

A Case of Pseudopheochromocytoma Associated with Clozapine Therapy

Dilek Arpacı^{1*}, Aysel Gurkan Tocoglu², Yasemin Gunduz³, Sumeyye Korkmaz², Lacin Tatlı³, Baris Isiloglu⁴ and Ali Tamer²

¹Sakarya University Education and Research Hospital, Department of Endocrinology, Sakarya, Turkey

²Sakarya University Education and Research Hospital, Department of Internal Medicine, Sakarya, Turkey

³Sakarya University Education and Research Hospital, Department of Radiology, Sakarya, Turkey

⁴Sakarya University Education and Research Hospital, Department of Psychiatry, Sakarya, Turkey

*Corresponding author: Dilek Arpacı, Sakarya University Education and Research Hospital, Sakarya, Turkey; Tel: 902642550865; E-mail: drarpaci@gmail.com

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Abstract

Background: An elevated plasma noradrenaline level is a consistent clinical effect of clozapine, which is due to its potent effect on α_2 -adrenergic receptors. Clozapine, a tricyclic dibenzodiazepine derivative, is used to treat refractory schizophrenia. In this report we present a case of pseudopheochromocytoma in a schizophrenic patient treated with clozapine.

Case: A 55-year-old female diagnosed with schizophrenia referred from psychiatry clinic to endocrinology clinic detected with bilateral adrenal masses. She was hypertensive and she used nifedipine. Urine catecholamines, especially normetanephrine, were extremely elevated; however, she did not have any pheochromocytoma-related symptoms. Adrenal imaging was not compatible with pheochromocytoma. Following psychiatric consultation, clozapine was withdrawn for 1 week, and then 24-h urine catecholamines were normal. Metaiodobenzylguanidine (MIBG) scan was normal.

Conclusion: Given the potentially significant morbidity associated with paranoid schizophrenia, especially in undiagnosed cases, we recommend timely urinary catecholamine screening in patients that develop hypertension or other typical symptoms following the use of clozapine.

Keywords: Noradrenaline; Clozapine; Adrenal; Catecholamine

Introduction

Pheochromocytomas [Pheos] are catecholamine-producing tumors derived from chromaffin cells of the adrenal medulla or extra-adrenal paraganglia, of which 95% exist in the adrenal glands. Clinical manifestations arise as a result of their excessive production of catecholamines.

The symptoms of Pheos include sustained or paroxysmal hypertension, palpitations, headache, sweating, anxiety attacks, weight loss, and hyperglycemia. The clinical presentation of Pheos varies from incidental adrenal adenomas to life-threatening hypertensive crises [1].

The prevalence of Pheos in patients with adrenal incidentalomas is 0.3%-5% [2] however; the most critical reported issue related to adrenal incidentalomas is that the diagnosis of Pheos must be ruled out. The recommended initial biochemical investigation for Pheos is measurement of plasma or urine metanephrenes and normetanephrenes. A level >4-fold urine level of catecholamines [ULC] indicates that Pheos is highly probable [3]. The 24-h metanephrene level (metanephrenes and normetanephrenes) is the most sensitive test for diagnosing Pheos. Negative test results exclude functional Pheos, except for dopamine-secreting Pheos or small tumors [4,5]. Radiologically Pheos appear circumscribed, and non homogeneous with cystic and hemorrhagic changes, based on CT scanning. The unenhanced attenuation value of Pheos on CT is usually

>30 HU. On the other hand, they exhibit high signal intensity on T2-weighted MRI. All of them are not specific for Pheos [6,7].

False positive Pheos test results may cause patient anxiety, leading to unnecessary imaging studies. False positive results for Pheos are due to physiological variations, laboratory errors, and drug interference [8,9]. Drug-related false positive elevations of ULC have been reported, and tricyclic antidepressants are among most common causes of false positive elevations of ULC [8,10,11]. Other medications reported to cause false-positive serum or urine studies are acetaminophen, phenoxybenzamine, amitriptyline, labetalol, haloperidol, levodopa, tamsulosin, venlafaxine, hydrochlorothiazide, and buspirone [12]. Selective serotonin re-uptake inhibitors [SSRIs] have been associated with false positive upper limits of normal [1].

Clozapine, a tricyclic dibenzodiazepine derivative, has an established role in the treatment of refractory schizophrenia. The literature includes a few case reports of a pseudopheochromocytoma syndrome associated with clozapine treatment. Elevation of the plasma noradrenaline level has been reported as a consistent clinical effect of clozapine, which is due to its potent effect on α_2 -adrenergic receptors [1-3]. Paradoxical hypertension with an elevated concentration of urinary catecholamines has also been reported in association with clozapine treatment, although rarely, and in association with other antipsychotic medications [13]. Here we present a patient with paranoid schizophrenia that was treated with clozapine and developed laboratory mimicking pheochromocytoma.

Case Report

A 55-year-old female diagnosed with paranoid schizophrenia, recurrent depressive illness, and generalized anxiety disorder based on ICD-10 criteria presented to Sakarya University Training and Research Hospital, Department of Endocrinology with bilateral adrenal masses. She had a history of hypertension and hyperlipidemia.

She used nifedipine for hypertension, atorvastatin for hyperlipidemia, and clozapine for schizophrenia. Size of her adrenal masses in the right adrenal gland 12×22 mm and in the left adrenal gland were 38×26 mm, respectively.

Physical examination of the patient showed a height of 150 cm, weight of 94 kg, BMI of 42 kg m⁻², and central obesity, and absence of plethora, purple striae, buffalo hump, and hirsutism. Laboratory findings were as follows: sedimentation rate: 25 mm/h; C-reactive protein: 3.38 mg/dL; fasting glucose: 88 mg/dL; serum creatinine: 0.8 mg/dL; serum calcium: 9.2 mg/dL; albumin: 3.7 g/dL; serum sodium: 140 mg/dL; serum potassium: 4.7 mg/dL. Complete blood count was normal. The basal cortisol level was 25 µg/dL, overnight (23000) cortisol was 3.1 µg/dL, early morning serum cortisol level was 18 µg/dL, and ACTH (adrenocorticotropic hormone) was 15 pg/dL. The 24-h urine cortisol level was 47 µg/d. The after overnight 1-mg dexamethasone suppression test [LDDST (low-dose dexamethasone suppression test)] cortisol level was 5.5 µg/dL; 2d later the 2-mg dexamethasone suppression test cortisol level was 1.8 µg/dL. Basal dehydroepiandrosterone sulphate (DHEAS) level was normal. As the patient's cortisol diurnal rhythm was intact and she didn't have any stigmata of Cushing's syndrome (CS), except for central obesity, CS was excluded.

The adrenal masses did not exhibit contrast enhancement in the out phase of sequence, which was consistent with adenoma according to an experienced radiologist. The 24-h urine catecholamines findings based on HPLC were as follows: vanillyl-mandelic acid was 8.3 mg/24h, which was within the upper limit of normal (0-6 mg/24h); metanephrine was normal; normetanephrine was 1641 µg/24h, which was significantly higher than normal (0-400 µg/24h). The patient did not have any pheochromocytoma-related symptoms, episodes of hypertension, palpitations, or flushing. Her adrenal imaging findings were not consistent with pheochromocytoma (Figures 1, 2 and 3).

MIBG scan was performed and it also was normal (Figures 4, 5) Based on these findings, clozapine-induced pseudo pheochromocytoma was considered; a review of the literature showed that a few cases similar to the presented case have been reported [12,13]. Comprehensive investigations excluded all other causes of hypertension and elevated urinary catecholamines, and the final diagnosis was clozapine-induced pseudo pheochromocytoma.

The risks versus benefits of discontinuing clozapine were considered in collaboration with the treating specialist physicians, and discontinuation of clozapine was advised. Following psychiatric consultation, clozapine was withdrawn for 1 week, after which 24-h urine catecholamines were normal: 5-hydroxyindolacetic acid: 4.6 mg/24h; metanephrine 119 µg/24h; normetanephrine: 283 µg/24h; vanillyl-mandelic acid: 3.3 mg/24h. In addition, plasma renin activity [PRA] and the plasma aldosterone concentration [PAC] were 0.94 ng/mL/h and 23 ng/dL, respectively. The PAC to PRA ratio was 24.8, but she did not have hypotension. Due to the high PAC to PRA ratio (>20) the saline infusion test was performed. Following 4-h saline infusion (500 mL/h) PAC decreased to 2 ng/dL (<5 ng/dL), and primary hyperaldosteronism was therefore also excluded.



Figure 1: Out of phase sequence in the axial plane, both in the adrenal gland, nodular lesion is seen that goes off (white arrows).



Figure 2: T2-weighted sequences in the axial plane, both hypo intense nodules in the adrenal glands are seen (white arrows).

Discussion

Clozapine is a tricyclic dibenzodiazepine derivative used for the treatment of schizophrenia. Its side effects include agranulocytosis and paradoxical hypertension with elevated 24-h catecholamines [13,14]. The neuropharmacological mechanisms of action of clozapine are complex, and include affinity for 5-HT₂ receptors and α₂-adrenergic receptors in vitro [15]. Clozapine has been reported to cause an elevated plasma noradrenaline concentration, perhaps via inhibition of presynaptic reuptake mediated by α₂-adrenergic receptors [16]. The other mechanism of clozapine-induced elevation in plasma NE levels is both increased spillover and decreased clearance or combination of them [17].



Figure 3: Axial T1-weighted fat-suppressed contrast-enhanced dynamic range plans related to the cross-section of nodular lesions in both adrenal glands contrast enhancement is not seen (white arrows).

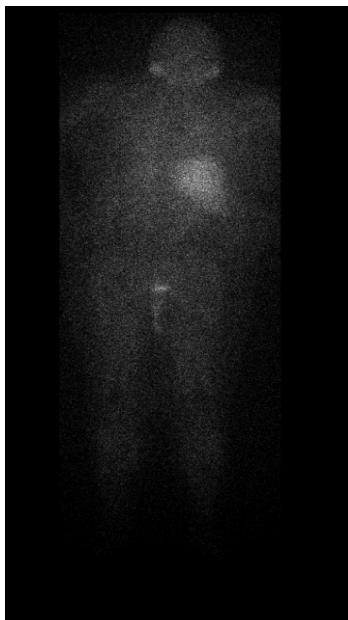


Figure 4: MIBG scans show normal findings (posterior Image).

resolved and the urine catecholamine concentration returned to normal in all cases.

The association between clozapine treatment and onset of hypertension is controversial. In the literature, prevalence of hypertension associated with clozapine therapy was reported 4-16% in various studies [21,22].

Given the potential for significant morbidity associated with pseudo pheochromocytoma syndrome, as undiagnosed cases are unlikely to receive clozapine treatment, we recommend early urinary catecholamine screening in all patients that develop hypertension or other typical symptoms following the initiation of clozapine treatment. The manufacturers of clozapine must develop international clinical guidelines for early diagnosis and management of pseudopheochromocytoma syndrome.

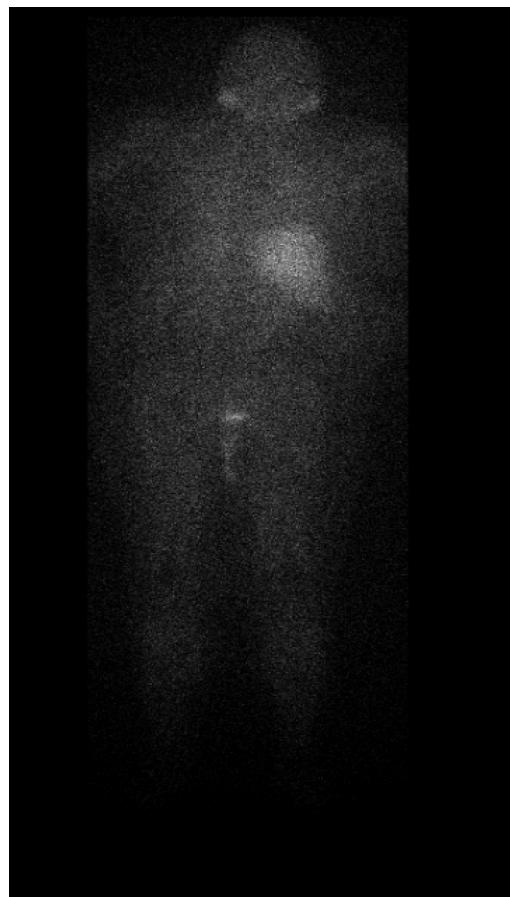


Figure 5: MIBG scans show normal findings (Anterior image).

The clinical effects of urine catecholamines remain uncertain. Some researchers have reported there are clinical effects [18,19], whereas others have reported there are no clinical effects, as in the presented patient [20]. Similar to the presented case, Li et al. [13] reported a 27-year-old male with mimicking pheochromocytoma; their patient used clozapine to treat catatonic schizophrenia, and developed hypertension and elevated urinary catecholamines. Following withdrawal of clozapine their patient's blood pressure and urinary catecholamines returned to normal. Krentzel et al. [14] reported 4 patients with pseudo pheochromocytoma syndrome that were treated with clozapine; following the withdrawal of clozapine the symptoms

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