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When is a pheo not a pheo? Depression in an adolescent leading to a pheochromocytoma-like biochemical profile

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Abstract

A pheochromocytoma was suspected in a 14 year old boy. Elevated urinary and plasma catecholamines as well as clonidine test were consistent with the diagnosis. However, imaging studies were negative, and biochemical abnormalities normalized with treatment of concomitant depression. It is important to consider an array of confounders, including psychiatric conditions, when testing for pheochromocytoma.

A previously healthy 14 4/12 year old boy presented with a 6 months history of a 10 kg weight loss, profuse sweating, fatigue, myalgia, sleep difficulties and loss of appetite. Other history was notable for ongoing feelings of sadness and anxiety, and three suicide attempts. On physical examination he was alert and oriented, his weight was 38.5 kg and his height 172 cm. The BMI SDS was –4.7. Blood pressure was 120/80 mm Hg and resting pulse was 130 bpm. He was sweating profusely, did not maintain eye contact, and was shivering. The remainder of his examination, including neurological was unremarkable. Diagnostic workup ruled out infectious and malignant causes. Thyroid function tests showed an increased fT4 level of 34.5 pmol/L (10–23), and a TSH level which was initially slightly low at 0.06 mIU/L (0.5–5.0), both of which normalized spontaneously in follow up tests. Medical psychiatry was also involved and provided supportive therapy and medication management. The sweating and resting tachycardia of 130 bpm prompted his primary team to perform an evaluation for pheochromocytoma with concerning results: his 24-hour urine collection revealed elevated dopamine and norepinephrine levels (Table 1).

To confirm the urinary catecholamine results and to localize the presumptive tumor, an extensive workup was carried out over the course of 1.5 years. Testing revealed a persistent elevation of urine catecholamines but negative anatomical and functional imaging studies (Table 1). In an effort to differentiate a true pheochromocytoma from a false positive elevation of catecholamines, a clonidine suppression test was carried out, which is reported to have 98%–100% specificity for pheochromocytoma, when positive.¹ Our patient's plasma normetanephrine and norepinephrine levels did not suppress sufficiently during the test, which was consistent with the presence of pheochromocytoma. During this test and the

initial workup, the patient was not consuming any drugs or medication. Follow up imaging studies were carried out over the next 12 months and were still negative (Table 1). Genetic testing for pheochromocytoma was also performed including examination for mutations in ret proto-oncogene (*RET*), succinate dehydrogenase complex, subunit B (*SDHB*), von Hippel-Lindau tumor suppressor gene (*VHL*), which were also negative.

In parallel to the medical workup, he was followed by medical psychiatry for his depression, anxiety and physical complaints. Two months after his initial presentation, the antidepressant Citalopram was prescribed, but the patient was poorly adherent and did not take the medication. Treatment with Fluoxetine was initiated seven months post presentation, with better adherence, and titrated up to 30 mg daily. He also underwent occupational and physical therapy. This led to some improvement in his mood, anxiety, somatic complaints and functioning, and a concomitant, progressive drop in his catecholamine levels, which on last measurement had normalized (Table 1).

Discussion

Pheochromocytoma is a challenging but important diagnosis, with plasma metanephrines being the gold standard for diagnosis.¹ In cases where this is insufficient, a clonidine suppression test is considered the most sensitive and specific additional diagnostic test. This test was introduced to address the problem of how to distinguish patients with pheochromocytoma from those with false-positive biochemical results.² By activating α_2 -adrenoceptors in the brain and on sympathetic nerve endings, clonidine suppresses norepinephrine release by sympathetic nerves. Therefore, decreases in elevated plasma norepinephrine concentrations after clonidine suggest sympathetic activation, whereas a lack of decrease suggests pheochromocytoma.

This patient had a convincing biochemical profile of pheochromocytoma which led to an extensive diagnostic imaging workup, which was all negative. During his entire workup he was followed by medical psychiatry, and demonstrated anxiety and depression which were felt to be secondary to an organic medical condition. However, treating his psychiatric condition with supportive therapy and treatment with a selective serotonin reuptake inhibitor (SSRI) led to marked improvement in his catecholamine production. Unlike tricyclic antidepressants, which are reported to cause a false positive elevation of catecholamines, the SSRI's are not reported to influence the measurement of catecholamines.^{1, 3}

Previous reports in adults have shown that an elevation of norepinephrine and dopamine, as in our case, rather than epinephrine, can occur in the setting of anxiety, depression or a bipolar disorder.⁴⁻⁵ To our knowledge, no similar data have been reported in children. The patient presented had multiple constitutional complaints and two years after his presentation, is still being investigated and treated by a multi disciplinary team, and receiving psychiatric treatment. Although all the medical and psychiatric issues involved have not been fully resolved, it is now clear that catecholamine elevations were false positives and the ongoing concern of pheochromocytoma was unwarranted. The elevations resolved with improvement in his psychiatric condition. In conclusion, although depression can be primary or secondary

to organic causes, if depression is suspected in the presence of abnormal catecholamine levels, a false positive result should be considered.

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Biochemical profile and clonidine suppression test results, and list of imaging studies performed

Table 1

Persistently elevated urine norepinephrine and dopamine, and normalization after initiation of psychiatric treatment. Clonidine suppression test failed to suppress catecholamines by 50%, consistent with pheochromocytoma. All imaging studies performed were negative.

Test/Time	Presentation	4 mo	6 mo	7 mo	12 mo	18 mo	
U Epinephrine (<109 nmol/24h)	86.9	80.8	Clonidine Suppression test *	Initiation of anti depressant therapy, including Fluoxetine	22	42.7	
U Norepinephrine (<473 nmol/24h)	<u>751.7</u>	<u>866.5</u>			171.4	280.3	
U Dopamine (<2,614 nmol/24h)	<u>2841.1</u>	<u>4156.1</u>			2016.8	2613.9	
U Total Metaneph. (<4.1 μmol/24h)	3.8	1.5			0.6	0.08	
Anatomical & Functional Imaging	MRI	Head & spine			Head & neck, abdomen, chest, extremities.	Neck, chest, abdomen & pelvis.	
	CT	Abdomen & pelvis					
	US	Abdomen & pelvis					Testes
	MIBG						
	FDG PET						
Octreotide scan							
*Clonidine Suppression test (6 months F/U)							
Plasma Epinephrine (<0.8 nmol/L)				0'	180'		
Plasma Norepinephrine (0.8–3.4 nmol/L)				<0.1	<0.1		
Plasma Dopamine				8.8	7.4		
Plasma Normetanephrine (0.12–0.45 nmol/L)				1.2	1.5		
				0.93	0.69		