Cushing syndrome (CS) has an incidence estimated to be approximately 10 per 1 million persons. In 10 to 20% of cases, CS is caused by primary adrenal cortisol hypersecretion. However, bilateral macronodular adrenal disease is an extremely rare cause of CS, representing less than 2% of all cases.

Case report

Primary bilateral macronodular adrenal hyperplasia (PBMAH) was incidentally identified in a 69-year-old woman (Blanca) who developed a biliary colic. She had a 30 years history of hypertension and was treated by three antihypertensive drugs. Concomitantly, one of her four sons (Pablo) was also referred after incidentally discover of a PBMAH. This 50-year-old man has developed one year before severe hypertension needing four antihypertensive drugs. Moreover, two years before, another son (Jaime) was also incidentally diagnosed for PBMAH through an amuliphenic cure. This 49-year-old man had no hypertension but severe osteoporosis discovered at the age of 42 after a spontaneous wrist fracture. None of these patients had clinical sign of Cushing’s syndrome (Figure 1).

Figure 1: Pedigree

Hormonal evaluation

However, hormonal evaluation showed in all patients: basal suppressed ACTH, plasma midnight cortisol (sleeping) > 50 ng/ml and no plasma cortisol suppression after 1-mg overnight dexamethasone (DVM) suppression test while urine cortisol measurements were variable (Table 1).

Table 1: Circadian rhythm of the corticotropic axis, plasma cortisol after 1-mg overnight dexamethasone suppression test and urinary free cortisol measurements (CFU)

In order to investigate cortisol responses to various stimuli independently from any ACTH variation, patients were given dexamethasone before a series of tests for illegitimate adrenocortical receptors detection. The tests were performed as previously described by Renzi et al. Results are expressed as percentage variation from basal, calculated as follows: (peak cortisol – basal cortisol)/(basal cortisol) × 100 % Response is positive when percentage is > 25%. Results are shown in Table 2.

Table 2: Results of clinical screening for illegitimate membrane adrenal receptors

Discussion

In this case, the bilateral nature of the adrenocortical tumors and the familial form of the disease suggests a genetic origin. PBMAH is often genetically determined and several genes have been identified, ARMC5 being the last one. A model of tumor suppressor gene has been proposed for ARMC5 alterations (Figure 4). Genetic testing targeted on ARMC5 gene is still in progress in this family. However, the associated-tumors phenotype exhibited by this family does not enter into the spectrum of the described malignancy predisposing syndromes: absence of hyperparathyroidism and biliary duct tumor association. Moreover, illegitimate receptor expression observed in the majority of PBMAH is until now not clearly explained. This aberrant receptor expression could be due to a cell dedifferentiation favored by a decrease of apopisis in ARMC5 mutated cells. It is interesting to note that the biliary duct tumor of our patient expressed hepatocellular markers indicating, also, a cell dedifferentiation.

Conclusion

This case is remarkable for several reasons:

- at our knowledge, it is the first described case of PBMAH associated to a digestive tumor
- it illustrates well the phenotype variability within one family with a rare genetic cause of Cushing’s syndrome as well as the presence of different type of aberrant receptors in the same family
- it highlights the importance of a complete clinical characterization to permit phenotype-genotype correlations
- the comparison of genetic profiles of the adrenal and digestive tumor tissues (germline and somatic mutations) could also give new data for a better knowledge of this disease

References