COLLEGE of AMERICAN PATHOLOGISTS

Testing for Pheochromocytoma/Paraganglioma

SYNOPSIS AND RELEVANCE

Laboratory testing for pheochromocytomas and paragangliomas can be complicated by numerous available tests. Accurate interpretation of results may be hindered by assay limitations and preanalytical variables. Adherence to the strategies in this module will:

1. Ensure that appropriate testing for pheochromocytomas and paragangliomas is performed, both screening and confirmatory tests.
2. Ensure that appropriate steps are taken to avoid erroneous test result interpretations due to assay limitations or preanalytical variables.

INSIGHTS

1. Metanephrines are relatively specific markers for pheochromocytomas and paragangliomas, although there are many pre-analytic variables that require consideration when performing these assays and interpreting results.
2. Plasma free fractionated metanephrines and urinary total fractionated metanephrines are appropriate assays for the diagnosis of pheochromocytomas and paragangliomas.
3. Plasma and urine catecholamine levels have no significant role in testing for pheochromocytomas and paragangliomas.
4. Avoid random urine specimens for testing total (free and deconjugated) fractionated metanephrines.
5. It is recommended that patients remain supine for 30 minutes before collecting venipuncture samples for testing. If supine samples cannot be collected, use of an appropriate reference range (sitting vs supine) is recommended. Testing should be avoided in the inpatient setting.

BACKGROUND

Pheochromocytomas and paragangliomas are uncommon histologically identical tumors that occur with a peak incidence in the 4th and 5th decades, and arise from chromaffin cells in adrenal and non-adrenal locations, respectively. The tumors are associated with an annual incidence of 0.6 cases per 100 thousand-person years.[1] Recognition and accurate diagnosis of these tumors is important as they may be potentially lethal if untreated (more common with paragangliomas). However, diagnosis may be difficult because signs and symptoms of excessive catecholamine secretion occur in less than 50% of patients and can also be seen in multiple non-neoplastic medical conditions. Moreover, patients may present in many different ways, including clinical symptoms (headaches, palpitations, and profuse sweating represent the classic triad), incidental findings on imaging studies, or discovery following identification of genetic test results or clinical syndromes associated with these lesions.[2-4] While most tumors are sporadic, hereditary forms occur in 10 clinically relevant syndromes (including multiple endocrine neoplasia type 2, neurofibromatosis type 1, and von Hippel-Lindau disease). At least 19 specific susceptibility genes have been associated with these tumors.[2] Accurate diagnosis and treatment requires an understanding of the clinical features (including associated syndromes), selection and interpretation of appropriate laboratory tests and imaging studies, and genetic factors. While this module is focused on laboratory testing, several recent reviews provide excellent summaries of the pertinent clinical, imaging and genetic considerations.[2-4]

Catecholamines (epinephrine, norepinephrine and dopamine) constitute important neurotransmitters and endocrine hormones, and laboratory measurements of catecholamine metabolites in blood or urine are very useful in the diagnosis of pheochromocytomas and paragangliomas. The major catecholamine produced by pheochromocytomas is epinephrine while the major catecholamine produced by paragangliomas is norepinephrine. Dopamine may rarely be secreted by these tumors, but it is more typically secreted by neuroblastomas. The leakage of catecholamines and their subsequent metabolism represents the primary source of catecholamine metabolites found in blood and urine. Metanephrine and normetanephrine, collectively referred to as "metanephrines," are the key metabolites and represent the most sensitive assay targets to detect pheochromocytomas and paragangliomas. Metanephrine is derived from epinephrine and normetanephrine from norepinephrine. Metanephrines can be further metabolized to vanillylmandelic acid (VMA), but this compound is not used in the diagnosis of pheochromocytomas or paragangliomas. The metabolic end-product of dopamine can be further metabolized to homovanillic acid (HVA), a compound which is not a metabolite of metanephrines. VMA and HVA, while useful in the diagnosis of neuroblastomas, are insensitive tests for detecting pheochromocytomas and paragangliomas.[5-7]

High-performance liquid chromatography with electrochemical detection or tandem mass spectroscopy represent gold standards for testing catecholamines and their metabolites. Plasma free fractionated metanephrines or 24-hour urine total fractionated metanephrines are currently the most widely advocated tests for detecting pheochromocytomas and paragangliomas; testing for catecholamines does not improve the sensitivity for detecting these tumors. Random urine total fractionated metanephrines testing is discouraged due to a lack of diagnostic utility. Plasma free fractionated metanephrines has a mean sensitivity of 97% and a mean specificity of 93% across 15 studies.[2] Mild elevations in plasma free fractionated metanephrines are commonly seen in patients without pheochromocytomas or paragangliomas. Borderline positive test results require additional testing or additional clinical workup. A negative result for plasma free fractionated metanephrines is helpful to exclude pheochromocytomas and paragangliomas, with the exception of very early or limited disease. The sensitivity of 24-hour urine total fractionated metanephrines varies in the literature but is generally considered to be slightly lower than plasma fractionated metanephrines, while the specificity is generally considered to be higher. Whether testing should be performed on plasma or urine is debated, and there are regional and institutional differences in recommended testing approaches.[3-9]

Interpretation of test results requires an awareness of multiple pre-analytical factors that can significantly influence catecholamine release. Medications and drugs of abuse may increase metanephrine levels, including L-DOPA, alpha-methyldopa, monoamine oxidase inhibitors, antihypertensive medications, diuretics, alcohol, and cocaine. Medications should be tapered or discontinued at least 2 weeks prior to laboratory testing. Similarly, exercise, stress, renal failure, severe congestive heart failure, myocardial infarction and acute illness may increase metanephrine levels. Even the stress of a venipuncture and upright posture has been shown to increase plasma metanephrine levels; for this reason, it is recommended that patients remain supine for 30 minutes before collecting venipuncture samples for testing. If supine samples cannot be collected, use of an appropriate reference range (sitting vs supine) is recommended. Testing is discouraged in the inpatient setting. Lastly, conjugated metanephrines are excreted in the urine and renal impairment will decrease clearance; in these circumstances, testing plasma free fractionated metanephrines is recommended.[2-4]

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