

***CLINICAL LAB INVESTIGATIONS:  
CASE STUDIES FOR THE  
LABORATORY PROFESSIONAL***

***CASE SET #24***

**A Chemistry Case:  
*Pheochromocytoma or Renal Disease?***



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## **Clinical Laboratory Investigations**

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## **LEARNING OBJECTIVES**

Upon completion of reading the case, the learner will be able to:

1. Describe the symptoms, etiology, and laboratory assessments used in the diagnosis of pheochromocytoma.
2. Discuss pre-analytical errors that may occur when testing patients for catecholamines.
3. Discuss renin and its role in hypertension.

## **Pheochromocytoma or Renal Disease?**

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### **Case Presentation**

#### **Patient History:**

A 38-year-old white male with complaints of blurred vision and severe headaches specific to the left side posterior was seen in an optometrist's office. Even though the patient had been in pain for several months, he had avoided visiting the doctor because he had no insurance and did not want to miss work for an optometry appointment. The patient had no significant previous medical history and did not smoke or use drugs. When he was finally examined, the optometrist discovered fluid behind the patient's eyes and found severe swelling of the optic nerves. The optometrist immediately sent the patient to the emergency room (ER) where his blood pressure reading was 241/153 mmHg on arrival.

The ER physician ordered a complete blood count (CBC), erythrocyte sedimentation rate (ESR), electrolytes, blood urea nitrogen (BUN), creatinine, and calcium. All results were normal except for the creatinine which was slightly elevated and the estimated glomerular function which was slightly decreased. See Table I.

Test	Results	Ref. Range	Units
Sodium	141	137-145	mmol/L
Potassium	3.5	3.5-5.3	mmol/L
Chloride	104	98-107	mmol/L
Carbon dioxide	27.9	22-30	mmol/L
Anion gap	9.1	7.0-16.0	mmol/L
Creatinine	1.4	0.66-1.25	mg/dL
Estimated GFR Non AFR American	58	>60	ml/min/1.73m <sup>2</sup>
Anion gap	9	7.0- 16.0	mmol/L
Blood Urea Nitrogen (BUN)	14	9-20	mg/dL

Table I: Initial laboratory results for serum electrolytes, creatinine and urea nitrogen.

The patient was admitted to the hospital with a provisional diagnosis of posterior reversible encephalopathy syndrome (PRES). In order to reduce his blood pressure and have further diagnostic tests performed, he remained in the hospital for several days. The patient was treated with metoprolol for high blood pressure, acetaminophen for pain, and alprazolam for anxiety. Two days after admission the physician ordered an extensive panel of laboratory tests on cerebrospinal fluid (CSF) which were all found to be normal. See Table II.

Test	Results	Ref. Range	Units
CSF color	colorless		
CSF appearance	clear		
CSF WBC count	3	0-5	per cu mm
CSF RBC count	0	0	per cu mm
CSF glucose	68.7	46-72	mg/dL
CSF total protein	47.4	12-60	mg/dL
Oligoclonal bands	negative		
Cryptococcal antigen	negative	negative	

Table II: Initial laboratory results for cerebrospinal fluid analysis

On the fourth day of hospitalization, the physician ordered catecholamines, metanephrines, and dopamine on a 24-hour urine sample. The catecholamines, metanephrines, and dopamine were all found to be highly elevated. See Table III.

Test	Results	Ref. Range	Units
24-hour Urine Volume	1650		mL
Epinephrine	127	2-24	mcg/24 hours
Norepinephrine	278	15-100	mcg/24 hours
Total Catecholamine (calculated)	405	26-121	mcg/24 hours
Dopamine	637	52-480	mcg/24 hours
Metanephrine	451	36-190	mcg/24 hours
Normetanephrine	614	35-482	mcg/24 hours
Total metanephrines	1065	115-695	mcg/24 hours

Table III: Initial Urine Catecholamines and Metanephrines(24-hour)

**Provisional Diagnosis:**

Based on the extremely high blood pressure, and the elevated catecholamine and metanephrine results the patient received a provisional diagnosis of pheochromocytoma. The patient remained in the hospital for eight days until his blood pressure stabilized. Upon discharge, he was scheduled for a Nuclear Medicine Localization Octreoscan which was performed as an outpatient.

**Further Testing:**

The patient underwent a nuclear scan of the neck, chest, abdomen, and pelvis. Images were taken at 4 hours, 24 hours and 48 hours after injection with indium-111. No abnormalities were found on the scan which essentially ruled out pheochromocytoma.

Since the scan was normal, the patient was then referred to an ophthalmologist, a neurologist, a nephrologist, and an endocrinologist to determine the etiology of his high blood pressure. Although the patient was very frustrated when he received a list of specialists to consult and yet have no specific diagnosis, he made appointments with the four specialists. His first appointment was with an ophthalmologist who confirmed that the patient's vision had been irreparably damaged; the vision in his left eye was determined to be 20/80.

The second appointment was with a neurologist. This visit to the neurologist was unremarkable and ended when the neurologist stated that since the symptoms were blood pressure and kidney related there was nothing he could do for the patient. The third appointment was a trip to the endocrinologist who repeated the 24-hour urine for catecholamines and ordered a chromogranin A on serum. All of these tests were found to be normal. See Table IV.

Test	Results	Ref. Range	Units
24-hour Urine Volume	1275		mL
Epinephrine	20	2-24	mcg/24 hours
Norepinephrine	75	15-100	mcg/24 hours
Total Catecholamine (calculated)	95	26-121	mcg/24 hours
Dopamine	400	52-480	mcg/24 hours
Metanephrine	180	36-190	mcg/24 hours
Normetanephrine	400	35-482	mcg/24 hours
Total metanephrines	580	115-695	pg/mL
Chromogranin A	35	< 93	ng/mL

Table IV: Laboratory results for repeat catecholamines and serum chromogranin A

The fourth appointment, with a nephrologist, led to further tests to rule out kidney disease. This decision was based on the patient's initial creatinine value of 1.4 mg/dL and the slightly decreased estimated glomerular function rate. The nephrologist ordered a plasma renin activity (PRA) level and repeated the BUN and creatinine. The creatinine and renin were found to be abnormal. See Table V.

Test	Results	Ref. Range	Units
Blood Urea Nitrogen (BUN)	16	9-20	mg/dL
Creatinine	1.4	0.66-1.25	mg/dL
BUN/Creatinine ratio	11.1		
Estimated GFR Non AFR American	55	>60	ml/min/1.73m <sup>2</sup>
Plasma Renin Activity	8	0.7-3.3	ng/mL/hr

Table V: Follow-up Kidney Function Tests

Based on the abnormal creatinine and renin results, the nephrologist ordered a magnetic resonance angiography (MRA). This test revealed that the patient had a renal artery thrombosis.

**Discussion:**

Adrenal glands are located on the top of each kidney with the adrenal gland composed of two distinct parts: the outer portion or the adrenal cortex and the inner portion which is the adrenal medulla. The adrenal medulla contains chromaffin cells which produce and secrete catecholamines.<sup>1</sup> Catecholamines include dopamine, epinephrine, and norepinephrine; epinephrine is produced in the greatest quantity.<sup>2</sup> Catecholamines which are the hormones responsible for the flight or fright response cause the heart to beat faster, blood pressure to increase, and redirects blood to muscles.<sup>3</sup> Tumors which arise from chromaffin cells produce and secrete large amounts of catecholamines.<sup>1</sup> One such tumor which is rare and usually benign is called a pheochromocytoma.<sup>2</sup> Since these tumors, secrete large amounts of catecholamines, patients with pheochromocytoma will have hypertension. Although it is a rare cause of

hypertension as only 5 out of 100,000 cases of high blood pressure are caused by pheochromocytoma, it must be ruled out as an etiology.<sup>2</sup> It is critical that a patient is diagnosed and treated quickly because if left untreated pheochromocytoma can be a life threatening disorder.<sup>2</sup> A 24-hour urine for free catecholamines which includes epinephrine, norepinephrine, dopamine, and the metabolic products metanephrine, normetanephrine, and vanillylmandelic acid (VMA) are usually the first tests ordered to rule out pheochromocytoma.<sup>1</sup> However, clinicians do not agree on the most sensitive or specific test to diagnose pheochromocytoma.<sup>3</sup> In addition, establishing whether or not a patient's catecholamine values are abnormal is often not straightforward. Patients with high blood pressure and hospitalized patients will have higher levels of catecholamines and metanephrines than normotensive healthy volunteers.<sup>1</sup> Since the consequences of a missed diagnosis can be fatal, it is best to err on the side of caution and sacrifice specificity for a more sensitive test.<sup>4</sup> Reasons for false positive tests include the following preanalytical errors: timing errors in the collection, certain medications, food, and beverages. Positive tests must be confirmed or disproved with additional procedures.<sup>1</sup> In this case, chromogranin A which is not routinely ordered because it is less sensitive and specific for pheochromocytoma was measured and found to be normal.<sup>5</sup> Chromogranin A, a protein secreted by neuroendocrine cells, is often used as a tumor marker for neuroendocrine tumors. However, it has been found to have low sensitivity and poor reproducibility.<sup>5</sup> The negative chromogranin A and the normal values on the recollected catecholamines led the nephrologist to look for other causes of the patient's hypertension.

The MRA on this patient showed a blockage in the renal artery which can lead to ischemia and activate the release of renin. Renin is an enzyme which is produced by the juxtaglomerular cells of the kidney and reacts with angiotensinogen to produce angiotensin I. In the lungs, angiotensin I is converted to angiotensin II by angiotensin-converting enzyme (ACE).<sup>7</sup> Angiotensin II causes vasodilation of the afferent arteriole and constriction of the efferent arteriole.<sup>7</sup> In addition, angiotensin II triggers the release of aldosterone and antidiuretic hormone.<sup>7</sup> If left untreated, this cascade of hormones leads to renovascular hypertension (RVHT) which is the most common cause of secondary hypertension.<sup>6</sup>

**Conclusion:**

Preanalytical errors leading to false positive laboratory testing results were the cause of a delay in correct diagnosis for this patient. At the time of the initial 24-hour urine collection, the patient was taking metoprolol to treat his high blood pressure. He was also drinking coffee and receiving acetaminophen for pain. Metoprolol, caffeine, and acetaminophen are all associated with drug-induced elevations in catecholamines and metanephrines.<sup>1</sup> It was essential to rule out pheochromocytoma; however, the falsely elevated catecholamines could have been prevented if the patient had been advised to avoid caffeine and acetaminophen during the 24-hour urine collection. In addition, the catecholamines should not have been ordered while the patient was taking a blood pressure medication that is known to cause a falsely elevated result. Whether or not the laboratory was consulted before the specimen was collected is not known. The patient continues to suffer from blood pressure spikes which are now attributed to RVHT. He takes lisinopril which is an ACE inhibitor, amlodipine, and clonidine to

control his blood pressure. In addition to hypertension, the patient has been diagnosed with stage 2 chronic kidney disease which was a result of the sustained high blood pressure.

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