Pheochromocytoma: A Disease with Many Faces

Marina Shargorodsky MD[1,3] and Reuven Zimlichman MD[2,3]

[1]Department of Endocrinology and Hypertension, [2]Department of Internal Medicine, and [3]Institute of Physiologic Hygiene, Wolfson Medical Center, Holon, Israel
Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

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Catecholamine-secreting tumors are frequently sought but rarely diagnosed. In many cases their presence is associated with spectacular cardiovascular disturbances. When diagnosed and treated properly, however, these tumors are mostly curable. Pheochromocytomas provide clinicians with a unique treatment opportunity since the response to either surgery or pharmacologic therapy is dramatic, but incorrect diagnosis and treatment can have catastrophic consequences.

Catecholamine-secreting tumors are extremely rare, with an incidence of 2–8 cases per million people. Despite their rarity, they should be considered in patients with hypertension, panic attacks, adrenal incidentalomas, autonomic disturbances or familial diseases with a predisposition to develop pheochromocytoma. Identification of pheochromocytomas is essential because the associated hypertension is curable upon diagnosis, localization and surgical resection of the tumor. In contrast, undiagnosed cases are at risk of lethal paroxysms and about 10% of cases are malignant. Patients with catecholamine-secreting tumors may be asymptomatic, however symptoms usually arise from the pharmacologic effect of excess catecholamines in the circulation. Hypertension may be sustained or paroxysmal, and spells may occur spontaneously or can be precipitated by postural change, medications, anxiety, increase in abdominal pressure, exercise, or manual compression of the tumor. A spell usually lasts from several minutes up to one hour. Clinicians usually screen patients for pheochromocytomas when paroxysmal symptoms are evident, but pheochromocytomas are usually not the most common cause of hypertension-related spells.

In their article in this issue of *IMAJ*, Hamdan et al. [1] report a rare manfestation of a rare disease – low back pain with vertebral lytic lesion. In another article in the current issue, Liel et al. [2] describe a confusing pheochromocytoma that appears together with meningiomas and mimics meningioma in the base of the skull. These are only two of the many faces of the diverse clinical presentations of this peculiar disease.

A "rule of 10" has been described for catecholamine-secreting tumors: 10% are multiple or bilateral, 10% recur after surgical removal, 10% are familial, and 10% are malignant. Several syndromes have been associated with phechromocytoma, such as MEN II a and II b, neurofibromatosis, and von Hippel-Lindau disease [3]. It is obvious that before any attempt to localize the pheochromocytoma, excess of catecholamine levels in the plasma or urine should be sought.

The diagnostic approach, which in the 1940s was based on clinical impression, exploratory laparotomy, histamine stimulation and phentolamine suppression tests, progressed to catecholamine measurements and intravenous pyelograms in the 1960s. In most laboratories today, plasma or urinary catecholamines are measured by high pressure liquid chromatography, usually with electrochemical detection. However, despite these developments, the

diagnosis of pheochromocytoma continues to be a diagnostic challenge in many cases. The most practical screening tests are still 24 hour urine collections for measuring catecholamines or their metabolites.

The present approach to biochemical diagnosis of pheochromocytoma has several limitations. Catecholamines are secreted in excess not only in patients with pheochromocystoma, and vice versa – pheochromocytomas do not always secrete enough catecholamines to produce typical symptoms and diagnostic plasma levels. In many cases pheochromocytomas secrete catecholamines periodically, and between the episodes catecholamine levels may be normal. In other cases, tumors of small size produce low amounts of catecholamines that are not high enough to confirm a solid diagnosis of pheochromocytoma. Thus the commonly used tests to measure plasma catecholamines and their metabolites do not absolutely confirm or exclude the possibility of pheochromocytoma.

The most prominent progress in recent years in the area of pheochromocytoma diagnosis was the introduction of tests to measure plasma levels of normetanephrine and metanephrine. A normetanephrine level above 2.5 pmol/ml and a metanephrine level above 1.4 pmol/L – more than 4 and 2.5-fold the upper reference limits – indicate a pheochromocytoma with 100% specificity. The development of tests for measuring plasma metanephrine and normetanephrine is a groundbreaking achievement. Finally, after many years of having to compromise with tests of partial sensitivity and specificity, we have at our disposal a test with almost 100% specificity.

Since the most sensitive test for this very rare disease is the evaluation of plasma metanephrine, this is recommended as the first step in evaluation of the patient. We must understand that most patients with pheochromocytoma can be diagnosed by the simple test of measuring plasma metanephrine. As mentioned above, a positive test has a 100% sensitivity; however, it is important to remember that many patients will have borderline or slightly elevated levels. For these patients, measuring plasma catecholamine levels and repeat testing of plasma metanephrine is necessary. Since metanephrines are secreted continuously by the pheochromocytoma, normal levels of plasma metanephrine and normetanephrine in a second test exclude pheochromocytoma, even if the results of the first test were positive. We must also bear in mind the need to exclude false positive tests of plasma metanephrine. One of the medications that can cause a false positive test is recent ingestion of paracetamol, a frequently used drug.

In patients with inconclusive tests for plasma metanephrine levels, namely patients with mild to moderate elevations, two additional tests are useful and recommended. The first is the clonidine suppression test, which is based on the fact that clonidine suppresses plasma catecholamine levels in sympathetic overactivity, while such an effect is not seen in patients with pheochromocytoma. It should be stressed that this test, usually reliable, loses its sensitivity in patients with a small or intermittently secreting pheochromocytoma. The second, the glucagon stimulation test, is especially useful in patients with elevated plasma metanephrines but normal plasma catecholamines. When this test is performed, a positive response has high specificity, while a negative test has low sensitivity and does not exclude pheochromocytoma.

To summarize, pheochromocytoma, with its many faces, continues to pose a diagnostic challenge in many patients. However, a major tool had been added to our armamentarium for diagnosis of the disease – the measurement of plasma and urine metanephrines and normetanephrines. A positive test, as defined above, definitively diagnoses the condition. A negative test excludes pheochromocytoma unequivocally. However, as with many tests, the "gray area" that lies in the middle of the spectrum remains problematic for clinicians in their attempt to reach the correct diagnosis.

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Correspondence: Dr. R. Zimlichman, Chief, Dept. of Medicine, Wolfson Medical Center, P.O. Box 5, Holon 58100, Israel.
Phone: (972-3) 502-8614
Fax: (972-3) 503-2693
email: zimlich@post,tau.ac.il