Clinicopathologic features of familial pituitary adenomas

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Abstract

Pituitary adenomas are common neoplasms. Initially considered as sporadic tumours, some of them are associated with familial syndromes such as familial isolated pituitary adenoma, multiple endocrine neoplasia type 1 and type 4, X-linked acrogigantism syndrome, Carney complex, pheochromocytoma/paraganglioma–pituitary adenoma, pituitary blastoma and McCune–Albright syndrome. They represent a group of diseases with different genetic background and variable phenotype. Here, we summarize the clinicopathological features of pituitary adenomas associated with these familial syndromes.

Keywords AIP; Carney complex; classification; diagnosis; DICER1; familial isolated; familial syndromes; genetics; McCune–Albright syndrome; multiple endocrine neoplasia type 1; pathology; pituitary adenoma; pituitary blastoma; X-linked acrogigantism syndrome

Introduction

Pituitary adenomas are benign tumours representing approximately 15–20% of intracranial neoplasms.[1] While the majority are sporadic tumours, a significant minority are associated with familial syndromes with different genetic background and variable phenotype.[2] The two most frequently seen forms are familial isolated pituitary adenoma (FIPA)[3] and multiple endocrine neoplasia type 1 (MEN1),[4] while the more uncommon forms include X-linked acrogigantism (X-LAG) syndrome,[5,6] Carney complex (CNC),[7] multiple endocrine neoplasia type 4 (MEN4),[8] somatotropinoma/paraganglioma,[9] pituitary blastoma[10] and McCune–Albright syndrome (MAS)[11] (Figure 1). Here, we present the clinicopathological features and morphological characteristics of pituitary adenomas associated with these familial syndromes.

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Familial isolated pituitary adenoma (FIPA)

FIPA (Online Mendelian Inheritance in Man, http://www.ncbi.nlm.nih.gov/omim, OMIM #102200) represents families with two or more members with pituitary adenomas without other syndromic features or simplex (i.e. sporadic) patients with germline mutation in genes associated with FIPA[3,12]: aryl-hydrocarbon receptor interacting protein (*AIP*) and G protein-coupled receptor 101 (*GPR101)* (Table 1). Within FIPA, currently three subgroups can be identified: *AIP*-mutation positive, *GPR101*-mutation positive X-linked acrogigantism (X-LAG) and the *AIP* & *GPR101*-negative group. There are significant phenotypic differences between the three types of FIPA kindreds.

AIP-mutation positive patients

17–20% of FIPA families and 11–17% of <30 years simplex pituitary adenoma patients possess a mutation in the *AIP* gene.[3,13] There is incomplete penetrance in *AIP*-mutation positive kindreds. The mean age of onset is around 20–24 years. A slight male predominance has been previously described (63.5%),[3] but ascertainment bias cannot be ruled out as a more recent comprehensive study did not find male predominance being statistically significant.[13] *AIP*-mutation positive patients present with growth hormone (GH) or GH and prolactin (PRL) producing tumours in 85% of the cases (Figure 2). *AIP*-mutation positive patients with acromegaly have larger and more invasive tumours.[3]

X-linked acrogigantism syndrome (X-LAG)

X-LAG (OMIM #300942) is a syndrome of pituitary gigantism, caused by microduplications on chromosome Xq26.3, encompassing the *GPR101* gene[6] (Table 1) which encodes an orphan G protein-coupled receptor of unknown function. A significant percentage of patients (~10%) with pituitary gigantism harbour this microduplication[14] which shows full penetrance. This is a distinctive clinical entity characterized by excessive growth caused by GH hypersecretion beginning during the first years of life in previously normal infants. GH excess originates from a pituitary adenoma or pituitary hyperplasia.[5] X-LAG occur as a simplex condition due to a *de novo* mutation in the majority of cases or it could be associated with FIPA; until now, two mother to child transmission has been described. The patients usually present with increased growth velocity before the end of the first year of their life. Acral enlargement and coarsened facial features can be noticed. GH and insulin-like growth factor 1 (IGF-1) blood levels are elevated and the oral glucose tolerance test (OGTT) is abnormal. Magnetic resonance imaging (MRI) usually discloses a pituitary macroadenoma or in some cases, pituitary enlargement suggestive of hyperplasia. Morphological findings are mixed GH-PRL producing adenomas or, less common, diffuse pituitary hyperplasia. Treatment includes surgery, medical therapy and in some cases, radiotherapy[5] as

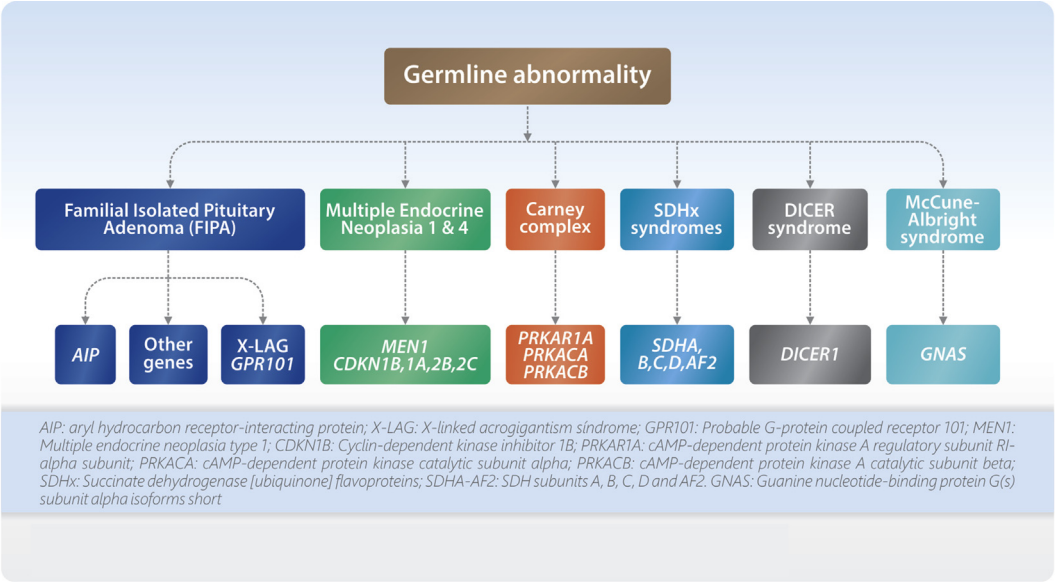

Figure 1 Pituitary adenomas due to germline mutations.

response to somatostatin analogues are poor. GH receptor antagonist treatment has been described successfully.[5]

AIP & *GPR101*-mutation negative patients

This is the largest group of FIPA cases. The age of onset of disease is similar to that of the sporadic cases, but larger and more invasive tumours have been identified. The tumour types are more varied than in the other types of FIPA: excess GH-producing adenomas still predominates, but the other tumour types represent over one third of the tumour types.[13] The affected families can be classified as i) homogenous, if the same type of pituitary adenoma is present, or ii) heterogeneous, if different types of tumours occur within the same family. Penetrance is low, probably lower that of *AIP*-mutation positive kindreds.[12]

Multiple endocrine neoplasia type 1 (MEN1)

MEN1 (OMIM #131100) is an autosomal-dominant disorder characterized by tumours of the pituitary, parathyroid, endocrine cells of the gastrointestinal tract, endocrine pancreas and adrenal cortex.[4] *MEN1*, a tumour suppressor gene localized on chromosome 11q13, encodes menin, a nuclear protein involved in transcriptional regulation, genome stability, cell division and proliferation (Table 1). Patients with MEN1 syndrome usually have a positive family history and *MEN1* gene mutations can be identified in 70%–95% of patients.[4] Clinical diagnosis is established when at least two of these features are present or when one feature is present together with a first-degree relative with established MEN1. Pituitary tumours in MEN1 syndrome patients can be documented in 10%–60% of cases and can be the first clinical manifestation in up to 25% of the cases. Pituitary adenomas associated with MEN1 differ from sporadic tumours.[15] MEN1-related pituitary adenomas are usually diagnosed at an earlier age, they are frequently macroadenomas, often resistant to medical therapy and have higher recurrence rates.[15] PRL-producing adenomas are the most frequent (62–60%), followed by clinically non-functioning adenomas (15%), GH-secreting and ACTH-secreting adenomas.[16] The proportion of plurihormonal adenomas and multiple adenomas is significantly higher in MEN1 patients.[17] In MEN1 patients with acromegaly and normal or enlarged pituitary gland on MRI, pituitary hyperplasia should be suspected and tumours (usually pancreas) producing a releasing hormone such as GHRH (GH-releasing hormone) must be searched for.[17]

Carney complex (CNC)

CNC (OMIM #160980), is an autosomal dominant syndrome produced by an inactivating mutation of the regulatory subunit 1-α of the protein kinase A (*PRKAR1A*) (Table 1). Recent studies have associated elements of the CNC phenotype with cAMP-dependent protein kinase catalytic subunit alpha (*PRKACA*)[18] and cAMP-dependent protein kinase catalytic subunit beta (*PRKACB*)[19] gene defects but their precise roles remain to be elucidated.[7] CNC is characterized by multiple skin lesions (blue nevus, spotty skin pigmentation and mucosal lentigines), cardiac, breast, cutaneous or mucosal myxomas, acromegaly or mild GH/PRL excess, breast ductal adenoma, psammomatous melanocytic schwannoma, thyroid carcinoma or multiple hypoechoic thyroid nodules, large-cell calcifying Sertoli cell tumours (LCCSCT), osteochondromyxoma and primary pigmented nodular adrenocortical disease (PPNAD).[7] The diagnosis can be established when two of the above mentioned features occur, or in the presence of one major feature and *PRKR1A* mutation or a first-degree relative with CNC. Clinical manifestations are variable even within members of the same family and one third of the patients present as simplex (sporadic) cases. Lentiginosis is the most common feature of CNC (70%) consisting of small, 2–10 mm brown to black maculae on the lips, eyelids, ears and genitals and can be