Pseudopheochromocytoma — an epidemic of the modern world? Case series and review of literature

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Abstract

Background: Pseudopheochromocytoma is a condition that occurs more frequently than other diseases presenting with similar symptoms such as: paroxysmal hypertension, diaphoresis, pallor, palpitations. However, due to the lack of specific guidelines and awareness among physicians, it is widely underdiagnosed. Conventional antihypertensive treatment is ineffective in controlling symptoms which leads to decreased quality of life in patients affected by this disorder.

Case presentation: In our paper, we present three female patients with paroxysmal hypertension who were admitted to the Department of Endocrinology for an investigation of suspected pheochromocytoma. The biochemical findings and imaging carried out at the hospital ruled out the diagnosis of an adrenal tumor in all three of the patients. Given the proposed criteria the clinical features of the patients were suggestive of pseudopheochromocytoma. In all three cases, the anxiolytic or SSRI treatment was applied with satisfactory symptom control.

Conclusions: After ruling out pheochromocytoma in patients presenting with paroxysmal hypertension, physicians should consider a diagnosis of pseudopheochromocytoma. Management of the disorder should include anxiolytic, antidepressant, α-adrenoceptor blockers, and β-adrenoceptor blockers treatment, with close cooperation between hypertension specialist and psychiatrist or psychologist. Early proper diagnosis can reduce emotional distress related to an extensive diagnostic process as well as the overall cost of healthcare in patients with pseudopheochromocytoma.

Key words: pseudopheochromocytoma; paroxysmal hypertension; pheochromocytoma; hypertension; panic attacks

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Introduction

Pseudopheochromocytoma (ps-pheo) is a condition presented with paroxysmal or episodic hypertension accompanied by headache, chest pain, pallor, diaphoresis, nausea, and palpitations which are not connected to any specific triggers [1–3]. It usually occurs in women aged 40–50. Patients generally have a history of trauma or abuse [1, 4]. After the episode patients usually experience fatigue [3]; blood pressure is normal or slightly increased between onsets [5]. Those symptoms usually raise suspicion of pheochromocytoma [1].

Contrary to adrenal tumors, patients with ps-pheo show no abnormalities or slight increase in biochemical findings such as 24-hour urine fractionated metanephrine and catecholamine levels or/and plasma fractionated metanephrine levels [4].

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Ps-pheo is a diagnosis of exclusion as it requires further examination. Additionally, negative abdominal imaging for an adrenal tumor supports the diagnosis [5]. Differential diagnosis of ps-pheo includes panic disorder, post-traumatic stress disorder (PTSD), labile hypertension and others [5].

Pathophysiology of ps-pheo is still unknown; however, the latest study indicated that increased cardiovascular responsiveness to catecholamines is accompanied by epinephrine secretion stimulated by the sympathetic nervous system (SNS). Mann et al. also concluded that SNS is composed of two paths, one stimulated by adrenal glands causing an increased level of epinephrine and the other by neural activity which stimulates the secretion of noradrenaline [6].

Ps-pheo symptoms imitate those of adrenal medullary tumors, yet patients require different treatments. This can pose a problem for physicians and lead to the mismanagement of their patients. The condition significantly affects the life quality [1, 7] in patients as paroxysmal hypertension leads to a higher number of hospitalizations.

Here, we present cases of three women with suspected pheochromocytoma who were admitted to the Department of Endocrinology for further evaluation.

Case presentation

Case 1

A 32-year-old woman with a history of frequent palpitations, paroxysmal hypertension up to 160/90 mm Hg accompanied by anxiety, diaphoresis, and paleness (no headache) that led to multiple emergency room visits. The patient associated the onset of symptoms with the first pregnancy. Since then, she reported a depressed mood, anxieties, and panic attacks. She reported an increase in body weight of 30 kg over the past 6 years.

During one of the visits to the emergency department, a computed tomography (CT) scan of the abdomen was carried out, but no abnormalities were found (Fig. 1).

An ambulatory 24 h urinalysis showed a nonspecific increased level of normetanephrine to 434.5 ug/day (reference ranges < 390 ug/day). No diet restriction was carried out prior to the test as high-performance liquid chromatography (HPLC) method was used to obtain the results. The patient was admitted to the Department of Endocrinology for the investigation of possible pheochromocytoma.

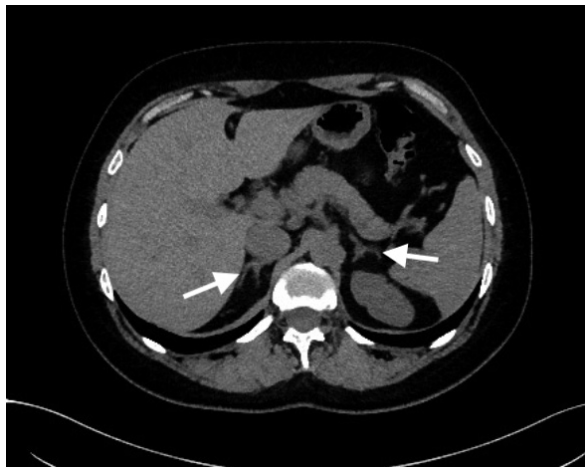

Figure 1. Abdominal computed tomography (CT) scan of the first patient showed no adrenal glands abnormality (arrows)

Work-up revealed normal metanephrine (MN) and normetanephrine (NMN) secretion in a 24h-urine collection. Moreover, normal morning cortisol concentration and normal response in low-dose dexamethasone suppression test was observed (cortisol level < 28 nmol/L). Thyroid function showed no abnormalities. Given the results, pheochromocytoma was ruled out as a possible diagnosis. The clinical image was suggestive of ps-pheo related to panic attacks. The patient was discharged from the hospital with escitalopram and referred to an outpatient psychiatry clinic**.** Summary of all three cases is included in Table 1.

Case 2

A 56-year-old female patient with a history of Lyme arthritis and ulcerative colitis was admitted to the Department of Endocrinology following a referral from her general practitioner for the investigation of paroxysmal hypertension with blood pressure rise to 160/100 mm Hg. She presented with fatigue, reduced exercise tolerance, diaphoresis, pruritus, easy bruising, hair loss, pallor, and tremor for the past 18 months. There was no anxiety disorders history. At the time of the admission, the patient received lacidipine, ramipril, and hormone replacement therapy.

Laboratory results reported a cortisol concentration of 378 nmol/L, and a 24-urinary secretion of MN and NMN showed no abnormalities. A normal response in the low-dose dexamethasone suppression test was observed (cortisol level < 28 nmol/L). Other bloodwork tests were within the reference range besides glucose (103 mg/dL) and potassium (5.4 mmol/L). A computed tomography (CT) scan was carried out to rule out lesions of the adrenal glands. No abnormalities were found (Fig. 2)

Table 1. Comparison of management of patients in presented cases

	Case 1	Case 2	Case 3
Comorbidities	None	Lyme arthritis, ulcerative colitis	Atrial fibrillation
Hypotensive treatment before ps-pheo diagnosis	Metoprolol	Lacidipine Ramipril	Bisoprolol Ramipril Doxazosin
Symptoms duration	6 years	18 months	8 years
Symptoms and main complaints	Paroxysmal hypertension up to 160/90 mm Hg Anxiety Diaphoresis Palpitations Pallor Depressed mood Panic attacks Increase in body weight of 30 kg	Paroxysmal hypertension up to 160/100 mm Hg Fatigue Reduced exercise tolerance Diaphoresis Pruritus Easy bruising Hair loss Pallor Tremor	Paroxysmal hypertension up to 200/120 mm Hg
MN and NMN in 24 h urine collection (HLPC) Upper reference limit [ug/24h]: — MN < 320 — NMN < 390	MN — 159 ug/24 h NMN — 356 ug/24 h	MN — 201 ug/24 h NMN — 241 ug/24 h	MN — 133 ug/24 h NMN — 252 ug/24 h
Abdominal CT	No pathology in adrenal glands	No pathology in adrenal glands	8 mm lesion of left adrenal gland (adenoma, no characteristics of pheochromocytoma)
Additional hormonal tests	Normal thyroid function No hypercortisolemia No primary hyperaldosteronism[1]		
Recommendations	Escitalopram 5 mg Referral to psychiatry out-patient clinic	Referral to psychiatry out-patient clinic Chlorprotixene 15 mg	Fluoxetine 20 mg
Outcome	No information, no contact with patient after hospitalization	No paroxysmal hypertension	Reduction of number of hypertensive attacks

[1]Only in the Case 3

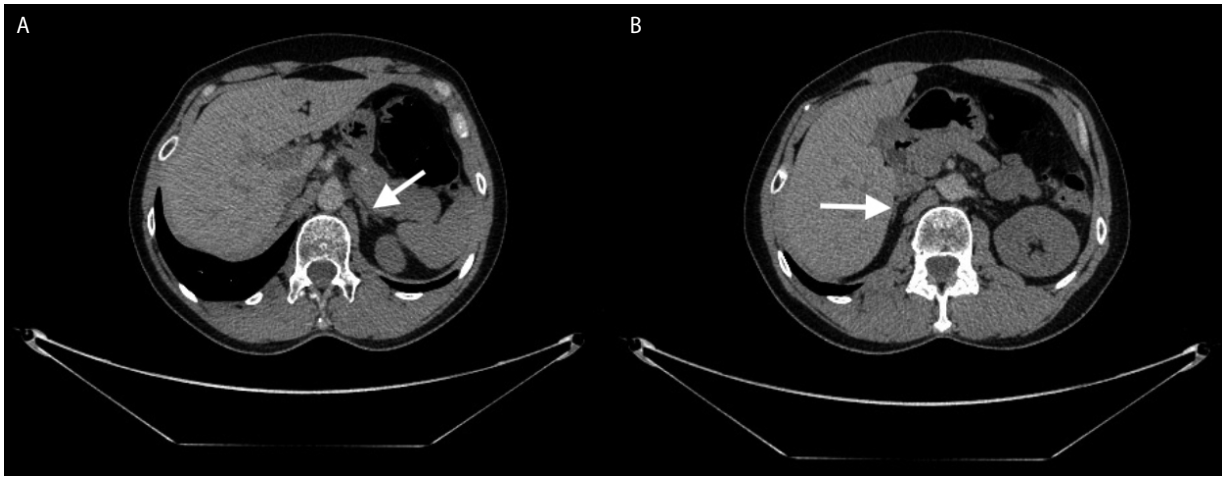

Figure 2. Abdominal computed tomography (CT) scan of the second patient showed no adrenal glands abnormality; left adrenal gland (arrow; **A**), right adrenal gland (arrow; **B**)

Results of the laboratory tests ruled out the pheochromocytoma diagnosis. The patient was discharged from the hospital and referred to the psychiatric health care. Psychiatrist administrated chlor-

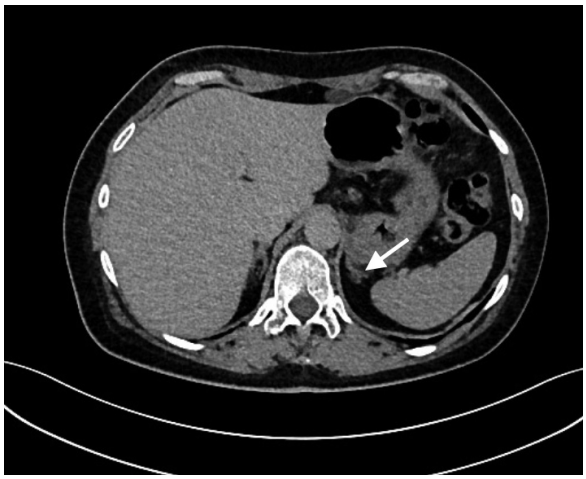

Figure 3. Abdominal computed tomography (CT) scan of the third patient showed small 8-mm lesion of the left adrenal gland (arrow)

protixene, and after 2–3 months no paroxysmal hypertension was noted.

Case 3

A 46-year-old female patient was admitted to the Department of Endocrinology for an investigation of secondary hypertension and evaluation of a left adrenal gland lesion. Paroxysmal hypertension started in 2013 and measured up to 200/120 mm Hg. Since then, the patient received angiotensin-convertase inhibitors (ACE-I) and beta-blockers which were ineffective in controlling hypertension (see Tab. 1 for details). In 2013 she was diagnosed with atrial fibrillation and underwent ablation in 2014. However, she reported a recurrence of symptoms in 2020. In 2021 she was admitted to the nephrology department for further diagnostics of hypertension.

The CT scan performed during hospitalization showed 8 mm lesion of left adrenal gland with typical characteristics of adenoma (Fig. 3).

Plasma renin concentration and plasma aldosterone concentration were also measured; however, the results were inadequate due to ACE-I taken by the patient. Additionally, 24 h-urine collection for MN and NMN revealed no pathology. During the hospitalization in the Department of Endocrinology plasma renin concentration, plasma aldosterone concentration and salt loading test were carried out which ruled primary hyperaldosteronism as a possible diagnosis. Additionally, a low-dose dexamethasone suppression test showed a normal cortisol response. No thyroid pathology was detected. The clinical image suggested an inactive focal adrenal lesion. The patient was discharged with selective serotonin reuptake inhibitors (SSRI), fluoxetine. After 2 months of SSRI therapy symptoms of paroxysmal hypertension were markedly milder.

Discussion

In the presented cases diagnostic tests excluded the possibility of pheochromocytoma. The symptoms of the first patient could be related to depressed mood, anxieties, and panic attacks after the first pregnancy but not triggered by them. Conversely, the second and the third patient did not acknowledge any underlying panic disorders or trauma. In their 1999 study, Mann et al. pointed out that some patients can identify a history of severe physical and emotional trauma while others did not report such history [1]. Good control of paroxysms in the third patient (who received anxiolytics treatment) speaks for diagnosis of ps-pheo. Given the proposed criteria the clinical features of the patients are suggestive of ps-pheo [5].

Hypertension ranks as one of the most frequently diagnosed conditions in the world and is the leading cause of premature death. It is estimated that hypertension affects 1.28 billion of adults aged 30–79 [8]. The prevalence of hypertension varies from region to region. Asymptomatic hypertension accounts for most of the cases and due to its nature is usually diagnosed incidentally. Patients who actively seek medical help are often those with symptoms affecting their life quality including incidental blood pressure elevations, headaches, palpitations, anxiety, and sweating, which usually raise suspicion of pheochromocytoma [6].

Catecholamine-secreting tumors are diagnosed in less than 0.5% [9] of patients with hypertension. It is a rare condition but highlighted by literature as undiagnosed cases carry high morbidity and mortality [10]. Kuchel et al. presented cases of 7480 hypertensive patients and only 8 of them were diagnosed with pheochromocytoma while 688 had paroxysmal or intermittent hypertension [11].

Despite their symptoms patients proven not to have a pheochromocytoma outnumber those with an actual tumor. After the exclusion of an adrenal tumor, the process of diagnosis becomes challenging as most physicians are not familiar with potential psychological causes such as stress and emotion [12]. Differential diagnosis of paroxysmal hypertension includes panic disorder, PTSD, labile hypertension, ps-pheo, and others.

The panic disorder occurs in 12% of cases with hypertension [13] and shares similar symptoms with ps-pheo. However, what differentiates

Table 2. Proposed treatment in pseudopheochromocytoma (ps-pheo)

Acute treatment[1]		Preventive treatment
At home	**In ER**	Transdermal clonidine Antihypertensive therapy[2] Antidepressants (SSRI, desipramine) Psychotherapy
Above 210/110 mm Hg and no systemic or neurological symptoms Below 210/110 mm Hg and no comorbidities	Above 210/110 mm Hg and neurological or systemic symptoms and/or comorbidities	
Relaxation maneuvers Oral alprazolam Oral clonidine or amlodipine	Labetalol *i.v.* [3], nicardipine *i.v.*[3] or clonidine *p.o.* Alprazolam, clonazepam or diazepam	

[1]Benzodiazepines should not be chronically used for longer periods of time; [2]Only in patients with hypertension between the episodes; [3]Unavailable in Poland; *i.v.* — intravenously; *p.o.* — per os; SSRI — selective serotonin reuptake inhibitor

these conditions is that the latter is characterized by episodes of a significant increase in blood pressure in absence of any psychological triggers [5, 14]. Subsequently, the patients presented in our cases do not fulfill the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for panic disorder [15].

PTSD is another trauma-related condition in which symptoms resemble those of ps-pheo; however, in patients with PTSD elevation of blood pressure is rarely seen [5]. Additionally, diagnosis of the PTSD requires at least 1 month of reported impairment in social, occupational, and other important areas of functioning [16].

Differential diagnosis of paroxysmal and labile hypertension is particularly challenging as those two terms are often used interchangeably by physicians. Although labile hypertension lacks a clear definition its relation to emotional distress has been well documented. Contrary to patients with ps-pheo, patients with labile hypertension acknowledge the presence of a psychological trigger that causes a rise in blood pressure that resolves without medical intervention [1, 17].

Paroxysmal hypertension may occur secondary to other causes such as certain medications (especially tricyclic antidepressants and monoamine-oxidase inhibitors), drug and substance abuse (cocaine, amphetamine, alcohol), obstructive sleep apnea, renovascular disease, and other endocrinopathies [1]. Although the presented patients' medical history does not match the characteristics of those triggers, yet they require further evaluation.

Due to a lack of unequivocal recommendations or guidelines, the management of patients with ps-pheo may be inadequate leading to unsatisfactory results. Most used antihypertensive drugs such as diuretics, ACE-I, and angiotensin receptor blockers (ARBs) provide poor outcomes in symptom management [5, 17]. Given the proposed etiology [1] of paroxysmal hypertension as well as recent reports in the literature, drugs that reduce the overactivity of the sympathetic nervous system should be incorporated into the treatment strategy [5, 17].

Therapy can be divided into acute and preventive treatment. Acute intervention can be provided at home if blood pressure is below 210/110 mm Hg or above without systemic or neurological symptoms. However, if patients experience systemic or neurological symptoms with blood pressure exceeding 210/110 mmHg and suffer from comorbidities emergency department care would be desirable (Tab. 2) [5].

In the emergency room surges of extremely high blood pressure can be managed with intravenous administration of labetalol or nicardipine [18, 19]. In cases of less severe episodes oral clonidine can also be considered. Anxiety experienced simultaneously with paroxysm can be treated with anxiolytics such as intravenous alprazolam. Alternatively, clonazepam or diazepam can be used [5, 12]. If paroxysm can be managed at home patients should be instructed to perform relaxation maneuvers [20]. If the elevated systolic blood pressure above 180 mm Hg persists patients should take an oral dose of alprazolam and clonidine or amlodipine (Tab. 2) [5].

Preventive pharmacological treatment in ps-pheo consists of anti-hypertensive and anxiolytics medication. The decision to administer preventive anti-hypertensive therapy depends on blood pressure levels between the paroxysms. Current literature does not recommend the usage of hypotensive drugs in normotensive patients between the episodes. However, chronic and sustained hypertension requires treatment according to the ESC/ESH (European Society of Cardiology/European Society of Hypertension) [5, 17]. Medications used as a preventive measure include α-adrenoceptor blockers and β-adrenoceptor blockers (doxazosin, terazosin, atenolol, metoprolol, carvedilol) and transdermal clonidine [5, 17]. Given the psychological component of the condition, antidepressants can be prescribed as a form of preventive therapy. Proposed

treatment includes SSRIs (citalopram, escitalopram, sertraline, paroxetine), benzodiazepines (clonazepam), and tricyclic antidepressants (desipramine).

Literature suggests that psychological intervention could be beneficial to patients with ps-pheo [17]. However, it is not effective in all cases as patients who tend to repress emotions are resistant to psychotherapy regardless of their history of trauma [5]. Nevertheless, physicians should reassure patients that without extremely high blood pressure a sudden cardiovascular event is unlikely to occur. Treatment in ps-pheo is summarized in Table 2.

Conclusions

The elusive nature of ps-pheo can pose difficulty in the diagnostic process exposing patients to emotional distress and reducing their quality of life [5]. Involvement of emotional components creates a lack of motivation to seek follow-up care. What is more, an extended diagnostic process increases the cost of healthcare in patients with ps-pheo compared to those with pheochromocytoma [17]. Knowledge insufficiency in physicians and lack of specific guidelines lead to the inability to recognize and treat ps-pheo [12]. Commonly used antihypertensive drugs such as ACE-I, ARBs, and diuretics are ineffective in the treatment of the disease and are unable to prevent paroxysms [12, 17]. Proposed medications include α-adrenoceptor blockers, agonist β-adrenoceptor blockers, and anti-depressants. Treatment should be managed in a cooperative effort between a hypertension specialist and a psychiatrist or psychologist [12].

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Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Oral consent was obtained from the patients for publication of this Case Report and any accompanying images.

Ethical approval and consent to participate

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