Overview of genetic testing in patients with pituitary adenomas

Vue d’ensemble des tests génétiques sur des patients atteints d’adénomes hypophysaires

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Abstract

Clinically-relevant pituitary adenomas occur with a prevalence of one case per 1000–1300 of the general population. Although most are sporadic, there are several inherited conditions that incur an increased risk of developing a pituitary adenoma. Multiple endocrine neoplasia type 1 and Carney complex (due to mutations in \textit{MEN1} and \textit{PRKAR1A}, respectively) are established pituitary adenoma predisposition conditions, while multiple endocrine neoplasia type 4 (due to \textit{CDKN1B} mutations) is an emerging rare condition. Familial isolated pituitary adenomas (FIPA) is a novel condition not associated with these multiple endocrine neoplasias. Mutations in the \textit{aryl hydrocarbon receptor interacting protein} gene account for about 15% of FIPA kindreds and are associated with about 10–20% of macroadenomas that occur in children, adolescents and young adults. When treating a pituitary adenoma patient, relevant familial and clinical factors such as associated tumors or syndromic features should be assessed at the outset in order to guide the correct choice of genetic testing in appropriate individuals.

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Résumé

Les adénomes hypophysaires avec expression clinique ont une prévalence d’un sur 1000 à un sur 1200 dans la population générale. La plupart sont sporadiques mais d’autres surviennent dans un contexte familial. La néoplasie endocrinienne multiple de type 1, le complexe de Carney (dues respectivement à des mutations du gène \emph{MEN1} et du gène \emph{PRKAR1A}) sont des maladies bien connues avec prédisposition aux adénomes hypophysaires alors que la néoplasie endocrinienne multiple de type 4 (due à des mutations du gène \emph{CDKN1B}) est une maladie rare. Le Familial Isolated Pituitary Adenomas (FIPA) est une nouvelle entité qui n’est pas associée aux néoplasies endocrinennes multiples. Des mutations dans le gène \textit{aryl hydrocarbon receptor interacting protein} (\textit{AIP}) sont mises en évidence dans environ 15 % des familles FIPA et sont associées à 10 à 20 % des macroadénomes qui surviennent chez l’enfant, l’adolescent ou l’adulte jeune. Lorsque les patients avec adénome hypophysaire sont pris en charge, les facteurs cliniques et familiaux (tumeurs associées, aspect syndromique) doivent être recherchés afin de guider un choix judicieux pour la réalisation de tests génétiques adéquats chez les individus appropriés.

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Pituitary adenomas occur frequently in the population, with clinically-relevant pituitary adenomas occurring in one case per 1000–1300 of the general population [1–3]. Most of these tumors are benign and usually occur sporadically but several inherited conditions occur in which there is an increased risk of pituitary adenoma. Multiple endocrine neoplasia type 1 (MEN1) syndrome or Carney complex with germline mutations in \textit{MEN1} and \textit{PRKAR1A}, respectively, are the best recognized of these [4,5]. Familial and genetic predisposition to pituitary adenomas extends beyond MEN1 and Carney complex to conditions such as familial isolated pituitary adenomas (FIPA) [6]. Mutations in the \textit{aryl hydrocarbon receptor interacting protein} (\textit{AIP}) gene account for about 15% of FIPA kindreds and appear to be a relevant cause of macroadenomas that occur in children, adolescents and young adults [7–12]. When faced with a patient with a pituitary adenoma, various clinical factors must be considered before choosing the correct approach to refer patients for genetic screening.

Genetic screening guidelines are already in place for MEN1 and the clinical features and associations of MEN1-related diseases are well established [13]. In patients with MEN1, pituitary adenomas occur in about 40% of cases and are more frequent in familial than sporadic MEN1 and are also more common in females [14,15]. Pituitary adenoma is the first
manifestation of MEN1 syndrome in 10% of familial cases of MEN1 and in 25% of MEN1 cases with no previous occurrence of MEN1 in the family. MEN1 mutation positive subjects that present with a pituitary tumor as their first abnormality in MEN1 syndrome tend to present earlier than other MEN1 patients [14]. Indeed patients with MEN1 mutations can present at a young age only with a pituitary tumor and without other features of MEN1 syndrome [16]. The majority of pituitary adenomas in the setting of MEN1 are prolactinomas (60%). MEN1 prolactinomas have relatively poorer response to dopamine agonist therapy as compared with sporadic cases.

The MEN1-like condition, MEN4, caused by germline mutations in the CDKN1B gene, adds to the complexity of testing choices. MEN4 patients frequently have pituitary tumors [17,18]. However, germline mutations in the CDKN1B gene do not have an important role in development of pituitary adenomas in FIPA kindreds [19].

Pituitary tumors in Carney complex are a less common disease manifestation than the cardinal diagnostic extra-pituitary manifestations of cutaneous pigmentation, myxomas, adrenal hyperplasia, etc. [20]. The mean age at diagnosis of pituitary adenoma in these patients is about 35 years and tumors are usually growth hormone secreting adenomas. Patients with PRKAR1A mutations rarely present with pituitary tumors in the absence of other signs of Carney complex [20]. An interesting feature of pituitary adenomas in Carney complex is a pattern of somatomamnetotropic cell multifocal hyperplasia against the background of normal pituitary, which does not present in MEN1. Pituitary adenomas with somatomamnetotropic hyperplasia can also occur in the presence of McCune-Albright syndrome (MAS), due to mosaicism for a mutation in the GNAS gene, but this is not known to occur in a familial setting [21].

Clearly a systematic evaluation of familiarity and associated diseases (or lack thereof) in patients with pituitary adenomas is the best first step. Syndromic cases can be assessed according to their symptomatology and genetic testing for MEN1, PRKAR1A, and GNAS can be considered as appropriate. For patients with familial non-syndromic pituitary adenomas, FIPA represents the most likely clinical condition. FIPA families can present not only homogeneous but also heterogeneous pituitary adenoma types within the same kindred [6,22]. AIP mutation-related pituitary adenomas are characterized by an early onset (50% before the age of 18 years) and a large predominance of somatotropinomas (80%) and mixed growth hormone/prolactin-secreting tumors, prolactinomas, non-secreting adenomas, and rare cases of Cushing disease. These tumors are usually large at diagnosis and appear to be more frequently resistant to treatment. The population is predominantly male and gigantism occurs in nearly a third of AIP mutation-related somatotropinomas [7]. Based on the demonstrated clinical characteristics of AIP mutation-related pituitary adenoma patients, AIP mutation testing should be actively considered in all FIPA families. Data from recent studies defined young age (less than 30 years at diagnosis) and large tumor size (macroadenoma) as the most important criteria of selection for AIP mutation screening in patients with apparently sporadic pituitary adenomas [7,10]. In particular, children/adolescents with pituitary adenomas should be assessed for AIP mutation testing [16], as up to 20.5% of those aged less than 18 with macroadenomas had pathogenic AIP mutations [10].

In the case of AIP mutations, the risk for unaffected mutation carriers remains unclear due to variable penetrance of pituitary adenomas among mutation carriers. Because early detection of at-risk individuals affects medical management, close clinical assessment of individuals during childhood and adolescent is particularly important. Testing of children that are at risk of being AIP mutation carriers should be discussed openly with parents/guardians potentially to rule out those that are not carriers and help focus clinical oversight of those truly at risk of pituitary adenoma development. In other adult carriers, a pragmatic approach is to organize baseline clinical and hormonal assessments in all proven carriers, and an MRI, particularly if any hormonal or clinical suggestion of a pituitary adenoma is noted. For those without clinical, hormonal or radiological evidence of a pituitary abnormality should still be followed up at regular intervals as a minority of pituitary adenomas in AIP mutated patients present after the age of 30. Optimal recommendations for follow-up and management of patients with AIP mutations are currently under consideration.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References