Clinical Chemistry Trainee Council
Pearls of Laboratory Medicine
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TITLE: Diagnosis of Pheochromocytomas

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Hello, my name is Dr. Jane Dickerson. I am a co-director of the chemistry lab at Seattle Children's Hospital, and a clinical assistant professor in the Department of Lab Medicine at the University of Washington. Welcome to this discussion on the diagnosis of Pheochromocytomas.

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Pheochromocytomas are a rare type of adrenal tumor of the medullary chromaffin cells. These cells produce catecholamines. Catecholamine-producing tumors, like pheochromocytomas, cause excessive secretion of catecholamines which lead to serious health consequences. 85% of these tumors are located within the adrenal gland. The remaining 15% of catecholamine-secreting tumors are located outside the adrenal gland, and these are known as paragangliomas. When we talk about catecholamines, we are really referring to epinephrine and norepinephrine. Collectively they are known as catecholamines because they contain a catechol group, shown here. They are normally synthesized in the medulla of the adrenal gland. These compounds play an important role in the "fight-or-flight" response because they trigger a rise in blood glucose (more energy for the fight-or-flight) and blood pressure.

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Pheochromocytomas get their name from their unique staining when exposed to chromium salts. They turn brown, as shown here in this image. "Pheo" meaning dark color and "chroma" from the chromium salts.

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Patients with pheochromocytoma can present with a variety of signs and symptoms. The classic presentation is known as "the Triad," which includes sweating, palpitations, and headache. Most patients do not actually present initially with the triad, but hypertension, along with abdominal pain, lack of color, and an impending sense of doom or feelings of panic. These symptoms can be transient, making the diagnosis difficult. Other less common symptoms include visual blurring, papilledema (swelling of the optic disk), weight loss, hyperglycemia, polyuria, and polydipsia.

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Pheochromocytomas are described as very rare neoplasms. The exact incidence is not known because it is likely underdiagnosed – but it is estimated at 0.8 in 100,000 people and 0.2% in those with hypertension. The majority (95%) of pheochromocytomas occur in the abdomen, and 80-85% in the adrenal gland. Pheochromocytomas which occur outside of the adrenal gland are more accurately described as catecholamine-secreting paragangliomas, although pheochromocytoma is commonly used to refer to any catecholamine-secreting tumor. Between 25-30% of pheochromocytomas are associated with a familial syndrome. Familial cases present with bilateral tumors in more than 10% of cases, and are associated with higher rate of malignancy. Sporadic cases present bilaterally less than 10% of cases, and are rarely (<5%) associated with malignancy.

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The prognosis and treatment of these tumors is optimistic for non-malignant tumors. The therapy is removal or resection of the tumor. There is risk associated with the operation, but this can be mitigated by pre-operative therapy. There are three accepted pre-operative therapies, and there is no consensus as to which one is best. The combined treatment with alpha- and beta-adrenergic blockade is aimed at preventing a dangerous hypertensive event during the operation. The patient is treated first with alpha-adrenergic blocker 2 weeks before the operation, followed by addition of a beta-adrenergic blocker 2-3 days prior. Calcium channel blockers have also been used as successful pre-operative therapy in patients who experience intolerable side effects to alpha-adrenergic blockers. Finally, metyrosine is used as a last resort option when the other therapies have failed. Metyrosine is an inhibitor of catecholamine synthesis, but should be used with caution due to its serious and disabling side effects. For pheochromocytomas that occur intra-adrenally, adrenalectomy is the best surgical option (removal of the entire gland) for sporadic or non-hereditary cases.

Malignant pheochromocytomas are also treated surgically, although there is no guarantee of complete cure. The five-year survival rate is less than 50% for malignant cases due to recurrence of the tumor.

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While the majority of pheochromocytomas are sporadic, between 25-30% of cases are associated with a familial disorder. The inheritance pattern is autosomal dominant, and there are several known hereditary disorders associated with pheochromocytoma. These include von Hippel-Lindau Type II, multiple endocrine neoplasia type II (aka MEN2), and neurofibromatosis type I. In addition, mutations in the succinate dehydrogenase complex (SDH) have been associated with a predisposition to develop pheochromocytoma; from a laboratory standpoint, the profile of catecholamine excretion can be unique with these mutations, notable for increases in dopamine. There are several other genes which have also been associated with a predisposition for developing pheochromocytomas, including KIF1Bb, PHD2, TMEM127, and MAX.

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Of the hereditary syndromes, pheochromocytomas are most common in MEN2, occurring in 50% of affected individuals. It is caused by a gain of function mutation in the RET proto-onco gene. 100% of affected individuals will develop medullary thyroid carcinoma (MTC), and half will go on to develop

pheochromocytoma. In these cases, pheochromocytoma is treated by resection of the affected adrenal gland or complete bilateral adrenalectomy if indicated. Another surgical option which is often attempted in hereditary bilateral pheochromocytoma, and especially MEN2 due to the low metastatic risk, is partial adrenalectomy. This is the complete removal of one gland and partial removal of the second gland, in an attempt to retain some adrenocortical function.

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Pheochromocytomas are actually rarely diagnosed because of the low prevalence of the condition. One study estimated that 1 in 300 cases being worked up for pheochromocytoma were positive for the disease. The main diagnostic criteria are elevated urinary catecholamines and metanephrines or plasma free metanephrines. Metanephrine and normetanephrine are the metabolites of the catecholamines, epinephrine, and norepinephrine.

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Catecholamines and metanephrines are now frequently measured by HPLC or HPLC-tandem mass spectrometry. 24-h urine fractionated catecholamines and metanephrines include epinephrine, norepinephrine, and the metabolites metanephrine and normetanephrine. Creatinine is also frequently measured to make sure the sample is appropriate (i.e. not too dilute or concentrated). Proper collection of these specimens is important for a reliable measurement, but complete collection is challenging in the outpatient setting.

Plasma free metanephrines (free refers to non-sulfated metanephrines) can be a more attractive option for diagnosis of pheochromocytomas. The metabolites of epinephrine and norepinephrine are produced continuously in the plasma by metabolism of catecholamines, and are independent of variations in catecholamine release by the pheochromocytoma.

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Catecholamines and metanephrines can both be measured in urine, but only the metanephrines are recommended to measure in plasma. This is because catecholamines are highly labile compounds and are acutely increased in times of stress and pain. The experience of phlebotomy itself can cause a rise in plasma catecholamines, and so, collection is cumbersome. The room must be dark and quiet; a butterfly needle is inserted and is flushed with heparin to prevent coagulation. Then, the patient is allowed to rest and “recover” from the poke before the blood is collected in a chilled green-top tube. The sample must be centrifuged almost immediately and frozen within an hour to prevent metabolism of the catecholamines. For all of the reasons, plasma catecholamines are no longer recommended for screening of pheochromocytomas.

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There is still conversation around what is the best test to diagnose catecholamine-secreting tumors: urine catecholamines, urine metanephrines, or plasma metanephrines. Several studies have investigated the sensitivities and specificities of these measurements, but the most commonly-cited study from 2002 is summarized in this table.

Sensitivities and specificities were calculated separately for sporadic and hereditary cases. The most sensitive methods are plasma and urine metanephrines, followed by urine catecholamines. Specificity is highest in plasma metanephrines and urine catecholamines. Because the sensitivities and specificities are similar, some guidelines suggest screening with plasma metanephrines because you can avoid a 24-h urine collection. Other guidelines based on a few other studies recommend screening with 24-h urine catecholamines in patients with a lower likelihood of disease.

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Other tests can be used to support diagnosis of a pheochromocytoma. The clonidine suppression test is used to confirm mild increases in plasma catecholamines or metanephrines. Clonidine, a centrally acting alpha-adrenergic agonist, normally suppresses catecholamine synthesis but has no effect on catecholamines produced in a pheochromocytoma. A baseline measurement of plasma catecholamines, normetanephrine, and blood pressure are obtained, and then again, three-hours after treatment with clonidine. In a patient without pheochromocytoma, the blood pressure and plasma normetanephrine should decline.

Chromogranin A is increased in 80% of pheochromocytoma cases, and can be used as additional testing to support diagnosis, although its specificity is low. It is measured with immunochemical techniques.

Finally, vanillylmandelic acid (VMA) can also be measured. VMA is the metabolite of metanephrine and normetanephrine. However, 24-hr urine VMA has poor sensitivity and specificity when compared with urine or plasma metanephrines.

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Genetic testing can be pursued to confirm familial pheochromocytoma. There are more than 10 genes associated which can be analyzed clinically. The utility of genetic testing in every patient is debatable, since the majority of pheochromocytomas are sporadic (70%). Currently, there is no consensus regarding the best screening approach. Some guidelines say genetic testing should be considered in patients who have a paraganglioma, bilateral pheochromocytoma, unilateral pheochromocytoma but with a positive family history, and unilateral pheochromocytoma occurring at a young age (<45 yr. old). While panels exist, a sequential approach is recommended due to the cost of these tests. Depending on the presentation, there are guidelines for the best sequential approach and should be prioritized based on age, tumor location, multifocal disease, the presence of other syndromic features, and biochemical phenotype.

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In summary, pheochromocytomas are rare catecholamine-secreting neoplasm, occurring sporadically in 70% of cases. Diagnostic criteria include increases in plasma and urine metanephrines and urine catecholamines. These tests have comparable sensitivities and specificities, but plasma-free metanephrines offer the convenience of a single draw, rather than a cumbersome 24-h urine collection. Screening with plasma catecholamines is not recommended.