

The clinical characteristics of pituitary adenomas (PA) in patients with primary hyperparathyroidism (PHPT) with and without MEN1 mutation.

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MEN1 germline mutations are identified in 70% of the familial forms of multiple endocrine neoplasias type 1 (MEN1), whereas the sporadic cases with MEN1 represent about 10% of cases. Little is known about clinical differences between MEN1 phenocopies with and without identification of MEN1 germline mutation particularly in terms of pituitary tumor characteristics.

Previously we have described the cases of isolated association of PA and PHPT from the GENEM database and found out the prevalence of females in this group with more frequent somatotropinomas than prolactinomas (13 vs 6). Consequently multicentric study was conducted to characterize the group of patients (24 cases) with isolated acromegaly and PHPT. In this group PA was diagnosed before PHPT (16pts) or simultaneously (7pts), and most cases were MEN1 negative (15pts).

Then we aimed to compare the clinical features of pituitary adenomas in MEN1 cases with and without germline MEN1 mutation.

Data were obtained in 39 patients: 22 with MEN1 mutation (Group-I) and 17 sharing MEN1 phenotype but tested negatively for germline MEN1 mutation (Group-II). All patients presented with pituitary adenomas and PHPT and/or gastroenteropancreatic neuroendocrine tumors (GEP NETs). The genetic diagnosis was performed by direct sequencing of MEN1 exons and intronic boundaries. In 17 MEN1-negative patients large deletions of MEN1 were excluded by MLPA and direct sequencing of CDKN1B gene did not reveal the presence of genetic mutations. Control group included 17 patients with sporadic pituitary adenomas and no evidence of other endocrine tumors (matched by type of secretion and follow-up period to those in Group-II).

Results: Group-II pituitary adenomas as primary tumor site were more frequent than in Group-I (70% vs 51%, $P=0.04$). Females were prevalent in both groups (F/M 2.66 vs 4.66, $P=0.07$). The distribution of the pituitary adenoma type was significantly different between two groups. In Group-II 52% had somatotropinomas, 17% prolactinomas, 17% nonfunctioning adenomas, 11% corticotropinomas. In contrast, in the Group-I 53% consisted prolactinomas and only one patient had acromegaly. All other patients with somatotropinomas ($n=9$) were from Group-II. The frequency of macroadenomas wasn't significantly different between two groups (55% vs 59%; $P=0.8$), but was higher in Group-II than in controls (59% vs. 44%, $P=0.041$).

In secreting PA normalization of pituitary hypersecretion was not significantly different in Groups I and II (50% vs 52%, $P=0.48$), whereas it was more frequent in controls than in MEN1-phenocopies (76% vs. 52%, $P=0.001$).

During the whole follow-up 81% patients in Group-I developed GEP NETs, whereas in the Group-II such tumors were identified in only 2 patients.

Conclusion: Pituitary adenomas in phenocopies of MEN1 have different clinical characteristics than those with germline MEN1 mutations. The pituitary tumorigenesis in these patients, especially in those with GH-producing pituitary adenomas and PHPT, might involve mechanisms others than either MEN1 or CDKN1B mutations.