Familial pituitary adenomas

Adénomes hypophysaires familiaux

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Résumé

Les adénomes hypophysaires sont des tumeurs intracrâniennes bénignes qui constituent un problème médical en raison de la surproduction hormonale et du risque de compression des structures adjacentes. La plupart surviennent dans un contexte sporadique tandis qu’un petit pourcentage se développe dans un contexte de syndrome familial comme les néoplasies endocriniennes multiples de type I (NEM1), le complexe de Carney (CNC) et les adénomes hypophysaires familiaux isolés (FIPA), plus récemment décrits, ainsi que les NEM4. Alors que les altérations génétiques responsables de la formation d’adénomes sporadiques demeurent largement inconnues, des avancées considérables ont été réalisées dans l’identification des gènes responsables de ces syndromes familiaux. Les mutations des gènes de la Ménine et de PRKAR1A ont été identifiées chez la majorité des patients respectivement porteurs de NEM1 et de CNC. Environ 15 % des fratries de FIPA présentent des mutations du gène aryl hydrocarbon receptor-interacting protein (AIP). Les mutations du gène CDKN1B codant p27Kip1 ont été identifiées dans les cas de NEM4. Les tumeurs familiales semblent différer de leurs homologues sporadiques, non seulement en termes de causes génétiques, mais aussi de caractéristiques cliniques. L’observation suggère que, spécialement dans les NEM1 et les FIPA, ces tumeurs sont plus agressives et touchent des patients à un âge plus jeune, justifiant d’autant plus l’importance de leur diagnostic précoce. Dans cette revue, nous résumons les caractéristiques génétiques et cliniques de ces adénomes hypophysaires familiaux.

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Mots clés : Tumeurs hypophysaires familiales ; NEM 1 ; Complexe de Carney ; FIPA

Abstract

Pituitary adenomas are benign intracranial neoplasms that present a major clinical concern because of hormonal overproduction or compression symptoms of adjacent structures. Most arise in a sporadic setting with a small percentage developing as a part of familial syndromes such as multiple endocrine neoplasia type 1 (MEN1), Carney complex (CNC), and the recently described familial isolated pituitary adenomas (FIPA) and MEN-4. While the genetic alterations responsible for the formation of sporadic adenomas remain largely unknown, considerable advances have been made in defining culprit genes in these familial syndromes. Mutations in MEN1 and PRKAR1A genes are found in the majority of MEN1 and CNC patients, respectively. About 15% of FIPA kindreds present with mutations of the aryl hydrocarbon receptor-interacting protein (AIP) gene. Mutations in the CDKN1B gene, encoding p27kip1 were identified in MEN4 cases. Familial tumours appear to differ from their sporadic counterparts not only in genetic basis but also in clinical characteristics. Evidence suggests that, especially in MEN1 and FIPA, they are more aggressive and affect patients at younger age, therefore justifying the importance of early diagnosis. In this review, we summarize the genetic and clinical characteristics of these familial pituitary adenomas.

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Keywords: Familial pituitary tumours; MEN 1; Carney complex; FIPA

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1. Introduction

Pituitary adenomas are the third most common intracranial neoplasms, comprising about 12.7% of all brain tumours [1]. Despite having generally benign characteristics, they are clinically significant because of hormonal hyperproduction or mass effects of the tumour. Recently, a large cross-sectional epidemiological study in the province of Liège, Belgium revealed a prevalence of approximately 1:1000 individuals for clinically relevant pituitary adenomas [2], several times more than previously estimated [3] thus raising the need to better understand their pathogenesis, subsequent manifestations and management. Monoclonality of pituitary adenomas and familial predisposition suggest the presence of underlying genetic factors [4,5]. Familial pituitary adenomas comprise about 5% of all cases [6] with half of them being part of multiple endocrine neoplasia type 1 (MEN1) [7] – a syndrome caused by mutations in MEN1 gene [8]. Far rarer is another familial condition associated with multiple endocrine disruptions and pituitary pathology predisposition – Carney complex (CNC), related to mutations in the protein kinase A regulatory subunit type 1 alpha (PRKAR1A) gene that encodes protein kinase A type I-α regulatory subunit [9]. However, both conditions are also diagnosed in a significant number of patients who lack these mutations. Recently the first mutation in human Cyclin-dependent kinase inhibitor 1B (CDKN1B) gene, encoding cyclin-dependent kinase inhibitor p27Kip1, was described in a MEN1-like German family, negative for MEN1 mutation, and this discovery resulted in the definition of another syndrome – MEN4 [10]. Familial isolated pituitary adenoma (FIPA), a clinical entity defined in the late 1990s [11,12], comprises the other half of familial pituitary adenomas. As indicated by the name, pituitary pathology is not apparently associated with other endocrine neoplasms. Depending on the pattern of pituitary tumours seen in the family, FIPA kindreds are divided into heterogenous or homogenous subgroups. Isolated familial somatotropinoma or familial acromegaly can be understood to comprise a subgroup of FIPA, namely homogenous somatotropinoma families [13]. After the discovery of aryl hydrocarbon receptor-interacting protein (AIP) mutations in a Finnish cohort of familial cases with prolactinomas and acromegaly [14], further analyses revealed presence of AIP mutations (Table 1) in about 15% of FIPA kindreds and in 50% of FIPA homogenous for somatotropinomas [15]. These mutations do not seem to contribute often to sporadic adenoma formation [16,17]. Another condition associated with pituitary pathology, McCune-Albright syndrome, could theoretically be associated with inherited pituitary disease. It is due to a mutation in GNAS gene, encoding the Gsα subunit, present in up to 40% of sporadic somatotroph adenomas [18]. Nevertheless, the tumorigenesis of the majority of sporadic pituitary tumours remains largely unknown. Different defects of tumour suppression genes, oncogenes, signal transduction and cell cycle regulation pathways have been implicated. In this review, we give more details on genetics and clinical presentation of familial pituitary adenomas.

2. MEN1

MEN1 involves the following common endocrine disorders: hyperparathyroidism in more than 90% of the cases, enteropancreatic endocrine tumours in 30–80% of the cases and pituitary adenomas in 20–50% of the cases [5]. Various non-endocrine tumours such as facial angiofibromas, collagenomas and lipomas are often concomitant features [19]. MEN1 is an autosomal dominant disease caused by mutations of MEN1 gene, on chromosome 11q13. It is a tumour suppressor gene with 10 exons, encoding a protein with 610 amino acid residues, called menin [20]. Menin is implicated in gene transcription and cell cycle and proliferation pathways. Being predominantly a nuclear protein, menin controls promoter activity of several endocrine and non-endocrine genes [21–24]. Interaction with histone methylation presents another mechanism of gene transcription control [25]. Furthermore, a number of protein-to-protein interactions have been described involving transcriptional regulators such as activating protein-1 (AP-1), JunD transcription factor, members of the nuclear factor-kappa B (NF-kB), Smad family and others [26–29]. Interestingly, MEN1 mutations show a bias towards endocrine cells, although menin is also expressed in non-endocrine tissues. A possible explanation could be differential regulation of menin expression via upstream genetic elements [30].

So far more than 500 different MEN1 mutations have been described and these result in a truncated protein in more than two thirds of the cases. There was not a distinct genotype-phenotype relation except for two aspects: greater prevalence of pituitary adenomas in familial MEN1 cases compared to de novo MEN1 cases [8] and prevailing prolactinoma presentation in two genotypes. These are the MEN1Burin variant described in four large kindreds in Newfoundland, Canada [30,31] and MEN1Tasman in Australia [32]. Founder mutations have been identified in both variants, a nonsense mutation and a splice site mutation in MEN1Burin [31] and MEN1Tasman, respectively [32]. However, unlike the Burin kindred, prolactinomas were unevenly distributed in the different branches of the Tasman 1 kindred which could be possibly due to modifier genes, requiring further investigation.

In MEN1, compared to sporadic pituitary adenomas, distribution by functional type is similar, with prolactinomas being most prevalent, about 60% of all cases [33]. However, some clinical aspects of MEN1 pituitary tumours seem to differ from

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<tr>
<th>Gene</th>
<th>Pituitary adenoma</th>
<th>Syndrome</th>
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<tr>
<td>MEN1 (11q13)</td>
<td>All tumour types</td>
<td>70–80% of Multiple endocrine neoplasia type 1</td>
</tr>
<tr>
<td>CDKN1B (12p13)</td>
<td>GH, ACTH</td>
<td>Less than 2% in MEN1-like syndrome</td>
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<tr>
<td>PRKAR1 (17q22-24) 2p16</td>
<td>Somatolactotrope hyperplasia and adenomas in CNC</td>
<td>60% of Carney complex</td>
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<tr>
<td>AIP (11q13-32)</td>
<td>All adenoma types</td>
<td>15% Familial isolated pituitary adenomas, aggressive behaviour</td>
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their sporadic counterparts. Macroadenomas were twice as prevalent in MEN1 patients compared to non-MEN1 subjects (85% vs 42%), the difference being even greater for macroadenomas (84% vs 24%). One third of MEN1 associated tumours were invasive. MEN1 adenomas responded well to therapy in only 44%, compared to more than 90% in sporadic tumours [33]. The interest in MEN1 related tumorigenesis led to the development of mouse models with heterozygous MEN1<sup>+/−</sup> and conditional MEN1<sup>−/−</sup> confirming pituitary and pancreatic pathology predisposition [34,35].

3. MEN4

Despite rigorous genetic analyses, no mutations are found in about 20–30% of MEN1 cases which implies the possibility of other genetic alterations. A breakthrough in this regard came with the mapping of a locus on chromosome 4 related to MEN-like condition in rats [36]. Later this was associated with a mutation in CDKN1B. The first human germine mutation (TGG > TAG at codon 76) of CDKN1B (12p13) was demonstrated in a German family presenting with acromegaly, primary hyperparathyroidism, renal angiomyolipoma and testicular cancer among the various members of the kindred [10]. Soon after, another mutation in CDKN1B, 19 bp heterozygous duplication in exon 1, was found in a Dutch female patient exhibiting a small-cell neuroendocrine cervical carcinoma, Cushing’s disease and hyperparathyroidism [37]. This finding confirmed the association of CDKN1B mutations with MEN1-like conditions, classified now as MEN4. These novel genetic alterations encouraged further screening of MEN1-like phenotypes without MEN1 mutations, leading to the discovery of several new mutations of CDKN1B, together with several mutations of other CDK4 genes [38]. So far, however, these mutations could explain MEN1-like phenotypes in less than 2% of cases [38,39]. The exact mechanisms of p27<sup>Kip1</sup> dependent tumorigenesis are not quite clear, phenotypes in less than 2% of cases [38,39]. The exact mechanisms of p27<sup>Kip1</sup> dependent tumorigenesis are not quite clear, phenotypes in less than 2% of cases [38,39].

4. Carney complex (CNC)

CNC is a rare autosomal dominant disease characterized by the presence of myxomas, spotty skin pigmentation (lentigines) and endocrine hyperactivity [43]. So far about 500 cases have been described, with 70% having a familial presentation [44]. Two thirds of cases are associated with germline mutations in the protein kinase A 1a regulatory subunit (PRKAR1A) gene, located on chromosome 17q22-24. Loss of heterozygosity (LOH) is observed in tumour tissues, confirming its role as a tumour suppressor gene. In most of the cases the consequence of mutation is a premature stop codon and absence of the protein kinase A (PKA) 1a regulatory subunit [45]. PKA is a cAMP dependent kinase and the loss of this regulatory subunit most probably leads to increased total cAMP-mediated activity by up-regulation of the other subunits of the PKA complex [46]. Apart from PRKAR1A gene mutations, there is another locus, still uncharcterized, on chromosome 2p16, shown to be implicated in the pathogenesis of some CNC cases [43].

Endocrine abnormalities in CNC include disorders such as primary pigmented nodular adrenocortical disease (PPNAD), testicular tumours (large cell calcifying Sertoli cell tumours, Leydig cell tumours), thyroid tumours and nodules and in 10% of cases, acromegaly. Growth hormone (GH) producing adenomas appear after the third decade, however, GH related abnormalities are frequently observed in adolescence [44]. In about 75% of patients hypersecretion of GH, insulin-like growth factor-I (IGF-I) or prolactin can be demonstrated [47]. On immunohistochemistry, pituitary tumours stain positively for GH and prolactin and occasionally for other adrenohypophysial hormones. A typical feature is a multifocal hyperplasia of somatotommatrophic cells presenting against a background of normal pituitary [48]. Interestingly, tissue specific knockout Prkar1<sup>a</sup> mouse models present quite similar pituitary abnormalities as in CNC in humans, such as GH elevation without overt formation of pituitary adenoma [49].

5. Familial isolated pituitary adenomas (FIPA)

Published literature on familial cases of isolated pituitary pathology dates back to the beginning of the 20th century with [50]. Afterwards, this condition of two or more cases of acromegaly in a family was termed isolated familial somatotropinoma (IFS). By the end of the 20th century, approximately 20 families had been reported [51]. Several characteristics distinguish IFS from sporadic acromegaly cases: greater frequency of gigantism, male predominance, much younger age of presentation and macroadenoma dominance [13,51]. By linkage analyses, genetic alterations responsible for this condition were narrowed to 11q13.1-q13.3 [52]. Later on, it proved to be the locus of AIP gene, found to be mutated in 50% of the cases [14,15].

Reports of other types of pituitary adenomas arising in a familial setting were extremely rare, including three cases of familial prolactinoma [53,54], one case with Cushing’s disease [55] and one with non-secreting adenoma [56]. In the late 1990s, we started gathering and classifying families presenting with two or more pituitary adenomas and negative for other known causes of endocrine neoplasia. Consequently, by 2000, we had described 27 patients with this condition, and proposed the term for this clinical entity–FIPA. On the basis of pituitary tumour type, FIPA kindreds were divided into homogenous (all families having the same type) and heterogenous (having different types) groups [11]. IFS could be now referred to as the broader clinical entity of homogenous FIPA. Later, a multicenter, worldwide collaboration increased the number of identified FIPA cases to 80 patients in 2002 [57]. By 2004, the collaboration with Italy, France, the United States and the Netherlands led to the full clinical, biochemical, radiological and pathological characterization of 64 FIPA families, including about 140 patients [6,12]. However, up to that time, this familial condition could not be related to any distinct gene abnormality, as MEN1 and CNC mutations were exclusion criteria. In 2006, Vierimaa et al. performed a detailed genome-wide screen and DNA mapping for potential genes implicated in familial pituitary tumorigenesis. As a result, inactivating mutations in the gene encoding AIP...
Vierimaa et al. revealed three mutations, of which Q14X is a founder mutation typical to the Finnish population. Later on, in a multinational collaboration, the presence of AIP mutation was examined in 73 families and subsequently found in 15% of all FIPA kindreds and 50% of FIPA homogenous for somatotropinomas [15]. The number of reported families quickly began to increase, reaching more than 130 in our collaborating group [67], FIPA kindreds being reported by other research groups as well, with total number of AIP mutations more than 40 [14,15,17,63,68–73] (Fig. 1). As for sporadic pituitary adenomas, AIP mutations were found in less than 4% [17,70,72]. In acromegalic patients diagnosed at <30 years of age, however, carriers of mutated AIP gene approximated 10–15% [70,72]. Interestingly, Cazabat et al. reported that in apparently sporadic acromegalic patients no de novo mutations were discovered, indicating that this is probably due to a low penetrance of the disease or to incomplete familial study [74]. Although extensive analyses of several FIPA kindreds show rates of disease penetrance of about 33%, the true risk of pituitary disease remains to be further explored [75].

On molecular level, most of the reported mutations lead to premature stop codons and truncated protein with loss of the third TPR domain, already shown to be essential for protein–protein interactions. C238Y, R271W, R81X, Q217X, and R304X for example disrupt interaction with PDE4A5, and annulled this effect [63]. In the future, animal models could help in elucidating the AIP induced tumorigenesis. Recently, a model of homozygous knock out AIP−/− mice was shown to be lethal in embryonic life [64].

In regard to AIP structure, it is an immunophilin protein of 330 amino acids which contains several conserved regions, three tetratricopeptide repeat (TPR) domains and one domain characteristic of the immunophilins proteins—FK506 binding protein-type peptidyl-prolyl cis-trans isomerase (FKBP-PP1), although this is thought likely to be inactive [58]. The third TPR domain is responsible for some protein interactions, as is the C-terminal, given that without the last 5 amino acids of the C-terminus, binding with AhR is not possible [65,66]. The N-terminus is most probably involved in stabilization and modulation of intracellular localization of AIP-HSP90-AhR complex.

on chromosome 11q13.3 were found. DNA analysis of the pituitary tumours showed LOH at the AIP locus, rendering AIP a tumour suppressor gene function [14]. AhR binding protein, encoded by AIP, together with a dimer of heat-shock protein 90 (HSP90), forms a complex with the aryl-hydrocarbon receptor (AhR) [58]. AhR is a transcriptional factor binding with environmental toxins, such as dioxin. It has been shown that AhR is involved in the regulation of genes implicated in cellular growth and cell differentiation, liver and vascular system development, maturation of the immune system and others [59]. The role of AIP binding to the AhR-HSP90 complex is not clear. However, it appears to be important for complex stabilization and cytoplasmic retention by preventing nuclear localization signal recognition [60]. AIP has been shown to participate in some other protein–protein interactions, such as phosphodiesterases PDE4A5 and PDE2A [59,61,62]. Recently, Leontiou et al. have shown that wild-type AIP homozygous knock out AIP expression leads to reduced cell proliferation, while mutated AIP disrupts protein–protein interaction with PDE4A5, and annulled this effect [63]. In the future, animal models could help in elucidating the AIP induced tumorigenesis. Recently, a model of homozygous knock out AIP−/− mice was shown to be lethal in embryonic life [64].

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On clinical level, there are distinct differences between FIPA families and sporadic pituitary adenomas, between AIP and non-AIP mutated carriers within the FIPA cohort and between MEN1 and FIPA adenomas. First, in FIPA pituitary adenomas are distributed by functional type as follows: prolactinoma (41%), somatotropinoma (30%), nonsecreting tumour (13%), somatotropinoma (7%), gonadotropinoma (4%), Cushing’s disease (4%) and thyrotrpinoma (1%). Practically is at least one prolactinoma, somatotropinoma or somatolactotrope adenoma per FIPA family. In the FIPA cohort, compared to the sporadic counterparts, patients present with pituitary tumours about 4 years earlier and the adenomas are more aggressive. Homogenous prolactinomas are usually microadenomas while the heterogenous families have almost invariably macroprolactinomas with more aggressive features. In multi-generational FIPA kindreds, younger generations are diagnosed about 10 years earlier than their ancestors [6]. A comparison between FIPA and MEN1 families also reveals interesting data: younger age of patients with homogenous acromegaly or Cushing’s disease in FIPA, as well as a much higher prevalence of somatotropinomas in FIPA (34% vs 9%). Prolactinomas on the other hand are more frequent in MEN1 (63% vs 41%). As for FIPA patients harbouring AIP mutations, they presented 12 years earlier with pituitary adenomas than non-AIP mutated FIPA members. They were mostly men and women were diagnosed at a significantly older age than men (29 vs 23 years). These data suggest a more aggressive course of the disease. As for adenoma morphology, AIP mutated adenomas were almost invariably macroadenomas [13,74].

6. Conclusion

Familial pituitary adenomas represent about 5% of all cases, with almost equal distribution between MEN1 and FIPA kindreds. In regard to therapeutic approach, it is similar as in sporadic pituitary adenomas. What matters in familial cases is awareness and active searching for such conditions for two main reasons: pituitary adenomas in a familial setting, especially FIPA, arise earlier and have more aggressive behaviour compared to their sporadic counterparts. This tendency is even stronger in AIP mutation positive patients. However, concerning diagnosis, there are still open questions such as who is to be screened and by which method. Having in mind the clinical characteristics of AIP mutations carriers, it seems reasonable to search for this mutation in FIPA kindreds and in patients with apparently sporadic aggressive adenomas, diagnosed at age <30 years. In the case of finding of such mutations, it still remains unclear what would be the risk of developing a pituitary adenoma in asymptomatic carriers. It is currently believed that family members of sporadic AIP carriers should have genetic screening counseling offered to them. Asymptomatic patients harbouring AIP mutation and showing slight hormonal abnormalities should undergo regular biochemical testing and at least one MRI assessment, although the optimal frequency of repeated testing remains to be agreed. Further clinical observations and appropriate animal models will throw light on these issues. Further extensive research is also necessary to elucidate the exact mechanisms of tumorigenesis and possible relations between genetic alterations and phenotype expression.

Conflict of interest statement

No conflict of interest.

References


