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## Biochemically Silent Sympathetic Paraganglioma, Pheochromocytoma, or Metastatic Disease in *SDHD* Mutation Carriers

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**Context:** Current guidelines do not consistently recommend imaging beyond the head and neck region in succinate dehydrogenase subunit D (*SDHD*) mutation carriers as long as catecholamine metabolite levels are within the reference range.

**Participants:** We report a series of 10 patients carrying pathogenic variants in the *SDHD* gene from five tertiary referral centers for paraganglioma (PGL) in the Netherlands, who presented with a sympathetic PGL (sPGL), pheochromocytoma (PHEO), or metastases outside the head and neck region in the absence of excessive catecholamine production. Two of six patients with a biochemically silent sPGL/PHEO developed metastatic disease. Additionally, four patients were found to have metastases outside the head and neck region from head and neck PGL. The average interval between the initial diagnosis and discovery of the silent lesions was 10 (range, 0 to 32) years.

**Conclusions:** The absence of excessive catecholamine production does not exclude the presence of manifestations of *SDHD* outside the head and neck region. These findings suggest that a more extensive imaging strategy in *SDHD* mutation carriers may be warranted for detection of biochemically silent lesions. (*J Clin Endocrinol Metab* 104: 5421–5426, 2019)

**P**athogenic variants of the succinate dehydrogenase subunit D (*SDHD*) gene (*SDHD* mutations) cause familial paraganglioma (PGL) syndrome type 1 (Online Mendelian Inheritance in Man: 168000) (1). In *SDHD*-linked patients, PGLs predominantly arise in the head and neck region, whereas sympathetic paragangliomas (sPGLs) in the thorax and abdomen and pheochromocytomas (PHEOs) in the adrenal glands occur less frequently. In general, *SDHD*-related PGLs in the head and neck (HN-PGL) are of parasympathetic origin and are therefore mostly nonfunctional. In contrast, intrathoracic or intra-abdominal sPGLs or PHEOs (present in 16% to 29% of *SDHD* mutation carriers) are of sympathetic origin and considered to cause hypersecretion of catecholamines (2–4). Although *SDHD* mutation carriers may develop multiple (HN)PGLs, the frequency of metastatic disease is low. In contrast, succinate dehydrogenase subunit B (*SDHB*)-related disease (PGL syndrome type 4; Online Mendelian Inheritance in Man: 115310) is often diagnosed as a single PGL, and *SDHB* mutation carriers more frequently develop sPGLs, PHEOs, and metastatic disease (5). Additionally, the incidence of other SDH-related manifestations such as gastrointestinal stromal tumors, renal cell carcinoma, and pituitary adenoma in *SDHB* mutation carriers is higher compared with *SDHD* mutation carriers (6). International guidelines do not consistently address screening strategies aimed at detecting biochemically silent disease in *SDHD* mutation carriers (7, 8). Commonly, screening of *SDHD* mutation carriers includes measurement of plasma or urinary metanephrines, the metabolites of catecholamines, in addition to routine imaging of the head and neck region. Despite functional positron emission tomography (PET) imaging having a high sensitivity for detecting *SDHD*-related PGLs, its role in the screening strategy of *SDHD* mutation carriers has not been studied yet (9–12). Recent recommendations suggest baseline and 5-yearly follow-up MRI of the chest, abdomen, and pelvis in silent *SDHD* mutation carriers (5, 13). In this case series, we describe 10 *SDHD*-linked patients who developed biochemically silent manifestations that were not detected using the standard-of-care monitoring protocol.

## Patients and Methods

In this retrospective, multicenter case series, we assessed patient records in five tertiary referral centers for PGL in the Netherlands. *SDHD*-related patients and nonsymptomatic *SDHD* mutation carriers >18 years of age were identified, in whom the genetic status had been confirmed using DNA mutation analysis. Clinical characteristics including sex, age, the occurrence and location of *SDHD*-linked tumors, age at diagnosis, and laboratory results from patients with biochemically silent

advanced disease were collected. Biochemical screening included the annual measurement of metanephrine, normetanephrine, and dopamine/3-methoxytyramine in two 24-hour urinary or plasma samples. *SDHD* mutation carriers or patients were referred to the outpatient clinics of the Departments of Otolaryngology and Endocrinology according to current protocols for PGL in the Netherlands (14). All carriers of *SDHD* mutations were offered annual clinical evaluation, biochemical screening for catecholamine excess, as well as MRI of the head and neck once every 3 years. In case of excessive catecholamine secretion (according to local reference values) additional imaging of the chest, abdomen, and pelvis was performed. Screening for *SDHD* mutations was performed by direct sequencing using the Sanger method on an ABI 377 genetic analyzer (Applied Biosystems, Carlsbad, CA) and by multiplex ligation-dependent probe amplification using the P226 MLPA kit (MRC Holland, Amsterdam, Netherlands). Patients were informed and gave written consent to participate. The study was found to be exempt from consideration by the Medical Ethical Committee of the Amsterdam UMC, location VU University Medical Center in Amsterdam.

## Results

Within a cohort of 522 *SDHD* mutation carriers, 10 *SDHD* mutation carriers were identified (2%), who had either an sPGL, PHEO, and/or metastatic disease in the absence of elevated levels of catecholamine metabolites. The median age at diagnosis of the first PGL or at confirmation of an *SDHD* mutation was 41 years (range, 15 to 57 years), and the silent lesions were identified at a median age of 51 years (range, 17 to 65 years). The average interval between the initial diagnosis and discovery of the silent lesion was 10 years (range, 0 to 32 years). Six patients had been diagnosed with a biochemically silent sPGL or PHEO (three intrathoracic PGLs, one abdominal PGL, and two PHEOs). Two of the six patients had developed metastatic disease that had likely originated from the silent sPGL/PHEO (Table 1). In these six patients, the median age at diagnosis of the first PGL or at confirmation of an *SDHD* mutation was 36 years (range, 23 to 55 years). The silent lesions were detected at a median age of 47 years (range, 40 to 55 years). The average interval between the initial *SDHD* diagnosis and discovery of the silent lesion was 11 years (range, 0 to 32 years). The metastases from the silent tumors were found 4 months and 3 years after the time of the diagnosis of the silent lesion. Additionally, four patients had biochemically silent metastatic disease outside the head and neck region in the presence of HN-PGL (Table 2). The median age at diagnosis of the first HN-PGL or at confirmation of an *SDHD* mutation in these four patients was 45 years (range, 15 to 57 years), and the metastases were identified at a median age of 56 years (range, 17 to 65 years). The average interval between the initial diagnosis and discovery of the

**Table 1. Clinical Characteristics of SDHD-Linked Patients With Biochemically Silent sPGL/PHEO**

Patient No.	Sex	SDHD Mutation	Age at PGL/SDHD Diagnosis (y)	Age at Silent PGL Diagnosis (y)	Reason for Additional Imaging	Silent PGL Location	Location of Metastases	Time to Metastases After Silent PGL (y)	Catecholamine Biochemistry	Treatment
1	M	c.274G>T p.Asp92Tyr	40	46	Suspected nephrolithiasis	PHEO	Lymph nodes, bone	0	M, NM, 3MT normal	Surgery, RT, PRRT
2	F	c.383C>T p.Leu128Pro	23	55	Clinical suspicion intrathoracic PGL	Para-aortic sPGL	N/A	N/A	M, NM, 3MT normal,	Surgery
3	M	c.284T>C p.Leu95Pro	33	40	Follow-up after resection sPGL	Aortopulmonary PGL	N/A	N/A	M, NM, 3MT normal	—
4	F	c.274G>T p.Asp92Tyr	43	44	Follow-up after resection sPGL	Aortopulmonary PGL	N/A	N/A	M, NM, D normal	Surgery
5	F	c.274G>T p.Asp92Tyr	28	48	Unknown	PHEO	N/A	N/A	M, NM, D normal	Surgery
6	F	c.274G>T p.Asp92Tyr	55	55	Staging after diagnosis lung tumor	Paravertebral	Bone	3	M, NM, D normal	Surgery, RT, SSA

Abbreviations: 3MT, 3-methoxytyramine; D, dopamine; M, metanephrine; NM, normetanephrine; PRRT, peptide receptor radionuclide therapy; RT, radiotherapy; SSA, somatostatin analog.

metastases was 8 years (range, 0 to 19 years). Below, we highlight two illustrative cases.

### Case 1

A 40-year-old male (patient 1 in Table 1) was referred for clinical follow-up because of a *SDHD* gene mutation that had been identified due to a family history of PGL. The 24-hour urine catecholamine profile and MRI of the head and neck were normal. Seven years later, he presented with nephrolithiasis. CT of the abdomen revealed an incidental adrenal tumor with a maximum diameter of 14 cm. MRI of the neck showed an 8-mm HNPGL (Fig. 1A). Blood pressure was normal and the patient did not report spells. Twenty-four hour urine analysis showed normal metanephrine and normetanephrine concentrations. The adrenal tumor was resected via an open laparotomy. Histopathological examination of the tumor confirmed the diagnosis PHEO. <sup>18</sup>F-fluoro-2-deoxy-D-glucose (<sup>18</sup>F-FDG) PET/CT imaging 4 months postoperatively showed metabolically active enlarged mediastinal and infrahilar lymph nodes, suspected for metastatic disease. Subsequent cytological analyses supported the recurrence of PHEO. Owing to the absence of symptoms and lack of radical surgical options, the patient was followed. The thoracic lesions remained stable for 3 years. Subsequently, the patient developed an acute radicular syndrome due to a lytic vertebral bone metastasis. A <sup>68</sup>Ga-DOTA<sup>0</sup>-Tyr<sup>3</sup>-octreotate scan showed multiple bone metastases in the ribs, spine, and pelvis (Fig. 1B). The diagnosis of metastatic PHEO was histologically confirmed by a bone biopsy of a rib lesion. No increase of serum normetanephrine, metanephrine, or 3-methoxytyramine concentrations was detected. The patient was treated with local radiotherapy of the painful bone locations, followed by peptide receptor radionuclide therapy.

### Case 2

A 15-year-old female carrier of an *SDHD* mutation (patient 7 in Table 2) was diagnosed with a left carotid body PGL with a maximum diameter of 6 cm. The carotid body PGL was completely removed via a cervical approach. Follow-up MRI scans did not reveal residual disease until 8 years after surgery when two lesions in the trajectory of the left internal carotid artery were found. The lower lesion of 7 mm was suggestive of local recurrence, whereas an upper lesion of 11 mm was identified as a vagal PGL. A “wait-and-scan” policy was adopted.

Two years later, the patient developed fatigue and episodes of fever. MRI of the head and neck showed slight growth of both HNPGLs. Plasma catecholamine metabolite levels had remained normal. Additional

**Table 2. Clinical Characteristics of SDHD-Linked Patients With Biochemically Silent Metastases of HNPGL**

Patient No.	Sex	SDHD Mutation	Age at PGL/SDHD Diagnosis (y)	Age at Diagnosis of Metastases (y)	PGL Location	Reason for Additional Imaging	Location of Metastases	Catecholamine Biochemistry	Treatment
7	F	c.383C>T p.Leu128Pro	15	17	HNPGL	General complaints and fever	Liver, lungs, bone	M, NM, 3MT normal	SSA
8	F	c.274G>T p.Asp92Tyr	45	55	HNPGL	Pain	Bone	M, NM, D normal	Surgery, PRRT, RT
9	M	c.274G>T p.Asp92Tyr	57	57	HNPGL	Pain	Bone	M, NM, 3MT normal	SSA
10	F	c.274G>T p.Asp92Tyr	46	65	HNPGL	Pain	Bone	M, NM, D normal	Surgery, PRRT, RT, SSA

Abbreviations: 3MT, 3-methoxytyramine; D, dopamine; M, metanephrine; NM, normetanephrine; PRRT, peptide receptor radionuclide therapy; RT, radiotherapy; SSA, somatostatin analog.

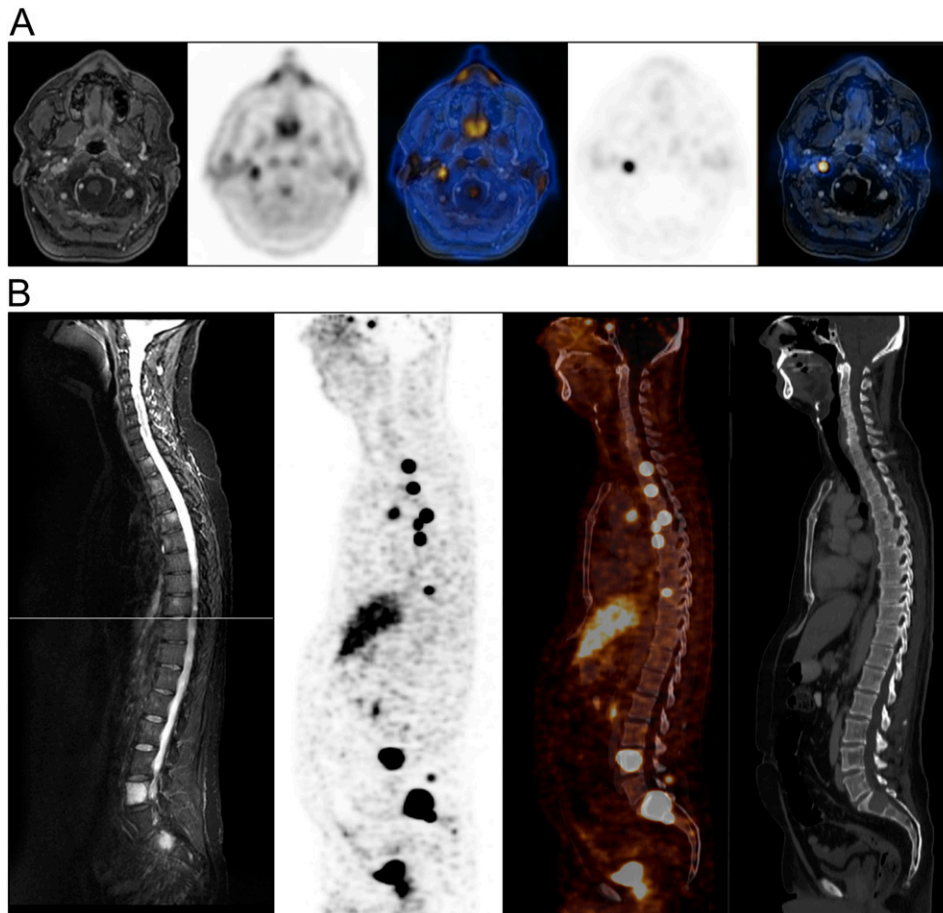
imaging of the chest and abdomen performed for persistent general complaints showed multiple lesions in the liver and lungs, suggestive of metastatic disease. A liver biopsy confirmed the diagnosis of metastatic PGL. Both the carotid body PGL and the largest liver lesion could be detected using <sup>111</sup>In-octreotide single-photon emission computed tomography imaging. <sup>18</sup>F-FDG PET showed increased metabolic activity in all tumor locations as well as in an additional detected sclerotic bone lesion in the L5 vertebra. <sup>18</sup>F-L-dihydroxyphenylalanine (<sup>18</sup>F-DOPA) PET did not identify additional lesions. Treatment with long-acting somatostatin analog lanreotide (60 mg monthly) resulted in complete remission of symptoms. The patient was monitored with spine MRI and <sup>18</sup>F-FDG PET/CT scans, which showed stable disease. Five years after the diagnosis of metastatic disease, the patient had stable disease. <sup>18</sup>F-FDG PET showed a significant decrease in metabolic activity of multiple metastatic lesions and a complete response at the level of L5.

### Discussion

In this multicenter case series, we describe 10 SDHD-linked patients with a biochemically silent sPGL, PHEO, or metastatic disease. The average interval between the initial diagnosis and the discovery of the silent lesions was 10 (range, 0 to 32) years. Havekes *et al.* (15) reported a single hormonally inactive PHEO in an SDHD patient and advocated future studies to establish whether routine imaging should be expanded for initial screening or follow-up monitoring. More recently, in a comprehensive imaging study, 26 previously unknown sPGLs and PHEOs, but no metastases, were detected in 132 SDHD mutation carriers (20%) using a protocol that included MRI and CT imaging, supporting this suggestion (16).

In the Netherlands, routinely monitoring SDHD mutation carriers for biochemically silent manifestations outside the head and neck region is not common practice. Biochemically silent abdominal PGL due to absence of intratumoral tyrosine hydroxylase activity has been reported in SDHB-linked patients (17). In part due to this observation, SDHB mutation carriers are subjected to more extensive monitoring than are SDHD mutation carriers: standard-of-care monitoring in SDHB mutation carriers includes MRI of the chest, abdomen, and pelvis every 3 years (14).

van Hulsteijn *et al.* (18) described a review of SDHD mutation carriers and found an 8% prevalence of metastatic PGL. Although the number of patients is limited in our report, two of the six patients (33%) with a silent sPGL/PHEO developed metastatic disease after the diagnosis of the silent manifestations. Of note, as imaging beyond the head and neck region in the absence of



**Figure 1.** Imaging studies of patient 1. (A) Transverse images of the jugular paraganglioma on the right side: MRI short tau inversion recovery,  $^{18}\text{F}$ -fluoro-2-deoxy-D-glucose ( $^{18}\text{F}$ -FDG) PET,  $^{18}\text{F}$ -FDG PET/MRI fused,  $^{68}\text{Ga}$ -DOTA<sup>0</sup>-Tyr<sup>3</sup>-octreotate ( $^{68}\text{Ga}$ -DOTATATE),  $^{68}\text{Ga}$ -DOTATATE PET/MRI fused (from left to right). (B) Sagittal images of the vertebral column showing multiple bone metastases: MRI,  $^{68}\text{Ga}$ -DOTATATE PET,  $^{68}\text{Ga}$ -DOTATATE PET/CT fused, CT (from left to right).

excessive catecholamine production is not routinely performed in the Netherlands, only a minority of the 522 *SDHD* mutation carriers is likely to have undergone additional imaging. In this case series, the additional imaging studies were often performed for other reasons than *SDHD*. Therefore, the true prevalence of silent lesions in the entire patient population in the five centers is likely to be higher than the 10 cases (10/522; 2%). Alternatively, the number of patients with metastatic disease from silent lesions outside the head and neck region probably reflects an overrepresentation due to selection bias; in several patients additional imaging was performed because of general complaints, possibly caused by advanced disease, resulting in the detection of metastatic disease in two cases. In the four patients with metastatic disease from HNPGL, the silent metastatic PGL was identified simultaneously in one case and after 2, 10, and 19 years after the initial PGL diagnosis, respectively. As early detection and treatment of PGL/PHEO may lead to better treatment outcomes, these delays as well as the late diagnoses of the primary silent tumors may have negatively affected the prognosis of these patients. We could

not identify additional patient-related risk factors for predicting detection of silent PGLs.

More intensive monitoring strategies such as whole-body MRI, somatostatin receptor PET imaging, or  $^{18}\text{F}$ -DOPA imaging have been reported to be effective in *SDHD* mutation carriers for detecting sPGL, PHEO, or metastatic disease (10–12, 16, 19–21). Comparative imaging studies, including cost-effectiveness analyses, in *SDHD* mutation carriers aimed at detection of bone metastases in particular are lacking. Functional imaging with  $^{68}\text{Ga}$ -DOTA<sup>0</sup>-Tyr<sup>3</sup>-octreotate appears to be superior compared with  $^{18}\text{F}$ -DOPA,  $^{18}\text{F}$ -FDG, MRI, and CT for the detection of metastatic PHEO/PGL lesions in soft and bony tissue (10, 12). However, rapid-sequence non-contrast MRI has a good diagnostic accuracy at relatively low cost (19). Therefore, we would suggest to further study whole-body non-contrast-enhanced MRI at the time of diagnosis of *SDHD* as the first-choice imaging modality in *SDHD* mutation carriers. In the absence of lesions at baseline, whole-body MRI could subsequently be repeated every 5 years or in case of clinical suspicion of a silent manifestation, as has been suggested (5).

In *SDHD* mutation carriers, the clinician should be aware of the possibility of sPGL, PHEO, and/or metastatic disease outside the head and neck region, even in the absence of increased concentrations of catecholamine metabolites. This finding supports more comprehensive imaging strategies including the thorax, abdomen, and pelvis, for example, at the time of first diagnosis of SDHD. Further research is necessary to assess the feasibility (and cost-effectiveness) of this intensified screening strategy and the effect of early intervention on the risk of developing metastatic disease in silent sPGL/PHEO.

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**Data Availability:** Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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