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Original article

Association of urinary bladder paragangliomas with germline mutations in the SDHB and VHL genes

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Abstract

Objective: Our primary goal was to examine the clinical characteristics of a series of patients with urinary bladder paragangliomas (UBPGLs), focusing particularly on their genetic backgrounds.

Materials and methods: We analyzed the medical records of patients who presented to the National Institutes of Health with UBPGL from 2000 to 2013 to determine their clinical characteristics and outcomes, biochemical phenotype, tumor size, and genetic background.

Results: Of the 27 patients with UBPGLs who were identified, 17 (63%) had underlying genetic mutations. Overall, 14 (51.9%) patients had a germline mutation in the succinate dehydrogenase subunit B gene (*SDHB*), and 3 (11.1%) had mutations in the von Hippel-Lindau gene (*VHL*). Of the 21 patients who had biochemical data available before their first operation, 19 (90.5%) presented with a noradrenergic biochemical phenotype; 7 (33.3%) patients had tumors that also secreted dopamine. In addition, 1 patient (4.8%) had elevated metanephrine levels, and 2 (9.5%) had normal biochemical data. In total, 13 (48.1%) patients in the series were diagnosed with metastatic disease, at either first presentation or follow-up; 6 of these patients (46.1%) had *SDHB* mutations.

Conclusions: UBPGLs typically present with a noradrenergic phenotype and are frequently associated with underlying germline mutations. Patients presenting with these rare neuroendocrine tumors should be screened for these mutations. In addition, patients with UBPGLs should be followed up closely for metastatic development regardless of genetic background, as almost half of the patients in this series presented with metastatic disease and less than half of them had *SDHB* mutations. Published by Elsevier Inc.

Keywords: Paraganglioma; Succinate dehydrogenase; SDHB; Urinary bladder; von Hippel-Lindau

1. Introduction

Pheochromocytomas (PHEOs) and paragangliomas (PGLs) are neuroendocrine tumors of chromaffin cells in the adrenal medulla (for PHEOs) or sympathetic or parasympathetic paraganglia (for PGLs). Extra-adrenal PGLs account for 15% to 20% of PHEO/PGLs and may be located anywhere from the bladder to the base of the skull [1]. PHEOs/PGLs secrete, synthesize, and metabolize catecholamines; measurement of catecholamines and their

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metabolites, metanephrines, is important both for diagnosis and biochemical phenotype determination. Secretory PHEOs/PGLs can be adrenergic (predominantly epinephrine and its metabolite metanephrine), noradrenergic (predominantly norepinephrine/normetanephrine), or dopaminergic (predominantly dopamine and its newly discovered metabolite methoxytyramine) [2]. PHEOs/PGLs can also be biochemically silent [3].

Approximately one-third of PHEOs/PGLs are associated with inherited mutations in 17 genes. The most important include the von Hippel-Lindau (*VHL*); rearranged during transfection (*RET*); neurofibromatosis 1 (*NF1*); succinate dehydrogenase (SDH) subunits A, B, C, and D; SDH complex assembly factor 2 (*SDHAF2*); transmembrane protein 127 (*TMEM127*); and myc-associated factor X (*MAX*) genes [4]. Of these, mutations in *SDHB*, *SDHC*, and *SDHD*, which encode subunits of mitochondrial complex II, are strongly associated with the development of extra-adrenal PGLs [4–8]. SDH is involved in the Krebs cycle, oxidative phosphorylation, and electron transport chain. Particular subunits are strongly associated with certain PGL locations; for example, *SDHD* mutations are often linked to head and neck PGLs, and *SDHB*-related tumors are commonly extra-adrenal [3–5,7,8]. PHEOs/PGLs are also found in 10% to 20% of patients with VHL mutations [4]. Although PHEOs are more common in VHL, extra-adrenal PGLs have been identified, including 1 reported case of a bladder tumor [9].

PGLs of the urinary bladder (UBPGLs) are rare, accounting for less than 6% of PGLs and 0.06% of bladder tumors [10]. UBPGLs often present with hypertension, hematuria, postmicturition syncope, or other symptoms due to increased catecholamines (e.g., headaches, palpitations, blurred vision, flushing, and sweating). However, approximately 17% to 39% are biochemically silent [11,12]. Although there have been several reports on UBPGLs, there has been no study focusing on their genetic characteristics. In the present study, we aimed to describe carefully the clinical characteristics, biochemical phenotypes, and genetic backgrounds of UBPGLs.

2. Materials and methods

2.1. Subjects

A retrospective medical record review of patients with PHEOs/PGLs seen at the National Institutes of Health (NIH) in Bethesda, Maryland, USA, from 2000 to 2013 was conducted. Only those with pathologically confirmed UBPGL were included. Imaging, biochemical, operative, and pathology reports were reviewed. Patients were imaged using a combination of computed tomography (CT), magnetic resonance imaging (MRI), ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy, octreotide (OCT) scans, and positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) and ^{18}F-fluorodopamine (FDA). Clinical presentations and patient outcomes were also recorded, including metastases development, defined as the presence of disease in sites where chromaffin cells are not normally present (e.g., lymph nodes, bones, liver, and lungs).

This study was approved by the Institutional Review Board of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development at the NIH. Each patient gave informed written consent upon enrollment in the study.

2.2. Genetic studies

Genomic DNA was extracted from whole blood samples for genetic testing of *SDHB*, *SDHC*, *SDHD*, and *VHL*. Polymerase chain reaction–based bidirectional sequencing was performed by Mayo Medical Laboratories, Rochester, MN, or by the Division of Molecular Diagnostics, University of Pittsburgh Medical Center, as previously described [13]. Large deletions were detected using multiplex ligation-dependent probe amplification and Luminex FlexMap Technologies [14]. None of the patients had clinical presentations suggestive of *RET* or *NF1* mutations. Testing for *MAX*, *TMEM127*, *SDHA*, and *SDHAF2* was not performed.

2.3. Catecholamine and metanephrine assays

Plasma or urinary catecholamine and metanephrine levels were measured using standard high-pressure liquid chromatography with electrochemical detection at the NIH or Mayo Medical Laboratories, Rochester, MN. Forearm blood samples were drawn with patients in the supine position at least 20 minutes after an intravenous catheter was inserted, as previously described [15].

2.4. Statistical analysis

A statistical analysis of the metastatic rates in the SDHB and non-SDHB groups was done using the Fisher exact test.

3. Results

Of the 531 patients with PHEO/PGL seen at NIH, 27 were treated for UBPGL. Of them, 15 were women (55.6%) and 12 (44.4%) were men, with a mean age at initial diagnosis of 29.5 ± 14.7 years (range: 6–58 y). Overall, 24 (88.9%) patients initially presented with UBPGL. The remaining 3 presented with UBPGL after previous resections of other primary PHEO or PGL. At UBPGL diagnosis, 19 (70.4%) patients were hypertensive, and 22 (81.5%) presented with signs and symptoms of catecholamine excess. Detailed clinical profiles are summarized in Table 1.

Most patients had elevated plasma/urine catecholamines/metanephrines. Of the 21 patients with available