Patients with syndromic features: multiple endocrine neoplasia type 2 (MEN2) or von Hippel-Lindau (VHL) antecedents

Clinical characteristics

Seventy-eight percent of syndromic cases (35/45), aged between 19 and 58 years (mean, 38.5y), harbored a mutation affecting the \textit{RET} oncogene and had personal or familial antecedents of MEN2 (supplemental figure 1). Sixty-three percent of these cases (22/35) showed bilateral PCC, and 48.5% (17/35) had developed PCC before or simultaneous with medullary thyroid carcinoma (MTC). The \textit{VHL}-positive index cases, aged between 13 and 47 years (mean, 28.8y), represented 22% (10/45) of all syndromic cases. Sixty percent of these cases (6/10) showed bilateral PCC, and 40% (4/10) developed PCC as first manifestation.

Discussion

As expected, the presence of syndromic antecedents of MEN2 or VHL, either personal or familial, is itself sufficient to be certain about the underlying genetic alteration. In our series, 100% of 45 different syndromic index cases were genetically diagnosed with a point mutation affecting either \textit{RET} or \textit{VHL}. The presence of adrenal bilateral PCC, found in more than 60% of both syndromic conditions, was the most useful feature in helping genetic diagnosis when the antecedents were not clear (e.g. a not proven suspicion of MTC). In this sense, a PCC was found earlier than or at the same time as MTC in 48.5% of our MEN2 patients, but all cases without familial antecedents at the genetic test were bilateral. The age at onset of PCC was significantly different between \textit{RET} and \textit{VHL} mutation carriers (\(P=0.013\)). The high age at onset of MEN2 in Spanish MEN2A patients (mean, 38 years) was recently described (1), so a
younger age at onset in a patient with bilateral PCC could be an indication of VHL syndrome in the absence of any other syndromic feature. This was also observed in our patients with bilateral PCC and no syndromic antecedents, since 41% of them carried a \textit{VHL} mutation, and the mean age of onset was 25 \textit{versus} 47 years in bilateral cases without mutation ($P = 0.003$).

\textbf{Familial cases without a germline mutation}

\textbf{Clinical characteristics}

Familial cases without germline mutations were grouped into two different subtypes: familial PCC (three cases), and familial PGL (two cases). The three familial PCC patients developed benign PCCs, one of them bilateral, as the only manifestation and their familial antecedents were always adrenal tumors developed either in maternal or paternal relatives. On the other hand, the two index cases from the familial PGL families developed H\&N PGLs and one of them also showed a thoracic tumor. Both families showed familial antecedents of PGL in the paternal branch, and no case of PCC was diagnosed in the six family members affected.

\textbf{Discussion}

Regarding the five index cases with familial antecedents and no mutation in one of the five susceptibility genes, we found two different subtypes, familial PCC and familial PGL, probably related to different genes. Dahia et al. (2) have recently described a familial PCC syndrome with digenic recessive inheritance for two different chromosomal regions: 2cen and 16p13. The genes located in 2q showed both loss of heterocigosity (LOH) and loss of
expression in a subset of familial adrenal tumors without mutations in any of the susceptibility genes. In addition, these familial PCCs had a transcriptional signature much closer to MEN2 and NF1 tumors than to VHL-related tumors (3). We had no tumor available from the three familial PCC cases to check 2q LOH, but clinical characteristics of both the index cases and their relatives agreed with this new familial syndrome. On the other hand, the two familial PGL cases without mutations in the five susceptibility genes could be caused by mutations in the fourth susceptibility locus described for familial PGL (PGL2); this locus is located on chromosome 11q13, and at present no candidate gene has been identified. The pattern of inheritance described for this locus includes maternal imprinting and a tendency toward multiplicity (4). Both PGL families from our series matched with this inheritance (paternal transmission), but only one of them also showed multiple H&N tumors in the four affected relatives. Further studies involving a joined effort in which all similar families are studied together are needed to pinpoint the candidate gene for PGL2.
Supplemental References


