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Editorial

Should Methoxytyramine Routinely Be Included in the Guidelines for Biochemical Assessment of Pheochromocytomas and Paragangliomas?

Mustafa et al published an intriguing report on a "Dopamine-secreting carotid body paraganglioma (PGL) in a patient with an *SDHB* pathogenic variant."[1] In their discussion, they raise important clinical questions including whether dopamine-secreting PGLs are underdiagnosed due to a lack of adequate screening. Of note, the most recent Endocrine Society clinical guidelines, now outdated, do not recommend routine screening for dopamine or dopamine metabolites in patients with suspected pheochromocytoma or paragangliomas (PPGLs).[2] In their conclusion, Mustafa et al urged a reassessment of current clinical screening guidelines, particularly in light of the high rate of metastases and heritability seen with dopamine-secreting PPGLs whether located in the head and neck or outside of it. They advised screening for dopamine hypersecretion in patients with presumed nonsecretory PGLs and those with succinate dehydrogenase (*SDH)* pathogenic variants. Recently the International Consensus Guidelines/Statement on *SDHD* and *SDHB* pathogenic variants were published.

The World Health Organization classifies PPGLs according to their location and origin.[3] PGLs are extra-adrenal neuroendocrine tumors that arise from the chromaffin-like cells of the autonomic paraganglia. Pheochromocytomas are neuroendocrine tumors arising from the chromaffin cells of the adrenal medulla, the largest paraganglion of the sympathetic nervous system, and are therefore termed intra-adrenal PGLs.[3,4] PPGLs can potentially produce catecholamines including norepinephrine, epinephrine, and dopamine.

However, depending on the specific biochemical phenotype (adrenergic, noradrenergic, or dopaminergic), each respective catecholamine is secreted in only ~70% of patients, in contrast to its corresponding metabolites, which are produced continuously and secreted independently of catecholamine secretion in almost all patients.[5] Most PPGLs (85%) are pheochromocytomas/intra-adrenal PGLs and 15% are extra-adrenal PGLs.[6]

PGLs and pheochromocytomas have the highest degree of heritability among all tumors—approximately 40% are associated with germline pathogenic variants and 30% to 40% are related to somatic driver pathogenic variants.[7] Germline pathogenic variants in the *SDH* (*SDHA*, *SDHB*, *SDHC*, and *SDHD*) genes occur in 35% to 40% of patients with these tumors. These mutations which encode the subunits of the mitochondrial enzyme SDH are categorized as pseudohypoxia cluster 1A mutations that mimic hypoxia through disruption of the Krebs cycle, cause accumulation of oncometabolites, activation of the hypoxia signaling pathway, promotion of DNA hypermethylation, and inactivation of tumor suppressor genes and ultimately lead to tumorigenesis including metastatic behavior.[8] Among cluster 1A tumors, the highest tendency to metastasize is associated with *SDHB* pathogenic variants.[8]

PGLs may arise anywhere from the skull base to the bladder but are often localized to the head (skull base) and neck, are termed head and neck paragangliomas (HNPGLs). Most sporadic HNPGLs do not produce norepinephrine or epinephrine and are associated with the parasympathetic ganglia near the carotid body or along the branches of the vagal or glossopharyngeal nerves. Nevertheless, in ~5% of cases, these tumors produce norepinephrine (reflected by elevations in plasma normetanephrine) and in up to 70%, they produce dopamine (reflected by elevations in plasma 3-methoxytyramine [3-MT]). Most of these 3-MT secretory PGLs occur in patients with *SDH* mutations. Thus, plasma 3-MT is the single best analyte to assess patients with HNPGLs though the current methods to measure 3-MT are believed to underestimate the prevalence of dopamine-producing PGLs as current assays are not sensitive enough to detect very low levels (nanomolar range) of plasma 3-MT found in small HNPGLs.[9] A new highly sensitive chemical procedure requiring only about 50 ul of plasma combined with mass spectrometry to assay 3-MT and metanephrines is now available.[9,10] This approach more accurately detects the presence of 3-MT and, as a result, enables the true prevalence of dopamine-producing HNPLs, (estimated to be between 30% and 73% of secretory HNPLs) to be established.[9]

Dopamine-producing PGLs have a deficiency in the enzyme dopamine hydroxylase which converts dopamine to norepinephrine and accounts for the predominance of dopamine and absence of the metabolites of norepinephrine and epinephrine.[11] The clinical presentation of patients with dopamine-producing PGLs is often characterized by multifocality and metastatic behavior (perhaps due to less differentiated tumor cells), normotension, and symptoms/signs related to a large space-occupying lesion (such as pain, hearing loss, or headaches), without the presence of the classic symptoms of catecholamine excess such as palpitations, headaches, and diaphoresis. The behavior of *SDHx*-associated PPGLs, which indeed also present with elevated plasma 3-MT levels in up to 70% of patients, is sinister—they are multifocal and aggressive with high metastatic and recurrence rates (particularly for *SDHB* and *SDHA* PPGLs) and predispose patients to the occurrence of other tumors (such as gastrointestinal stromal tumors, renal carcinoma, and pituitary tumors).[12]

Measurement of the dopamine O-methylated metabolite plasma free 3-MT by using liquid chromatography with tandem mass spectrometry (LC-MS/MS), the most accurate, precise, and preferred method to assay this metabolite, is the most sensitive assay currently available to detect the presence of dopamine-producing PPGLs. This automated method using LC-MS/MS allows for ultrasensitive quantification of plasma-free 3-MT and

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metanephrines—in the picomolar range.[10] Detecting more than a twofold elevation in plasma 3-MT highly suggests a dopamine-producing PPGL.[8] Without assaying for 3-MT, these tumors will likely go undiagnosed or undetected until an advanced stage since the measurement of plasma or urinary dopamine or urinary 3-MT is unreliable.[5] The presence of a dopamine-producing tumor is also an independent risk factor for metastases thus measurement of this metabolite particularly in the high-risk patient (*SDH* mutation, previously surgically removed dopamine-producing PPGL, or a phenotypic pheochromocytoma that appears to be biochemically silent) is critical. The International Consensus Guidelines/Statement on *SDHD* and *SDHB* pathogenic variants recommended screening and surveillance of patients with PPGLs and *SDHB/D* pathogenic variants with plasma or urine metanephrines as well as the plasma dopamine metabolite, 3-MT.[13,14] Recent advances in machine learning tools that combine plasma 3-MT with other clinical indicators (age, sex, location and size of primary tumor, plasma metanephrines, prior history of PPGLs, and the presence of multifocal disease) show great promise in the ability to identify and predict metastatic dopamine-producing PGLs.[15]

In conclusion, we agree with Mustafa et al that screening for dopamine hypersecretion, (based on the measurement of plasma 3-MT) should be considered to assist with diagnosis and monitoring in the following scenarios: patients with a history of familial PGLs and *SDHx* pathogenic variants, including asymptomatic carriers; patients with biochemically silent PPGLs, and patients with an imaging phenotype suggestive of a PPGL but a negative metanephrine screening test. The best method to screen these patients is to assay 3-MT using automated LC-MS/MS.

Disclosure

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Ann T. Sweeney, MD
Division of Endocrinology
Department of Medicine
St Elizabeth's Medical Center
Brighton, Massachusetts

Michael A. Blake, MB, BCh
Division of Abdominal Imaging
Department of Radiology
Massachusetts General Hospital
Boston, Massachusetts

Sina Jasim, MD, MPH
Division of Endocrinology, Metabolism and Lipid Research
Washington University in St, Louis School of Medicine St. Louis, Missouri

Karel Pacak, MD, PhD, DSc
Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIH, Maryland
AKESO, Prague, Czech Republic

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