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CASE REPORT

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Consanguineous couple with SDHD gene mutations: Diagnosis, treatment, and implications of family genetic testing

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Key Clinical Messages

The newly published clinical consensus guideline on the management of PGL/PCC is helpful for decision-making for diagnostics and treatment. Still, the treatment of patients with SDHD gene mutations requires an individual approach and those patients belong to multiprofessional teams. It is often assumed that spouses are genetically unrelated. However, the genetic relationships between spouses should always be examined empathetically and impartially.

KEYWORDS

glomus tumor, hereditary pheochromocytoma, paraganglioma syndromes, SDHD gene mutation

1 | INTRODUCTION

Paragangliomas and pheochromocytomas are rare entities. A significant proportion of cases are hereditary and occur as part of paraganglioma/pheochromocytoma (PGL/PCC) syndrome, which is caused by various pathogenic gene variants. A clinical consensus guideline on the management of PGL/PCC in patients harboring pathogenic germline variants of *SDHD* (encoding succinate dehydrogenase subunit D) was recently published.[1] However, some detailed questions remain unresolved and need to be discussed and decided by a multiprofessional treatment team.

A consanguineous married couple in which both spouses were carriers of the *SDHD* mutation presented to our department for the management of PGL/PCC syndrome.

2 | PATIENT HISTORY/EXAMINATION

The wife's initial medical presentation was in 2006 at the age of 31 years with swelling of the neck of unknown cause on both sides. Glomus tumors on the left and right sides were found to be the cause of these symptoms, and they were successfully removed. A genetic test was performed and revealed the presence of a heterozygous pathogenic variant (*c.33C>A*,*p.Cys11**) of the *SDHD* gene. No further manifestations were evident at the time, and no pathogenic gene variant had been detected in the patient's family before. Therefore, as an index patient, she informed her relatives, most of whom underwent genetic testing. The son of the index patient, conceived with a former partner, had inherited the same mutation. Additionally, this heterozygous,

pathogenic *SDHD* variant was detected in a great cousin of the index patient. He also had glomus tumors on both sides of the neck and underwent glomus extirpation on the left side in 2008. The right glomus tumor appeared to remain stable over time. Years later, he clinically developed arterial hypertension that was difficult to control; the cause was determined to be an active bilateral pheochromocytoma. Therefore, a transabdominal adrenalectomy on the right side was performed in 2021, and due to insufficient success in controlling blood pressure, a partial transabdominal adrenalectomy on the left side was performed in 2022. This great cousin had a daughter and a son with a women who was not a carrier of the SDHD gene mutation. Their daughter was later on tested positive for the heterozygous, pathogenic *SDHD* variant, their son did not undergo any genetic testing and has not until today.

A few years previously from now, the index patient married her great cousin, and the couple presented at our clinic together for follow-up examinations. The family tree with information about the *SDHD* gene status is presented in File S1.

At presentation, the wife stated that her self-measured blood pressure was normotensive. Since the first operation, she has had habitual hoarseness and slight difficulty swallowing due to hypoglossal and recurrent laryngeal nerve palsy, with no other complaints.

The husband reported that his blood pressure has been well controlled since the removal of one adrenal gland in 2021 and the partial removal of the other one in 2022 and that he no longer experienced blood pressure fluctuations. Due to postoperative adrenal insufficiency, he received hydrocortisone replacement.

3 | OUTCOME AND FOLLOW-UP

The wife underwent serological testing, which showed normal serum levels for metanephrine, normetanephrine and 3-methoxytyramine. Upper endoscopy and whole-body anatomical imaging (radiolabeled somatostatin receptor (SSTR)-based hybrid imaging, DOTATOC-PET/CT) were performed to diagnose disease spread on a whole-body scale. There was no evidence of a suspected malignant cervicothoracoabdominal lesion (see File S2) and there was no evidence of a gastrointestinal stromal tumor (GIST).

The husband also had normal serum levels for metanephrine, normetanephrine and 3-methoxytyramine. On DOTATOC-PET/CT, the known glomus tumor on the right was consistent in size with that on previous examinations. In the base plate of the lumbar vertebral body 1, a small multisclerosing lesion with increased SSTR expression was observed, which could correspond to osseous metastasis or a benign change (see File S3). Gastroscopy revealed no evidence of an *SDH*-associated GIST. Sonography of the thyroid showed stable nodules in comparison to the previous examination.

Following the decision of the multidisciplinary tumor board (MTB), we recommended the wife to be seen again for follow-up by clinical assessment, metanephrine, normetanephrine and 3-methoxytyramine measurement in serum as well as DOTATOC-PET/CT after 12 months. Upper endoscopy should be performed every 2–3 years.

The MTB recommended the husband to undergo short-term follow-up by clinical assessment, biochemical measurements, and DOTATOC-PET/CT at 3–6 months to monitor the dynamics of the change in the lumbar vertebral body 1 and 12 months thereafter if the findings were stable. Diagnosis of spread using endoscopy should be performed every 2–3 years.

The wife's son and the husband's daughter who had both been conceived with former partners were carriers of the pathogenic *SDHD* gene variant and have not yet undergone any examination other than genetic testing. The MTB recommended repeated blood pressure measurements, clinical assessment, and biochemical measurements to monitor for new PPGLs.

4 | DISCUSSION

Hereditary paraganglioma–pheochromocytoma (PGL/PCC) syndromes are genetic diseases in which paragangliomas composed of neuroendocrine cells can occur in various locations from the skull to the pelvis, and pheochromocytomas can occur as paragangliomas of the adrenal medulla.

Sympathetic paragangliomas cause an excess of catecholamines, while parasympathetic paragangliomas are usually nonsecretory. Extra-adrenal parasympathetic paragangliomas occur primarily in the head and neck area, whereas extra-adrenal sympathetic paragangliomas are located primarily in the lower mediastinum, abdomen, and pelvis and are predominantly secretory. Pheochromocytomas often lead to an excess of catecholamines, which are clinically evident by spikes in blood pressure, a feeling of heat, palpitations, headaches, and sweating. The risk of metastasis varies depending on the underlying gene variant but is generally greater for extra-adrenal parasympathetic paragangliomas than for pheochromocytomas. Various tumor diseases, including clear cell renal cell carcinoma, gastrointestinal stromal tumors (GISTs) and pulmonary chondromas, are associated with hereditary PGL/PCC syndrome.[2]

Approximately 30% of PGLs and PCCs are caused by genetic mutations. The gene mutations associated with PGL/PCC can be divided into three clusters. Cluster 1 (the pseudohypoxic group) includes the genes *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF2*, *FH*, *VHL*, *IDH1/2*, *MHD2*, *EGLN1/2*, and *HIF2/EPAS*. Cluster 2 (the kinase group) includes *RET*, *NF1*, *TMEM127*, *MAX*, and *HRAS*, and Cluster 3 (the Wnt signaling group) includes *CSDE1* and *MAML3*.[3,4]

The most common pathogenic variants that lead to PGL/PCC syndrome are detected in the *SDHB*, *SDHC*, and *SDHD* genes (Cluster 1).[5] The pathogenic *SDHD* variant in the patients in this case report was part of Cluster 1. Genetic penetrance varies between 8% and 37% for *SDHB* mutations and 38% and 64% for *SDHD* mutations.[6]

Although the pathogenesis and genetics of PGL/PCC syndrome are well understood, the optimal follow-up strategy and therapy is still under debate. Three groups should be considered: First, patients with a proven gene mutation and proven PGL/PCC (patients with hereditary PGL/PCC syndrome); second, patients with PGL/PCC without genetic testing; and third, patients with a proven gene mutation without evidence of tumors who were tested in a human family genetic screening.

Very recently an urgently needed clinical consensus guideline on the management of phaeochromocytoma and paraganglioma in patients with germline *SDHD* pathogenic variants was published.[1] It is emphasized that all monitoring and treatment decisions must be made by a multidisciplinary team and each case should be considered individually. Further recommendations of this guideline as well as recommendations of a former international consensus[7] can be summarized as follows:

4.1 | Initial testing for patients with *SDHD* PPGLs

Patients should receive an evaluation by clinical assessment and biochemical testing (metanephrines in serum/urine and serum methoxytyramine). A head and neck MRI and an SSTR-based hybrid imaging DOTATOC-PET/CT should be performed.[1] If PPGL occur before knowledge of a positive mutation status, they should be tested for *SDHx* mutation, especially in young age of onset and positive family history.[7-9] This was the case with our index patient, in whom PPGL were initially noticeable and the *SDHD* gene mutation was subsequently detected. As a result, family screening was conducted.

4.2 | Implications for SDHD gene mutation carriers without symptoms

In human genetic screenings, as in the present case, people can test positive for a PGL/PCC-associated *SDHD* gene mutation without PGL or PCC being present. In this case initial testing via physical examination, including blood pressure measurement, determination of serum or urine metanephrine levels and MRI/PET-CT, is recommended. If the initial screening results are negative, blood pressure and serum metanephrine measurements should be performed annually, and MRI of the head, neck, thorax, abdomen, and pelvis should be performed every 2–3 years. If the results of the initial screening are positive, the person should be seen at a specialized center to determine the best course of action.[7]

4.3 | Evaluation of surgical interventions and therapeutical radiation for patients with *SDHD* HNPGLs

Patients with vagal paragangliomas should rarely be considered for resection due to high risk of operation-related vocal cord palsy. Observation is an effective approach in many cases. If the tumor develops urgent indications for therapy such as compression of vital neighboring, therapeutic radiation is usually recommended before surgery.[1]

This case report illustrates the difficulty of finding the right balance between the timely implementation of surgical removal and watchful observation due to awareness of significant surgical risks: The wife had been operated on her glomus tumor and suffered from hypoglossal and recurrent laryngeal nerve palsy with a complicated course, whereas one of the husband‘s glomus tumors was and still is under follow-up with good clinical success and absence of any related symptoms.

4.4 | Patients with *SDHD* non-HNPGLs and phaeochromocytomas

For patients with functional thoracic, retroperitoneal or pelvic PGL and patients with pheochromocytoma, surgical tumor resection is the first priority, especially if full tumor removal is possible,[1] as performed on the husband with consequently good control over his blood pressure.

4.5 | Medical management of patients with *SDHD* PPGLs

In norepinephrine-associated manifestations, the use of α-adrenoceptor blockers is recommended, especially before any surgical and non-surgical treatment interventions.[1]

4.6 | Surveillance of patients with *SDHD* PPGLs

Blood pressure measurements, clinical assessment, and biochemical measurements are recommended annually unless there are special circumstances or disease progression. A whole-body MRI is recommended every 2–3 years and SSTR PET/CT should be scheduled on an individual basis. In metastatic disease, the frequency of imaging and therapeutic decisions should be discussed by the multiprofessional team as happened in our case.

AUTHOR CONTRIBUTIONS

Johanna Braegelmann: Conceptualization; formal analysis; writing – original draft. **Annie Mathew:** Formal analysis; supervision. **Dagmar Führer-Sakel:** Supervision; writing – review and editing. **Harald Lahner:** Conceptualization; supervision; writing – review and editing.

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DATA AVAILABILITY STATEMENT

The data that support these findings are available on request from the corresponding author.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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