**Unique characteristics of von Hippel-Lindau disease-associated pancreatic neuroendocrine tumors by various diagnostic criteria**

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**Abstract**

**Introduction**

von Hippel-Lindau (VHL) disease includes hemangioblastomas (HB), renal cell carcinomas (RCC), pheochromocytomas, and pancreatic neuroendocrine tumors (vPNET). Diagnosis is based on International (two HB, one HB and one visceral lesion, or VHL family history plus HB\visceral lesion) or Danish criteria (two clinical manifestations, or VHL family history\pathogenic variant plus HB\visceral lesion). Unlike sporadic PNET (sPNET), most vPNET are non-functioning, have lower grade and fewer metastases, yet head-to-head comparisons are scarce.

**Objective**

To compare the characteristics of vPNET and sPNET and test the hypothesis that VHL diagnosis by International or Danish criteria comprise two distinct populations.

**Methods**

PNET diagnosis was identified using the MDClone platform and data collected included demographics, tumor characteristics and VHL clinical features and family\genetic diagnoses. Patients were sub-grouped to sPNET, and to those diagnosed with VHL according to the International (IC) and Danish criteria (DC).

**Results**

The cohort included seventeen (58%) patients with vPNET out of 29 with VHL, and 65 with sPNET. Patients with vPNET were younger at diagnosis compared with sPNET (50.1±4.7 vs 62.8±1.5 years, $p<0.001$), and the tumors were comparable in terms of stage and grade, but sPNET were more frequently located to pancreatic body/tail ($p = 0.048$).

Patients in IC group were younger at diagnosis with VHL, vPNET and RCC than the DC group. Presenting manifestation was HB (52%) and PPGL (31%) in the IC group vs. RCC (62%) and PNET (30%) in the DC group. Finally, 90% of the patients in the IC group had a pathogenic variant in the *VHL* gene and 2/3 had a family history of VHL, none in the DC group had either ($p<0.05$ for both).

**Discussion**

Patients with vPNET diagnosed by IC and DC form distinct clinical groups, with greater similarity of the DC group to sPNET. It is thus possible that diagnosis based on the Danish clinical criteria may include patients with sporadic disease. We therefore suggest that all patients with clinically based diagnosis of VHL should undergo genetic validation of VHL diagnosis.