MEN1 and pituitary adenomas

NEM1 et adénomes hypophysaires

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Abstract

MEN1 gene mutations predispose carriers to pituitary tumors. Molecular pathways involved in the development of these tumors seem different to what is known in sporadic tumors. Clinical studies showed that all types of adenomas can be found with a predominance of prolactinoma and macroadenoma compared to a control population. These MEN1 tumors seem more aggressive, invasive and resistant to treatment requiring a very careful long-life follow-up. Occurrence of these tumors can be described in the pediatric population and it can be the first and only manifestation of MEN1 for some years asking the question of the systematic screening for MEN1 gene mutation in pediatric population with pituitary adenoma.

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Résumé

Les mutations du gène NEM1 prédisposent les patients porteurs aux tumeurs de l’hypophyse. Les altérations moléculaires induites par l’inactivation de ce gène induisent le développement de tumeurs hypophysaires selon des mécanismes qui semblent différents des cas sporadiques. Les études cliniques de cohorte ont montré que tous les types d’adénomes peuvent être rencontrés au cours du NEM1 avec une prédominance des prolactinomes et des macroadénomes comparé à une population témoin. Ces tumeurs hypophysaires NEM1 semblent plus agressives, plus invasives et plus résistantes aux traitements ce qui nécessite pour ces patients une prise en charge particulièrement attentive tout au long de la vie. La survenue de ces tumeurs est décrite dans la population pédiatrique où elle peut être la première et la seule manifestation du NEM1 pendant quelques années posant la question de la nécessité de la recherche systématique des mutations du gène NEM1 dans la population pédiatrique présentant un adénome de l’hypophyse.

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Multiple Endocrine Neoplasia type 1 (MEN1) is a genetic disease that predisposes carriers to development of various endocrine tumors [1,2]: primary hyperparathyroidism in nearly every patients, neuroendocrine enteropancreatic tumors and pituitary adenomas in respectively 30 to 80% and 30 to 50% of the patients. Other lesions of endocrine origin (adrenal and thymic-bronchial tumors) or not (cutaneous) are also more and more frequently described. MEN1 diagnosis requires the presence of two of the main lesions in sporadic case or only one in familial case [3]. MEN1 disease is transmitted in an autosomal dominant manner with a high penetrance during the life span and increase of overall mortality [4]. MEN1 gene, located on 11q13, is a tumor suppressor gene which encodes for menin, a 610 amino-acids nuclear protein [5]. Menin interacts with other proteins, which have complex roles on regulation of transcription, cell division and proliferation [2,6].

Although menin alterations are associated with high frequency of pituitary adenomas, it does not seem to play an important role in the pathogeny of sporadic pituitary tumors. Indeed, the systematic study of MEN1 gene mutations in large series of patients harboring pituitary adenomas only report frequency of less than 3% [7]. Furthermore, somatic mutations of MEN1 gene are found in only 3,5% of pituitary tumors [8]. Recently, analysis of the transcriptome has been performed in a MEN1 mammosomatroph tumor occurring at an exceptional early age (5 years) and compared to sporadic tumor [9]. Authors concluded that there was only “a rare overlap between the expression profiles of the MEN1 tumor vs. that of its sporadic counterpart” suggesting a difference in the molecular pathway of tumorigenesis.

Considering that MEN1 associated pituitary tumors may harbor distinct patterns compared to sporadic tumors, clinical
Pituitary tumors have been studied in large series of MEN1 patients. In the Groupe d’études des tumeurs endocrines (GTE) cohort of 324 patients collected in 2002, Verges et al. [10] has shown that 42% of the patients presented with a pituitary adenoma with an age of onset between 12 to 83 years (mean 38 years). Pituitary adenoma was the first manifestation of the disease in 17% of all MEN1 patients. Type of adenoma was prolactinoma in 62%, somatotropinoma in 9% and Cushing in 4% with 15% considered non-secreting. The other tumors were multifunctional adenomas with very unusual association: PRL and ACTH or PRL and FSH/LH. Although repartition between the types of adenomas was not statistically different from the control population, there was a large excess of macroadenoma particularly for prolactinomas (84% macroprolactinomas in MEN1 patients). Evolution seemed also to be different in MEN1 patients with description of more complicated cases with difficulties for control of the tumor and for regression of its excessive hormonal secretion reported twice more frequently than in the control population. In this population, usual guidelines for care of pituitary adenomas cannot be used and follow-up must be very careful and prolonged life-long.

This clinical study has been completed by a pathological analysis performed on a case-control multicenter series of 77 pituitary tumors from MEN1 patients vs. 2509 non/MEN1 patients [11]. The authors concluded that MEN1 tumors occurred in younger patients and were larger, more invasive and aggressive tumors. Furthermore, MEN1 pituitary tumors could harbor unusual characteristics as double adenomas which have been identified in 4% of the patients and multi-hormonal unexpected association like PRL and ACTH or PRL-GH and FSH/LH. Increased frequency of prolactinoma has also been described in selected MEN1 families. The first example was the MEN1Burin variant described in four families of Newfoundland sharing a common ancestor [12] and characterized by large excess of prolactinomas and reduced occurrence of gastrinomas compared to “usual” MEN1 patients. This “prolactinoma” MEN1 variant has been described in other kindreds with, for the moment, no correlation between this phenotype and genotype [13,14]. However, it is interesting to notice that, in this kindred, isolated cases of prolactinomas could be observed before occurrence of other lesions of MEN1.

Recently, we performed a specific study in the young patients (under 21 years) of the GTE cohort (personal data). We showed, in 114 patients in whom the disease had begun, that pituitary tumors were the second tumor in frequency (after parathyroid hyperplasia) and were more frequent than pancreatic lesions in this population. First pituitary cases occurred around 10 years of age (earlier cases have been described in other series), tumors were mostly prolactinomas (33 over 45 cases) and macroadenomas (22 over 45). Some invasive and aggressive cases were described with sometimes resistance to medical treatment suggesting, at least for some cases, an unusual behavior of these tumors. Isolated cases were reported before any other lesions in nearly 15% of the patients raising the question of the interest of systematic screening of MEN1 gene alteration in the selected population of young patients with pituitary adenoma.

The recent study of Stratakis et al. [15] began to address this question. In a cohort of young patients diagnosed with pituitary adenomas, mutation of MEN1 was found in an isolated case of prolactinoma and further characterized as an intronic mutation with low familial penetration. Other authors are performing the same kind of studies on other cohorts of pediatric patients and results are expected soon.

Conclusion: MEN1 mutations are associated with development of pituitary adenoma which can be the first and only lesion in younger age. Evolution of these tumors, more often aggressive, invasive and sometimes resistant to treatment does not seem to look like what is known in sporadic pituitary adenoma and these patients need very careful life-long follow-up.

Disclosure of interest

The author has not supplied his declaration of conflict of interest.

References

