A legacy of tinnitus: multiple head and neck paragangliomas

Tricia M.M. Tan,[1] Emma C.I. Hatfield,[1] Rajesh V. Thakker,[2] Eamonn R. Maher,[3] Karim Meeran,[1] Niamh M. Martin,[1] Jeremy J. Turner[1]

[1]Department of Investigative Medicine, Division of Investigative Science, Imperial Healthcare NHS Trust, London, UK; [2]Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK; [3]Department of Medical and Molecular Genetics, Institute of Biomedical Research, University of Birmingham, Edgbaston, Birmingham, UK

Abstract

We describe the case of a patient who presented with a right-sided glomus jugulare tumor and bilateral glomus vagale tumors. These proved to be nonmalignant paragangliomas on histopathological analysis. Genetic analysis revealed a germline heterozygous missense mutation (Pro81Leu) in the succinate dehydrogenase subunit D (*SDHD*) gene. We discuss the clinical presentations of the familial paraganglioma syndrome type 1, which is caused by mutations in *SDHD*, and the implications for the clinical diagnosis and care of such patients.

Case Report

A 35-year old lady presented with right-sided pulsatile tinnitus, conductive deafness, and a vascular lesion in the floor of the right external auditory meatus. Magnetic resonance imaging revealed a right-sided glomus jugulare tumor and bilateral glomus vagale tumors (Figure 1). Both her paternal grandfather and her father had undergone neck surgery for tumors. She was an only child and had a two-year-old son. She was normotensive, with no clinical features of von Hippel-Lindau (VHL) syndrome or neurofibromatosis type 1 (NF1). Serum calcium, urine catecholamine excretion, and serum calcitonin were within normal limits. Radiolabeled metaiodobenzylguanidine scanning and MRI imaging of her abdomen did not demonstrate any intra-abdominal paragangliomas. She underwent partial excision of her right glomus jugulare tumor, with complete excision of both the glomus vagale tumors. Histology showed nonmalignant paragangliomas. Genomic DNA analysis revealed a germline heterozygous missense mutation (p.Pro81Leu) in exon 3 of the succinate dehydrogenase subunit D (*SDHD*) gene. Therefore she was diagnosed with familial paraganglioma syndrome type 1 (PGL1).

Discussion

Paragangliomas are neuroendocrine tumors of the autonomic nervous system. Abdominal and thoracic paragangliomas are derived from sympathetic tissue and secrete catecholamines, like pheochromocytomas, which are derived from the adrenal medulla. Head and neck paragangliomas are derived from parasympathetic tissue and usually do not secrete catecholamines.[1] Up to a third of paragangliomas and pheochromoctyomas are associated with hereditary causes; i.e., mutations in V*HL, RET* (causing multiple endocrine neoplasia type 2A-MEN2A), *NF1*, and the SDH complex genes *SDHB*, *-C* and *-D*.[2]

The SDH complex is bound to the inner mitochondrial membrane and participates in both the electron-transport chain and the Krebs cycle as part of complex II. It consists of four subunits A-D. Mutations in subunits B, C, and D are associated with hereditary pheochromocytomas and paragangliomas: the PGL1 syndrome with mutations in *SDHD*, PGL3 with mutations in *SDHC*, and PGL4 with mutations in *SDHB*.

Multiple mechanisms have been implicated in the pathogenesis of SDH subunit-related tumors. These include abnormal activation of hypoxia-inducible pathways, producing a pseudohypoxic state similar to that seen in tumors from patients with VHL disease.[3,4] The HIF-1 and HIF-2 transcription factors are major mediators of the hypoxic gene response and the HIF-α subunits are rapidly degraded in normoxic cells via a VHL protein (pVHL)-dependent mechanism.[5] Activation of HIF pathways with SDH subunit inactivation has been linked to accumulation of succinate and resulting inhibition of the prolyl hydroxylase enzymes that are necessary for HIF-α subunit modification and proteosomal degradation, as pVHL is unable to bind the unmodified sub-

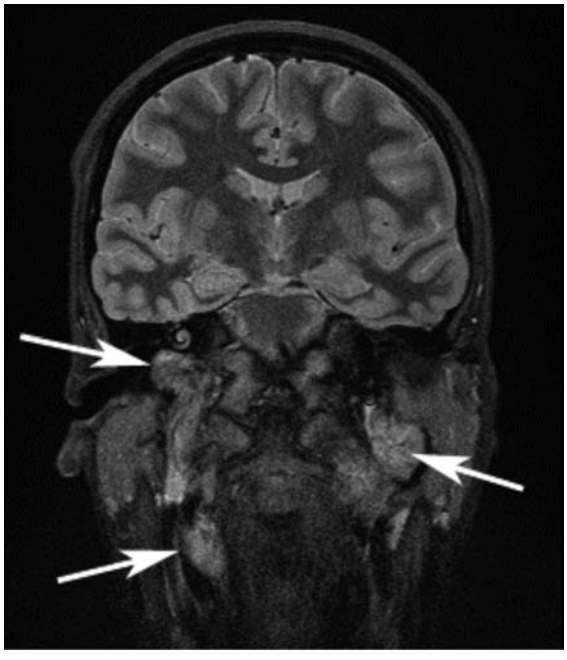

Figure 1. Magnetic resonance image scan of the neck. Fast T2-weighted MRI scan demonstrates the right glomus jugulare tumor (adjacent to right cochlea, arrow), and bilateral glomus vagale tumors (arrows).

Correspondence: Jeremy J. Turner, Elsie Bertram Diabetes Centre, Norfolk and Norwich University Hospital, Norwich, NR4 7UY, UK
E-mail: Jeremy.turner@nnuh.nhs.uk

Contributions: TMMT, ECIH, KM, NMM, JJT, all were involved in the clinical care of the patient described; RVT, ERM, provided and interpreted the genetic studies.

Conflict of interest: the authors report no conflicts of interest.

Received for publication: 4 July 2009.
Revision received: 9 August 2009.
Accepted for publication: 10 August 2009.

Rare Tumors 2009; 1:e29
doi:10.4081/rt.2009.e29

units.[4] In addition, animal models of SDH inactivation suggest that reactive oxygen species may be increased and also might provoke a pseudohypoxic state.[6] Therefore *SDHB/D* mutations may predispose to a failure of normal developmental apoptosis of sympathetic neuronal cells leading to persistence of "pheochromocytoma precursor cells".[5] PGL1/*SDHD* disease is inherited as an autosomal dominant trait, but demonstrates parent-of-origin effects in that tumors only develop when the mutation is inherited from the father, with possible rare exceptions.[6] Typically, head and neck paragangliomas are found, but pheochromocytomas and abdominal or thoracic paragangliomas can develop also. The tumors often are multiple, and tend to develop early, with a median age of first presentation of 31 years. In addition, there is an age-dependent penetrance, with 48 percent, 73 percent, and 100 percent being diagnosed by the ages of 30, 40, and 70 years, respectively.[7] In contrast to PGL4/*SDHB* disease, where metastatic disease is common, the tumors in PGL1 tend to be benign.[7]

Conclusions

The clinical data accumulated regarding familial paraganglioma syndromes raise several important implications for their clinical management.

- Firstly, patients with familial disease or multiple tumors should be offered genetic testing. In addition, individuals with apparently sporadic pheochromocytoma or paraganglioma disease will require genetic screening if risk factors such as extra-adrenal sympathetic paraganglioma, malignant paraganglioma, or young age at diagnosis (e.g., below 40 years) are present.[2] Depending on the clinical presentation, mutation analysis of *VHL, SDHB, SDHC, SDHD*, and/or *RET* genes may be indicated.
- Secondly, the relatives of patients in whom a pathogenic mutation is detected should be offered genetic screening, even if they are asymptomatic, because of the age-dependent penetrance. The inheritance pattern of PGL1-related disease will influence the screening program (see following) and the counseling given to patients and their relatives. In our patient's case, her son is not likely to develop tumors because of the parent-of-origin effect on penetrance. However, he will require genetic screening when he is older, because if he is a carrier of the *SDHD* mutation, then his children may be at risk.
- Thirdly, carriers of these mutations will require regular, lifelong, clinical, biochemical, and radiological screening. In order to reduce the lifetime exposure to ionizing radiation, it is necessary to use imaging modalities such as MRI or ultrasound.

Optimum clinical management requires the multidisciplinary expertise of surgeons, endocrinologists, clinical geneticists, and radiologists.

References

1. Lenders JW, Eisenhofer G, Mannelli M, et al. Phaeochromocytoma. Lancet 2005;366:665-75.
2. Gimenez-Roqueplo AP, Lehnert H, Mannelli M, et al. Phaeochromocytoma, new genes and screening strategies. Clin Endocrinol 2006;65:699-705.
3. Pollard PJ, El-Bahrawy M, Poulsom R, et al. Expression of HIF-1alpha, HIF-2alpha (EPAS1), and their target genes in paraganglioma and pheochromocytoma with VHL and SDH mutations. J Clin Endocrinol Metab 2006;91:4593-8.
4. Selak MA, Armour SM, MacKenzie ED, et al. Succinate links TCA cycle dysfunction to oncogenesis by inhibiting HIF-alpha prolyl hydroxylase. Cancer Cell 2005;7:77-85.
5. Lee S, Nakamura E, Yang H, et al. Neuronal apoptosis linked to EglN3 prolyl hydroxylase and familial pheochromocytoma genes: developmental culling and cancer. Cancer Cell 2005;8:155-67.
6. Pigny P, Vincent A, Cardot Bauters C, et al. Paraganglioma after maternal transmission of a succinate dehydrogenase gene mutation. J Clin Endocrinol Metab 2008;93:1609-15.
7. Benn DE, Gimenez-Roqueplo AP, Reilly JR, et al. Clinical presentation and penetrance of pheochromocytoma/paraganglioma syndromes. J Clin Endocrinol Metab 2006;91:827-36.