstr z akromegalią

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Abstract

In the majority of cases, acromegaly is sporadic. However, it can also occur in a familial setting as a component of MEN-1, MEN-4, Carney complex (CNC) or as the extremely rare syndrome of isolated familial somatotropinoma (IFS), the latter belonging to familial isolated pituitary adenomas (FIPA). The diagnosis of IFS is based on the recognition of acromegaly/gigantism in at least two family members, given that the family is not affected by MEN-1, MEN-4 or CNC.

The authors present a case study of two sisters: a 56 year-old patient (case no. 1) and a 61 year-old patient (case no. 2). In both sisters, acromegaly was recognised in the course of pituitary macroadenoma. Neither of the sisters showed features of MEN-1, MEN-4 or Carney complex.

The authors suppose that the presented cases are manifestations of IFS. However, this diagnosis has not been confirmed yet because of the poor availability of genetic tests. **(Pol J Endocrinol 2011; 62 (6): 554–557)**

Key words: *familial acromegaly, isolated familial somatotropinoma, Carney complex, MEN syndrome*

Streszczenie

Akromegalia w większości przypadków ma charakter sporadyczny, może jednak występować rodzinnie jako element zespołu MEN-1, MEN-4 czy zespołu Carneya (CNC) oraz wyjątkowo jako izolowany rodzinny guz somatotropinowy (IFS), należący do grupy rodzinnych izolowanych gruczolaków przysadki (FIPA). Rozpoznanie IFS opiera się na stwierdzeniu co najmniej dwóch przypadków akromegalii/gigantyzmu w rodzinie, która nie jest obciążona zespołem MEN-1, MEN-4 czy zespołem Carneya.

Autorzy przedstawiają historie dwóch sióstr: 56-letniej (przypadek nr 1) i 61-letniej (przypadek nr 2), u których rozpoznano akromegalię w przebiegu makrogruczolaków przysadki mózgowej, przy braku innych zaburzeń endokrynologicznych typowych dla zespołu MEN-1, MEN-4 czy zespołu Carneya. Autorzy sądzą, że przedstawione przypadki są manifestacją IFS, czego jednak ze względu na małą dostępność do badań genetycznych dotychczas nie potwierdzono. **(Endokrynol Pol 2011; 62 (6): 554–557)**

Słowa kluczowe: *rodzinna akromegalia, izolowany rodzinny guz somatotropinowy, zespół Carneya, zespół MEN*

Introduction

Pituitary adenomas occur with an annual incidence of 20 cases per million, with adenomas derived from somatotrophs and secreting GH accounting for 3 cases per million [1]. Although the majority of GH-secreting adenomas are sporadic, a small number of them (about 5%) occur with a familial aggregation. Within family-related adenomas, more than half are due to MEN-1 (multiple endocrine neoplasia type 1), MEN-4 (multiple endocrine neoplasia type 4) or Carney complex [2]. In the late 1990s, several cases of family-bound isolated pituitary adenomas, unrelated to the syndromes mentioned above (non-MEN1/CNC familial isolated pituitary adenomas — FIPA), were described. The clinical course of FIPA differs significantly from sporadic cases and is characterised by a larger tumour size and younger patient age at diagnosis [3–5]. Daly et al. performed a retrospective study of the incidence of FIPA in 22 European clinics of medical universities. Among all FIPA cases, isolated familial somatotropinomas (IFS) accounted for 18%. Patients with IFS presented with more aggressive tumour growth and were ten years younger at the moment of establishing diagnosis, compared to the patients with sporadic adenomas [3].

Both the clinical picture and genetic background of MEN-1 have been well recognised. MEN-1 syndrome is inherited in an autosomal dominant pattern. Its most frequent clinical components are: hyperparathyroidism (95%), endocrine enteropancreatic tumours (54%) and pituitary adenomas (42%). Among pituitary adenomas, 9% secrete growth hormone and cause

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acromegaly, with mean recognition between 30 and 50 years of age [5].

Carney complex exhibits an autosomal dominant inheritance pattern. It is characterised by cutaneous and cardiac myxomas, spotty pigmentation, schwannomas and primary pigmented nodular adrenocortical disease (PPNAD) accompanied by ACTH-independent Cushing's syndrome**.** Hypersecreting tumours of the thyroid, testes and ovaries can also be present. Somatotropinomas are the commonest pituitary adenomas in CNC, accounting for 10–21% of all of them. The patient's age at diagnosis varies between 11 and 27 years [6, 7].

IFS is defined as the occurrence of at least two cases of acromegaly or gigantism in a family that does not exhibit MEN-1, MEN-4 or CNC [8, 9]. It is an extremely rare syndrome of family-related pituitary adenoma. To date, it has been recognised in fewer than 90 families in the world [2, 4, 10–13].

The aim of this study was to present a study of two sisters in whom clinical manifestation of acromegaly is very probably due to isolated familial somatotropinoma.

Case report

Case no. 1 (patient A.B.)

Acromegaly was recognised in December 2009. At the time of diagnosis, the patient was 55 years old. However, typical symptoms including hands and feet enlargement, acral, nose, tongue, mandible enlargement and excessive sweating were already present ten years prior to establishing the diagnosis.

For a few years before the diagnosis was made, the patient had been treated for degenerative arthritis of the knees and of the vertebral column and for carpal tunnel compression syndrome. She complained of snoring and sleep apnoea. At the moment of recognition, the oral glucose tolerance test (OGTT) was performed and glucose intolerance was detected. Furthermore, the presence of nodular goitre was detected. The diagnosis of acromegaly was confirmed on the basis of laboratory tests (increased GH and IGF-1 levels, lack of suppression of GH level after OGTT). Magnetic resonance imaging revealed a macroadenoma of the pituitary gland with dimensions of 13 × 10 mm. Neither pituitary insufficiency nor visual impairment were present at that moment. The test with 100 ug of octreotide acetate was performed and the result revealed the reduction in GH level of about 90%. Thus, following the recommendations of the Polish Society of Endocrinology [14], the patient was qualified for treatment with the long-acting release somatostatin analogue — octreotide LAR (Sandostatin LAR) in order to prepare her for surgery. Since February 2010, every four weeks, the patient has received 20 milligrams of Sandostatin LAR intramuscularly with good effect (improved general feeling, cessation of hyperhydrosis, decreased oedemas and normalization of GH and IGF-1 levels). No change in tumour size in MRI was observed. During therapy, particularly directly after each injection, an increased rate of defecations including diarrhoea was observed. Furthermore, the development of gallstones was revealed. As these problems were not present before treatment with Sandostatin LAR, they should be considered as side effects of the therapy.

Case no. 2 (patient B.W.)

The 61 year-old patient, the five years older sister of the patient described in case no. 1, was hospitalised in our Clinic in December 2009 because of recurrence of acromegaly symptoms. The initial diagnosis of acromegaly had been made one year earlier at another clinic, the patient being then 59 years old. For eight years before the diagnosis was confirmed, gradual hand and feet enlargement, excessive sweating, headaches, joint pain, soft tissue overgrowth and skin thickness had been observed. At the moment of recognition, the increased level of IGF-1 and lack of GH suppression after OGTT were revealed. MRI showed a non-homogenous tumour 15 × 16 × 13 mm, compressing cavernous sinuses. The patient received three injections of Sandostatin LAR every four weeks and transsphenoidal microsurgical extirpation was performed. After the surgery, an improvement of general feeling was observed. Furthermore, the patient noticed a reduction in excessive sweating, decreased oedemas of the extremities and headache cessation, which was accompanied by normalisation of GH and IGF-1 levels. However, after a four week remission, the patient complained of a recurrence of hyperhydrosis and other acromegaly symptoms. Control laboratory tests revealed an increase in IGF-1 level. MRI performed four and eight months after the surgery showed recurrence/the residual tumour with dimensions of 13 × 9 mm without expansion to cavernous sinuses or extension to the optic chiasm. Therefore, the patient received three injections of 30 mg of octreotide LAR every four weeks in order to prepare her for her reoperation. At that moment, the patient was admitted to our clinic for the first time. The laboratory tests performed in the ward did not reveal any abnormalities in the hormonal function of the pituitary. The normal value of GH was considered to be the result of effective treatment with somatostatin analogue performed prior to hospitalisation. During the patient's stay in the clinic, nodular goitre with normal thyroid function, colon polyps and gallstones were detected. Following the recommendations of the Polish Society of Endocrinology [14], the patient was offered to continue a somatostatin analogue therapy before the second operation for the adenoma, but she declined. Therefore, she underwent

transsphenoidal reoperation in December 2009. It was followed by the development of postoperative diabetes insipidus. The patient now receives somatostatin analogue due to the fact that clinical and laboratory determinants of active acromegaly are present.

Discussion

The majority of somatotropin tumours occur sporadically. They develop as the result of monoclonal proliferation of somatotrophs caused by somatic mutation. The molecular background of this process remains unclear [15]. Familial acromegaly, as mentioned in the introduction, is very rare. When suspected, MEN-1, MEN-4, CNC or IFS have to be considered. At the moment, the diagnosis of IFS is made by exclusion of the remaining familial syndromes based on the clinical picture and genetic tests.

Among IFS patients analysed by Frohman, the median age at diagnosis was 25 years (64% of cases with onset before 30 years of age). In 42% of families, the disease appeared only among members of one generation, whereas in the remaining families it was expressed across multiple generations. Furthermore, it was 1.5 times more frequent in women than in men. In 88 cases, the disease was recognised in the course of macroadenoma, and only in two cases microadenoma was revealed. Gigantism was described in 25% of cases [10]. According to the data collected from available literature by Gadelha, in around 70% of IFS patients, the diagnosis occurred before the age of 30 and the disease was inherited in an autosomal-dominant pattern with incomplete penetrance [9].

Familial acromegaly present in the two sisters A.B. and B.W. is most probably the clinical manifestation of isolated familial somatotropinoma. On the one hand, the diagnosis was made later (at age 55 and 59) than the median age of recognition of IFS. On the other hand, neither of the sisters nor their relatives present MEN-1, MEN-4 or CNC features. Furthermore, the incidence of somatotropin tumours in MEN-1 or CNC is not very high, with frequencies of 6–9% [5] and 10% [2] respectively. The recognition of IFS in our patients was based on clinical evaluation only because genetic tests that could exclude MEN-1 or CNC were unavailable.

MEN-1 syndrome is due to a mutation in the tumour suppressor MEN-1 gene located on chromosome region 11q13. The gene codes menin - the protein which controls the growth and differentiation of the cells. Mutation of the menin gene results in the loss of the gene's function; and menin deficiency, in turn, promotes tumour development in certain endocrine tissues. A few hundred mutations of this gene have been identified to date [16, 17]. Indications for screening for these mutations include: the coexistence of at least two tumours typical of MEN-1; the presence of at least one tumour typical of MEN-1 in patients less than 30 years old; and the recognition of gastrinoma or the presence of multiple tumours of parathyroid glands. Therefore, a suspicion of IFS, as in the case of the two sisters, is not a formal indication for screening for these mutations. Furthermore, the lack of mutation on chromosome 11q13 is not tantamount to excluding MEN-1 syndrome. In about 20% of patients with classic MEN-1 disorders, no mutation in chromosome 11q13 is present.

In 2006, MEN-4 syndrome was described for the first time. It is characterised by germline mutation in the suppressor p27 ^{Kipl} gene. Patients show the MEN-1 phenotype but they do not carry MEN-1 gene mutation [18, 19].

According to the current state of knowledge, CNC can be caused by a mutation in the tumour suppressor gene located on chromosome region 17q23-24. The gene codes type 1 alpha regulatory subunit of protein kinase A (PRKAR1A). CNC can be also related to a mutation in a yet unidentified gene located on chromosome region 2p15-16. The presence of one of these mutations leads to the enhancement of the signal transmitted by GHRH and to the proliferation of somatotrophs. Most commonly, the syndrome develops in the first or second decade of life [16, 20, 21]. In the literature available, no recommendations have been found concerning performing genetic tests when CNC is suspected.

Screening for mutations responsible for IFS seems to be even rarer. This is probably due to the fact that only a few hundred cases of both CNC and IFS have been described to date.

The genetic basis of IFS, which is the least common cause of familial acromegaly, has not yet been fully explained. Previously, IFS and some cases of sporadic acromegaly were connected to the loss of heterozygosity at chromosome 11q13. This chromosome plays a role in MEN-1 pathogenesis as well. However, in the case of IFS, no mutation typical of MEN-1gene is present in this chromosome [22, 23]. In later years, another suppressor gene linked to chromosome region 11q13-13.3 and related to IFS but not to MEN-1 pathogenesis has been identified. It has been suggested that this gene plays a role in the control of cells' proliferation. And a potential second locus at chromosome region 2p16-12 was considered to have a similar function [9]. More recently, other researchers have narrowed the region of analysis to 2.21 Mb on chromosome 11q13.3 and, according to them, this locus could be related not only to IFS but also to sporadic adenomas secreting GH [24]. In recent years, further research has confirmed the connection

of IFS to germline mutation of AIP (aryl hydrocarbon receptor-interacting protein) gene located at chromosome region 11q13. This mutation has been seen in approximately 40% of studied IFS families [13, 25, 26]. Furthermore, the presence of this mutation was related to development at a younger age and of larger adenomas and characterised by more aggressive course compared to sporadic somatotropin-secreting adenomas [4, 13]. The presence of AIP gene mutation is found in about 15% of all FIPA cases [27].

The sisters described in our pair of case reports do not present the clinical features typical of MEN-1 or Carney complex. However, in order to confirm the diagnosis of IFS, conducting genetic tests should be considered. Although in the majority of cases, IFS concerns two family members [28], it is theoretically possible that in one family two sporadic somatotrophic adenomas in two relatives could coexist. However, owing to the fact that acromegaly in the general population is very rare, such a situation does not seem likely. Besides, in the available literature, no such case has been found. Therefore, most probably, the acromegaly present in the sisters described in our case reports is a clinical manifestation of IFS.

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