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NEUROENDOCRINOLOGIA

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Indice

FAMILIAR PITUITARY TUMORS

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INTRODUCTION

Familial neoplasias have helped clinicians to elucidate molecular mechanisms of disease, in a cognitive process sequentially involving linkage analysis, mapping, and characterisation of pathogenically relevant genes. Familial pituitary adenomas have currently been characterised in the settings of three known syndromes. Multiple Endocrine Neoplasia type 1 (MEN1) is a syndrome associating pituitary adenomas, parathyroid tumors and tumors of the endocrine gut. This autosomal dominant condition is linked to mutation of the menin gene at 11q13. To date almost 300 families have been described and genetically characterised. In some 5-10 % of cases, no mutations are found among the ten coding exons, although clinical phenotype is present in these patients. Prolactinomas are usually the most likely phenotypes encountered in MEN1. Among series of sporadic adenomas, prevalence of MEN1 is only 3-5% of cases[1]. Carney Complex (CNC) is a familial multiple neoplasia and lentiginosis syndrome with features overlapping McCune Albright syndrome. In 1985 Carney and colleagues described in 40 patients cardiac myxomas, skin lesions (both myxomas and pigmented lesions), primary pigmented nodular adrenocortical disease, growth hormone secreting pituitary adenomas, testicular tumors and myxoid fibroadenomas of the breast[2]. More recently thyroid tumors have also been described. Genetic defect at Ch2p16 and Ch17q24 had been implicated in the pathogenesis of CNC. Molecular pathway that involves a defective cAMP-dependent protein kinase (PKA) type 1-regulatory subunit had been made responsible for tumorigenesis in CNC. The incidence of acromegaly in CNC has been estimated at less than 10%, although evidence of somatomammotropic hyperplasia and hyperprolactinemia are increasingly found in prospective series(3). Finally, Neurofibromatosis type 1 (NF1) also known as Von Recklinghausen disease, should be considered as a third differential diagnosis of familial pituitary syndromes. This is an inherited autosomal dominant condition present in 1/3000 individuals. A GTPase mutation has been associated in the development of schwanomas and pigmented cutaneous lesions. A tumor suppressor gene coding for a protein neurofibromin has been located in Ch17q11.2. Some reported cases of prolactinomas and non-functional pituitary adenomas have been described associated with neurofibromatosis[4]. When one can reasonably exclude these three syndromes, the terminology of familial isolated pituitary adenomas (FIPA) should be used. Absence of MEN1 syndrome has been described in nearly 72 familial isolated somatotroph (GH), 10

familial lactotroph (PRL) and two brothers with non-functional (NF) adenomas[5]. The aim of this study is to present, in a large series of 54 familial cases, clinical and genetic arguments suggesting that FIPA are an entity distinct from MEN1 syndrome and probably, a new entity of pituitary tumorigenesis.

PATIENTS AND METHODS

A retrospective and co-operative international study including Belgium, Italy, France and Germany was undertaken including data from 1984 to 2000 to identify no consanguine families with two or more affected siblings presenting with GH, PRL (1 pituitary cancer), gonadotroph (LH/FSH), corticotroph (ACTH) and NF FIPA. Patients underwent a yearly physical examination and biological studies to assess the presence of MEN 1 and clinically exclude other familial syndromes. Clinical features, radiological and secretion status of pituitary adenomas were retrieved in all patients. Acromegalic patients had echocardiographic studies to assess the presence of cardiac myxomas related to CNC. Exons 1 to 10 of MEN1 gene were sequenced in leukocytes of at least one sibling. LOH with microsatellite markers D11S449, D11S1883 and D11S1889 was tested in 6 cryopreserved tumoral tissue DNA of operated patients, as previously described[6].

RESULTS

Population

There were 25 pedigrees and 54 affected members, 17 males and 37 females. Mean age at diagnosis was 36±14 years. Follow-up was 8.4±7 years. Second siblings were diagnosed earlier than their parents (25±7 vs 50±12 years, $p<0.05$). During follow-up, repeated measures of calcium and PTH remained normal in all patients. Gastrine, insuline and polypeptide P were normal in 30 screened cases. No myxomas were detected in acromegalics by echography. There were 22 PRL and one malignant PRL (2M/21F), 20 GH (8M/12 F), 8 NF (5M/3F), 2 ACTH (2F), and one LH/FSH-secreting adenomas (1M). Only 51/54 tumors were identified by pituitary MRI (38 macroadenomas/13 microadenomas) and 34/54 tumors were available for immunohistochemical studies. Sequential analysis of 23 blood samples and 6 tumors of patients were available for genetic studies. No mutation of MEN1 gene was observed in these samples. Additionally a loss of one Chr 11 was observed in one GH tumor.

Prolactinomas

Data of the malignant case has been previously reported[7]. Briefly, this man had a brother with a NF pituitary adenoma. He underwent pituitary surgery four times and was irradiated several times for an invasive prolactinoma. A fifth operation failed to individualise a residual tumor in spite of a level of PRL of 1400000 mg/L. An epidepride hole body scintigraphy detected several bone metastases, then confirmed by MRI.

Cabergoline at a dose of 1mg/day failed to control hyperprolactinemia and malignant behaviour. The patient died of disseminated malignancy. There were 10 macroadenomas and 12 microadenomas. An invasive pattern (suprasellar extension or cavernous invasion) was seen in 13/23 cases. Mean tumoral diameter of this group was 12.8±7.5 mm. Mean serum prolactin, excluding the malignant case was 4777±5100 mU/L.

Acromegaly

There were 19 macroadenomas and 1 microadenoma. All of them were invasive. Mean tumoral diameter of this group was 34.5±14 mm. Mean IGF1 was 1093±1073 mg/L and GH= 28±22 mg/L. Pathological studies evidenced 6 mixed GH/PRL tumors and 2 silent GH tumors. Three giants patients were diagnosed with a mean age of 18 years (range 17-19). There were 3 giant tumors with a mean diameter of 49 mm (40-52) among adult patients diagnosed with a mean age of 30 years (range 19-49). When considering GH secretion and pathological features in both subgroups there were no significant differences compared to the other acromegalics. Giant tumors had as expected a worst surgical outcome.

Non-functioning adenomas

In this group there were only 8 macroadenomas. An invasive pattern was seen in all cases. Mean tumoral diameter of this group was 26±6.4 mm. NF and acromegalics adenomas were significantly hugger when compared to prolactinomas ($p<0.05$).

Other tumoral phenotypes

There were two Cushing's disease (2F) harbouring microadenomas and one male with a gonadotrophinoma immunostainning LH and FSH in more than 10 % of cells.

DISCUSSION

This is the largest series documenting familial isolated cases harbouring multiple phenotypes. Most of our knowledge about FIPA comes from acromegaly. This is a recognised entity, with an autosomic dominant inheritance with variable penetrance, distinct from other familial pituitary syndromes. Others and we have reported nearly 25 families and 72 affected sibling's[8]. GH/TSH/alpha-subunit adenoma in a familial setting has been described once[9]. Genetic defect is presently unknown. Tamburrano suggested a relationship between acromegaly and HLA, as two affected sibs were haploidentical[10]. Benlian speculated over possible genomic imprinting effects to explain an excess of acromegaly in the maternal branch of published pedigrees[11]. Some other groups had found LOH in Ch 11 and 2, thus partly confirming our findings in one familial acromegalic tumor[12]. No animal model of acromegaly is known, but there is an inherited form of early onset lactotroph adenoma in the rat in which more than 50% of siblings are

affected[13]. In Israel, three pedigrees of familial isolated prolactinomas have been reported in 1995, before clonation of the MEN1 in 1997[14]. More recently the same group did not find MEN1 mutations in 2 families of isolated prolactinomas[15]. We also have published a Belgian family with two affected sibs harbouring prolactinomas, not related to MEN1 gene mutation[16]. Moreover, one Japanese family of NF FIPA[17] and two sisters with Cushing's disease were also described[18]. To our knowledge, gonadotrophinomas have not been described in a familial setting until now. Based on the prevalence of sporadic pituitary adenomas, the chance occurrence of acromegaly or Cushing disease in a same family seems very small. Most of our familial cases of acromegaly concern pedigrees with 2 or 3 affected relatives. One of us (BT) is studying a family in Borneo with 5 acromegalic sibs. In this big family, linkage analysis of 33 screened subjects is know in progress (unpublished observations). Similar arguments can be raised in more prevalent phenotypes, like sporadic prolactinomas or NF adenomas. Although most of our familial cases of prolactinomas include two affected sibs, we are confident again that this is not chance occurrence. For instance, there is an Israeli family with 3 prolactinomas[14]. In all these families, dominant inheritance with reduced age dependent penetrance seems the most parsimonious model to explain the recurrences. Interestingly, in this series as in the literature, early onset of FIPA seems to be the rule. In accordance with these findings, we have observed anticipated apparition of symptoms in the second generation. Anticipation in familial cases is a genetic phenomenon usually explained by Knudson's two hits hypothesis. Whether our familial pituitary adenomas are just a variant of MEN1 with low expression of other endocrine affections or constitute a new entity is a question difficult to answer with our present knowledge. From a clinical point of view, we had followed-up for a long period of time these patients. We did not observed new endocrine tumors nor our data suggests a linking to other familial syndromes. From a genetic basis, somatic and germinal DNA analysis of exons 1 to 10 suggest this is another entity not linked to mutation of currently known MEN1 gene. As knowledge about MEN1 gene continuously progresses, i.e. novels transcripts of MEN1 which vary in the content of their 5'-untranslated region may represent biologically important transcripts and their role in mutation should be further studied[19], our study sets the necessary groundwork for genetic linkage analysis to have a complete understanding of the genetic defect of FIPA.

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PHARMACOLOGICAL THERAPY OF ACROMEGALY

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Acromegaly is a debilitating disorder resulting from excessive secretion of growth-hormone (GH), usually caused by somatotroph adenoma of the pituitary gland. Pituitary surgery is the first line treatment in acromegalic patients, but only half of them are cured according to strict biochemical criteria. The presence of somatostatin receptors on GH-secreting pituitary adenomas allows treatment with somatostatin analogues in most acromegalic patients. Their suppressive effects on somatotroph hypersecretion are reversible. Therefore, long-acting release forms avoid the drawbacks of repeated subcutaneous injections or continuous infusion using a pump. Long-acting formulations have been produced by the incorporation of octreotide or lanreotide in either microspheres or microparticles of biodegradable polymer, and these depot formulations are injected intramuscularly every month or 7-14 days, respectively. In short and long-term clinical studies, Sandostatin LAR and SR Lanreotide 30 mg achieve a control of GH hypersecretion similar to that previously obtained with sc daily injections or continuous infusion of octreotide. Up to 50 % of acromegalic patients may be considered as «cured» (GH < 2 µg/l and age-sexe-normalized IGF-I) during such medical treatment. During somatostatin analogue treatment, the main side effects reported by the patients are minor digestive problems such as diarrhea, mild abdominal pain, nausea lasting less than 48-72 hours after im injections. In most patients the frequency of gastrointestinal side effects improve during long-term treatment, and do not lead to the interruption of the therapy. Mild and transient pain at the injection site with a local induration is an other side effect recorded with im injections of long-acting somatostatin analogues. The most potentially important side effect during somatostatin analogue treatment is an increased tendency to gallstone formation, but the incidence of new gallstone seems to be reduced during long-acting somatostatin analogue administration. In conclusion, long-acting somatostatin analogues are effective and well tolerated in most acromegalic patients. However, new long-acting formulations of somatostatin analogues may improve the quality of life, and new somatostatin receptor analogues may achieve a better control of GH hypersecretion in a larger number of acromegalic patients.