Pheochromocytoma

Clinical Background

Pheochromocytoma is a catecholamine producing tumor (epinephrine, norepinephrine).

Epidemiology

- Incidence – 2-8/1,000,000 in the U.S.
- Age – peaks in 30s-50s
- Sex – M:F, equal
- Occurrence – most are sporadic (90%)

Risk Factors

- Multiple Endocrine Neoplasia 2 (MEN2)
  - *RET* gene
  - Types
    - 2a – medullary thyroid carcinoma (MTC), pheochromocytoma (multicentric, bilateral), parathyroid adenoma
    - 2b – MTC, pheochromocytoma (multicentric, bilateral) intestinal ganglioneuromatosis
    - Familial medullary thyroid cancer (FMTC) – MTC only
- von Hippel-Lindau (VHL)
  - *VHL* gene
  - Type 2 (A, B and C)
    - A – retinal and central nervous system (CNS) hemangioblastomas, epididymal cystadenomas, pheochromocytomas (multicentric, adrenal, bilateral) and endolymphatic sac tumors
    - B – renal cell cysts and carcinomas, retinal and CNS pheochromocytomas, epididymal cystadenomas (multicentric, adrenal, bilateral) and endolymphatic sac tumors
    - C – pheochromocytoma only
- Familial paraganglioma syndrome (PGL syndromes)
  - *SDHB* (PGL4) and *SDHD* (PGL10) genes
  - Head and neck tumors, pheochromocytoma (adrenal and extra-adrenal), abdominal and thoracic paragangliomas
- Neurofibromatosis type 1 (von Recklinghausen disease)
  - *NF-1* gene
  - Multiple fibromas on skin and mucosa, café au lait spots and pheochromocytoma
- Other rare syndromes
  - Ataxia-telangiectasia
  - Sturge-Weber
  - Tuberous sclerosis

Pathophysiology

- Located in adrenal medulla 90% of the time
- May occur where chromaffin cells are present; about 90% are benign
  - Chromaffin tumors produce catecholamines

Clinical Presentation

- Hypertension (HTN)
  - Sustained HTN in >50% of patients

    - May be severe
- Paroxysmal attacks
    - Sudden onset
    - Duration – several minutes to hours
    - Headache, diaphoresis, chest pain, pallor, tachycardia, nausea
- May be induced by certain drugs (opiates, anesthetics, glucagon, MAO inhibitors)
- Cardiac signs
    - Tachycardia, arrhythmia, bradycardia
    - Heart failure
    - Hypertensive encephalopathy
    - Myocardial infarction
    - Sudden death
- Metastatic disease
    - Most common sites of metastases – lung, lymph nodes, bones, liver

Diagnosis

- Indications for testing – sudden attacks of hypertension, headache, tachycardia
- Laboratory testing
    - Plasma metanephrine and normetanephrine
        - First line testing
        - Metabolic products of catecholamines
        - False-positives do occur
        - Less cumbersome than urine testing
    - Urine metanephrine and normetanephrine
        - First line testing alternative
        - 24-hour specimen
        - May be a better test in patients at low risk for tumor (fewer false positives)
    - Urine catecholamines
        - Confirmation of either of the two above tests
        - Epinephrine and norepinephrine
    - Plasma catecholamines
        - Epinephrine and norepinephrine
        - Alternative testing for pheochromocytoma but not recommended as first line
    - Clonidine stimulation test is rarely needed
    - Histology – tissue biopsy with chromogranin A staining is diagnostic
- Imaging studies
    - Following biochemical confirmation – MRI/CT and metaiodobenzylguanidine (MIBG) scan
    - CT has 93-100% sensitivity for detecting intra-adrenal tumors ≥5 cm in diameter and 90% for extra-adrenal tumors; sensitivity for MRI is slightly higher
    - Specificity of CT/MRI ranges from 50-90%
    - If initial MRI/CT is negative, use functional imaging with MIBG scan

Differential Diagnosis

- Essential hypertension
- Anxiety attack
- Subarachnoid hemorrhage
- Diencephalic seizures

Screening

- Consider genetic testing for family members based on clinical presentation

Monitoring

- Laboratory testing
  - Chromogranin A
  - Neuroendocrine marker
    - Nonspecific for pheochromocytoma
    - May be used to monitor response to treatment or relapse since levels have been noted to correlate well with plasma metanephrines and tumor mass

Lab Tests

Indications for Laboratory Testing

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at www.aruplab.com.

Test Name and Number	Recommended Use	Limitations	Follow Up
Metanephrines, Plasma (Free) 0050184 Method: High Performance Liquid Chromatography	Diagnose pheochromocytoma		If indeterminate, order urine metanephrines
Metanephrines, Urine 0080436 Method: Gas Chromatography/Mass Spectrometry	Diagnose pheochromocytoma	Smaller increases in catecholamine concentrations usually are the result of physiological stimuli, drugs, or improper specimen collection Causes of higher concentrations include improper collection of specimens, life threatening illness, intense physical activity and neuroendocrine tumors	

Catecholamines Fractionated by LC-MS/MS, Urine Free 0080407 Method: Tandem Mass Spectrometry	Diagnose pheochromocytoma	Moderately elevated concentration are caused by essential hypertension, intense anxiety, intense physical exercise and drug interactions (including some over-the-counter medications and herbal products) Smaller increases in catecholamine concentrations usually are the result of physiological stimuli, drugs, or improper specimen collection	
Chromosome FISH, Metaphase 2002299 Method: Fluorescence in situ Hybridization	FISH probes for specific microdeletion/microduplication syndromes must be specified; if no specific syndrome is in question, genomic microarray should be ordered instead of screening of multiple microdeletion/microduplication syndromes Indicate names of probes needed for testing ARUP Molecular Cytogenetics (FISH) Probe menu		
Immunohistochemistry Stain Offering arup005 Method: Immunohistochemistry	For fixed tissue samples, consultative services as well as immunohistochemical staining for CAM5.2 (LMW), Chromogranin A, PGP9.5 and synaptophysin are available		

Additional Tests Available

Test Name and Number	Comments
Catecholamines Fractionated, Plasma 0080216 Method: High Performance Liquid Chromatography	Diagnose pheochromocytoma
Catecholamines Fractionated (Epinephrine, Norepinephrine), Plasma 0080957 Method: High Performance Liquid Chromatography	

Chromogranin A 0080469 Method: Enzyme Immunoassay	

Guidelines

NCCN Neuroendocrine Tumors Panel. NCCN Clinical Practice Guidelines in Oncology, Neuroendocrine Tumors. Version 1.2008, [Last Updated: 12 May 2008; Accessed: 30 Mar 2009]

Pacak K, Eisenhofer G, Ahlman H, Bornstein SR, Gimenez-Roqueplo AP, Grossman AB, Kimura N, Mannelli M, McNicol AM, Tischler AS. Pheochromocytoma: recommendations for clinical practice from the First International Symposium. October 2005.Nat Clin Pract Endocrinol Metab. 2007; 3 (2) :92-102.

General References

Adler JT, Meyer-Rochow GY, Chen H, Benn DE, Robinson BG, Sippel RS, Sidhu SB. Pheochromocytoma: current approaches and future directions.Oncologist. 2008; 13 (7) :779-793.

Chrisoulidou A, Kaltsas G, Ilias I, Grossman AB. The diagnosis and management of malignant phaeochromocytoma and paraganglioma.Endocr Relat Cancer. 2007; 14 (3) :569-585.

Eisenhofer G, Siegert G, Kotzerke J, Bornstein SR, Pacak K. Current progress and future challenges in the biochemical diagnosis and treatment of pheochromocytomas and paragangliomas.Horm Metab Res. 2008; 40 (5) :329-337.

Gao B, Kong F, Xu Z. Development of differential diagnosis for benign and malignant pheochromocytomas.Int J Urol. 2008; 15 (9) :771-777.

Grossman A, Pacak K, Sawka A, Lenders JW, Harlander D, Peaston RT, Reznek R, Sisson J, Eisenhofer G. Biochemical diagnosis and localization of pheochromocytoma: can we reach a consensus?.Ann N Y Acad Sci. 2006; 1073 :332-347.

Ilias I, Pacak K. A clinical overview of pheochromocytomas/paragangliomas and carcinoid tumors.Nucl Med Biol. 2008; 35 Suppl 1 :S27-S34.

Karagiannis A, Mikhailidis DP, Athyros VG, Harsoulis F. Pheochromocytoma: an update on genetics and management.Endocr Relat Cancer. 2007; 14 (4) :935-956.

Khan S, Lloyd C, Szyszko T, Win Z, Rubello D, Al-Nahhas A. PET imaging in endocrine tumours.Minerva Endocrinol. 2008; 33 (2) :41-52.

Lenders JW, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma .Lancet. 2005; 366 (9486) :665-675.

Lewis CE, Yeh MW. Inherited endocrinopathies: an update.Mol Genet Metab. 2008; 94 (3) :271-282.

Mittendorf EA, Evans DB, Lee JE, Perrier ND. Pheochromocytoma: advances in genetics, diagnosis, localization, and treatment.Hematol Oncol Clin North Am. 2007; 21 (3) :509-525.

Scholz T, Schulz C, Klose S, Lehnert H. Diagnostic management of benign and malignant pheochromocytoma.Exp Clin Endocrinol Diabetes. 2007; 115 (3) :155-159.

Tischler AS. Pheochromocytoma and extra-adrenal paraganglioma: updates.Arch Pathol Lab Med. 2008; 132 (8) :1272-1284.

Tsegay E, Anyango G, Van Sell SL, Miller-Anderson M. Pheochromocytoma: a rare tumor in adults and children.RN. 2008; 71 (6) :31-34.

Yu R, Nissen NN, Chopra P, Dhall D, Phillips E, Wei M. Diagnosis and treatment of pheochromocytoma in an academic hospital from 1997 to 2007.Am J Med. 2009; 122 (1) :85-95.

Zapanti E, Ilias I. Pheochromocytoma: physiopathologic implications and diagnostic evaluation.Ann N Y Acad Sci. 2006; 1088 :346-360.

References from the ARUP Institute for Clinical and Experimental Pathology®

Crockett DK, Frank EL, Roberts WL. Rapid analysis of metanephrine and normetanephrine in urine by gas chromatography-mass spectrometry.Clin Chem. 2002; 48 (2) :332-337.

Heider EC, Davis BG, Frank EL. Nonparametric determination of reference intervals for plasma metanephrine and normetanephrine.Clin Chem. 2004; 50 (12) :2381-2384.

Kushnir MM, Urry FM, Frank EL, Roberts WL, Shushan B. Analysis of catecholamines in urine by positive-ion electrospray tandem mass spectrometry.Clin Chem. 2002; 48 (2) :323-331.

Margraf RL, Mao R, Highsmith WE, Holtegaard LM, Wittwer CT. Mutation scanning of the RET protooncogene using high-resolution melting analysis.Clin Chem. 2006; 52 (1) :138-141.

Singh RJ, Grebe SK, Yue B, Rockwood AL, Cramer JC, Gombos Z, Eisenhofer G. Precisely wrong? Urinary fractionated metanephrines and peer-based laboratory proficiency testing.Clin Chem. 2005; 51 (2) :472-473.

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Diagnostic Algorithm(s)

PDF algorithm(s) available at www.arupconsult.com.

Pheochromocytoma Testing Algorithm

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