Head and neck paragangliomas and von Hippel-Lindau disease

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Background:
Head and neck paragangliomas (HNP) are highly vascular tumors of neural crest origin that are benign in the majority of cases. They may occur as sporadic as well as hereditary entities [1]. Since the year 2000, the so called "paraganglioma syndromes" (PGL) have attracted attention. To date, three out of four PGL have been characterized on a molecular genetic basis. PGL 1 is associated with mutations of the succinate dehydrogenase subunit D (SDHD) gene, PGL 3 is caused by SDHC and PGL 4 by SDHB gene mutations [1]. Patients with PGL have a high risk for the development of HNP and pheochromocytomas [1]. Von Hippel-Lindau disease (VHL) is characterized by retinal angiomas, haemangioblastomas of the central nervous system, kidney tumors, pancreatic cysts and pheochromocytomas. Only five cases of VHL patients with HNP have been published in the international medical literature [2-6]. Table 1 gives an overview on tumor syndromes that are associated with tumors of the paraganglial system.

Methods:
In 1983 we founded a registry for VHL patients. Until 2008, 395 index cases could be registered. We systematically reviewed our VHL registry for patients with HNP.

Results:
Three VHL patients presented with an HNP. The first of those patients (mutation VHL 404 T>A) was diagnosed with a malignant abdominal extra-adrenal pheochromocytoma and lymph node metastases in 1997 at age seven. Two years after resection of the tumor, lymphadenectomy and chemotherapy there was a local recurrence which was resected and radiated. In 2003, there was an adrenal pheochromocytoma (Fig. 1 and 2) and in 2005 the boy was diagnosed with a left sided carotid body tumor (Fig. 3). Both tumors underwent resection. Right now, the disease is stable with a known vertebral bone metastasis (Fig. 4).

Another male VHL patient (mutation VHL 404 T>A) presented with a carotid body tumor on the right at age 33. The tumor was completely resected. So far, no other VHL associated tumors could be detected in this patient.

The third patient was diagnosed with a left carotid body tumor at age 33 in the year 2000 (mutation VHL 505 T>C). The tumor underwent complete resection. Currently, she has multiple haemangioblastomas of the spinal cord that are followed up by serial MRI.

Discussion:
Approximately 33% of all head and neck paragangliomas (HNP) are associated with a hereditary tumor syndrome [1]. The paraganglioma syndromes 1, 3 and 4 (PGL 1, 3, 4) make up for the vast majority of those tumors [1]. In our international VHL registry, we detected three VHL patients who developed an HNP. The results of our study demonstrate that patients with von Hippel-Lindau disease seem to have an increased risk for the development of HNP. So far, this rare association has found very little attention in international medical literature [2-6]. The possible occurrence of an HNP has to be kept in mind when it comes to molecular genetic counselling, therapy and follow up of VHL patients. We suggest that all VHL patients should undergo a thorough yearly work up of the head and neck including an otoscopy, pure tone audiometry, examination of the lower cranial nerves as well as a color coded Doppler sonography.

Table I

<table>
<thead>
<tr>
<th>Tumor Syndrome</th>
<th>Gene Mutation</th>
<th>Location</th>
<th>Tumor Type</th>
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<tbody>
<tr>
<td>PGL 1</td>
<td>SDHD</td>
<td>11q23</td>
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<tr>
<td>PGL 3</td>
<td>SDHC</td>
<td>1q21</td>
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<tr>
<td>PGL 4</td>
<td>SDHB</td>
<td>1p36</td>
<td>HNP</td>
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Table 1 gives an overview on tumor syndromes that are associated with tumors of the paraganglial system.

Literature:

Figures 1-4 (from left to right): Male VHL patient (mutation VHL 404 T>A)

Figure 1: Coronal magnetic resonance imaging (MRI) demonstrating a pheochromocytoma of the right adrenal gland (arrow)

Figure 2: Axial MRI of the tumor shown in Fig. 1

Figure 3: Axial MRI of the neck with a left sided carotid body tumor (Shamblin Class I)

Figure 4: Axial MRI revealing a vertebral bone metastasis