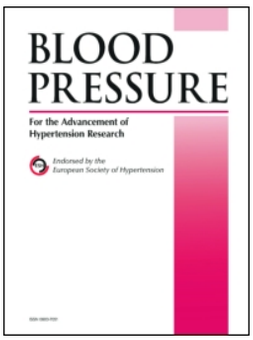

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CASE REPORT

Unrecognised pheochromocytoma in pregnancy discovered through metoclopramide-triggered hypertensive emergency

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ABSTRACT

Purpose: Pheochromocytoma, a catecholamine-secreting tumour leading to neurological and cardiovascular life-threatening conditions through hypertension crisis, occurs in 0.1-0.5% of hypertensive patients, but it is extremely rare in pregnancy (0.0018-0.006%). Some classes of drugs, even commonly used in pregnancy, can trigger catecholamine secretion, precipitating the clinical situation.

Materials and Methods and Results: We report a 33-year-old woman, gravida 2 para 1, with previous mild hypertension, was admitted to the emergency room, at 28 2/7 weeks of gestation due to headache, tachycardia and severe arterial hypertension (220/120 mm Hg) triggered by the antiemetic metoclopramide used for a week because of nausea. In the emergency room, a paradoxical rise in blood pressure followed intravenous labetalol infusion was observed. Both metoclopramide and labetalol-triggered hypertensive crisis raised the suspicion of an undiagnosed pheochromocytoma. Diagnostic work-up showed elevated normetanephrine urinary excretion and a right adrenal pheochromocytoma by abdominal magnetic resonance imaging. Oral alpha-1 and beta-1-adrenergic antagonist and calcium-channel blocker were started. At 33-weeks of gestation, she underwent a caesarean section giving birth to a female child. Seven weeks later she underwent a video-laparoscopic right adrenalectomy which normalised her blood pressure.

Conclusions: Both metoclopramide, a selective dopamine type-2 receptor antagonist and partial agonist of 5-hydroxytryptamine 4 receptor, and labetalol, a non-selective β-adrenoreceptor-blocker with weak α1-adrenergic antagonism, exacerbated an acute hypertensive crisis revealing an unrecognised pheochromocytoma in a pregnant patient. Careful attention to potential drug-triggered catecholamine crises and especially early recognition of pheochromocytomas, are mandatory in hypertensive pregnant women. A missed or delayed diagnosis could result in catastrophic results affecting foetal and maternal outcomes.

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Metoclopramide; pheochromocytoma; pregnancy; hypertension emergency; labetalol

Introduction

Pheochromocytoma (PHEO) and paraganglioma are neuroendocrine tumours of chromaffin cells derived from the adrenal medulla (80-85%) and sympathetic ganglia (15-20%). The prevalence of PHEO in hypertensive patients ranges between 0.1 and 0.5%, reaching 7% when an incidental adrenal mass is present. PHEO is extremely rare during pregnancy with a prevalence ranging from 1 in 15000-54000 women (0.0018-0.006%) [1,2]. PHEO may represent a life threatening condition for the mother and the foetus. Increased catecholamine secretion is responsible for the elevated risk of acute cardiovascular and neurological events [3,4]. Recent data reported maternal and foetal mortalities of 8 and 17%, respectively [5]. Given the evidence that prompt antenatal diagnosis is associated with lower risks of maternal and foetal mortalities, an accurate identification of PHEO during the antenatal period is mandatory, especially in young hypertensive women. A large series of drugs can exacerbate the life-threatening catecholamines crisis in PHEO including dopamine D2 receptor antagonists, β-adrenergic receptor antagonists, sympathomimetics, caffeine, norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, steroids and anaesthetics

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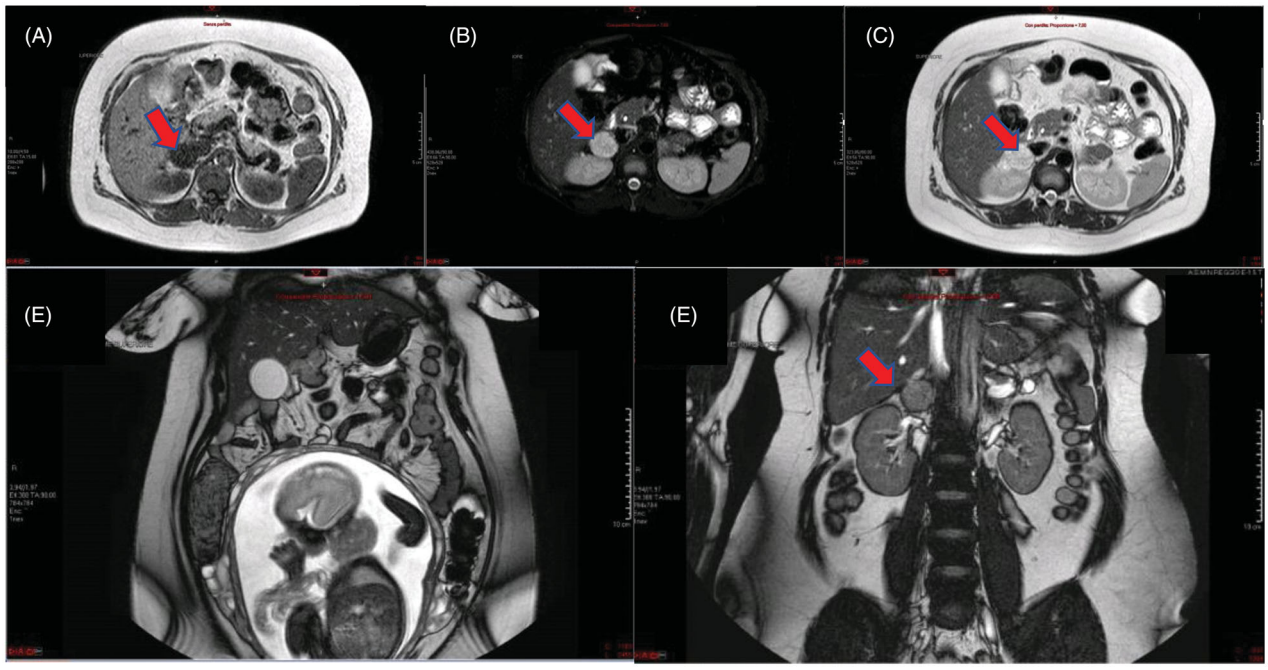

Figure 1. Abdominal Magnetic Resonance Imaging (T1 and T2 sequences). Magnetic resonance showed a 3 cm oval regular bounded lesion in the right adrenal (E), hypointense in T1 (A,B) and at intermediate-high signal in T2 sequences (C). No lesions in the liver, spleen, pancreas, kidneys and lymph-nodes (D).

[6]. Drug use in pregnancy should always be carefully considered because of the risk to harm the mother and the foetus. However, antiemetics, antiacids, antihistamines, analgesics are among the most used drugs during pregnancy. Here we report a case where metoclopramide and labetalol triggered a catecholamine-mediated hypertensive crisis in a pregnant hypertensive woman, revealing an unrecognised PHEO. This clinical case strongly supports the role of accurate antenatal screening for PHEO in young hypertensive women, and in particular, the careful use of drugs during pregnancy in order to prevent the risk burden of maternal and foetal morbidity and mortality related to a missed diagnosis.

Case presentation

A 33-year-old woman, gravida 2 para 1, non-smoker, with one-year history of grade I hypertension was treated until the beginning of her pregnancy with low doses of a beta1-selective adrenergic blocker (bisoprolol 2,5 mg once a day) associated to a thiazide-type diuretic (hydrochlorotiazide 6.25 mg/day). At the beginning of the pregnancy, her general practitioner switched the antihypertensive therapy to alpha-methyldopa (500 mg thrice a day), a centrally acting sympatholytic agent that decreases the adrenergic outflow by an alpha-2 agonistic effect. From the 18th week of gestation, because of poor blood pressure control, a L-type calcium-channel blocker, 20 mg/day (Nifedipine extended-release), was added. Gestational diabetes occurred in the first trimester and insulin therapy was started (Insulin lispro 6 U s.c. at 7.00 a.m.; Insulin lispro 10 U s.c. at 12.00 a.m.; Insulin lispro 10 U s.c. at 06.00 p.m. Insulin glargine 15 U s.c. at 09.00 p.m.). The prior pregnancy was conducted three years earlier without complications. She was examined 2 years earlier while still normotensive, because of the appearance of abdominal "striae rubrae", reddish purple, flat, thinned skin marks associated with proximal muscle pain and marked weakness. Her body weight was in the normal range and laboratory tests were negative for hypercortisolism. Her familial medical history revealed that both parents were affected by arterial hypertension.

At 28 2/7 weeks of gestation, she was admitted to the emergency room because of acute headache and a severe hypertensive crisis (220/120 mmHg, heart rate was 102 bpm). Peripheral oedema was absent. She was treated with intravenous administration of labetalol, an α1-, β1-, and β2-adrenergic receptors antagonist with predominant β-adrenoreceptor blocking activity and a weak α-blocking activity (an intravenous bolus of 20 mg over 2 min, followed by a continuous infusion at a rate of 2 mg/min), which led to a paradoxical worsening of blood pressure levels (230/130 mm Hg). A treatment with urapidil, a peripheral α1-adrenergic antagonist (initially given as

intravenous bolus of 25 mg over 5 min and followed by a continuous infusion at a rate of 0.5 mg/min), and magnesium sulphate (40 mEq in saline solution 250 ml in a 4-hour infusion period), was immediately started to reduce blood pressure levels and to control the catecholamine-related hypertensive crisis. A brain computed tomography (CT) scan was negative for acute cerebral events, whereas laboratory findings showed a serum creatinine of 0.4 mg/dl (35.4 umol/L), leukocytosis (15,100/mm^3), mild hypokalaemia (3.3 mmol/L) and proteinuria (dipstick ++/++++). The patient was also treated with intravenous supplementation of potassium chloride (40 mEq in saline solution 250 ml in 6-hour infusion period), and magnesium sulphate further continued (40 mEq in saline solution 250 ml in a 12-hour infusion period) to reduce potential arrhythmias. A careful recent clinical history indicated the onset of symptoms (weakness, irritability, anxiety, headache) one week earlier when she reported taking metoclopramide (oral tablet 10 mg once a day for 2 days, and twice a day for the 5 days before hospital admission) to treat nausea and dyspepsia.

Results

Suspecting a metoclopramide-induced PHEO crisis, we performed a hormonal workup which revealed a daily urinary normetanephrine excretion almost eight times the upper normal value (3798 ug/24h, normal values range: 162-528 ug/24h), while metanephrine and metoxityramine levels were within the normal range. Plasma aldosterone and renin levels were normal. The abdominal ultrasound showed normal foetal growth, but revealed a nodular mass involving the right adrenal gland. Abdominal magnetic resonance imaging confirmed an oval lesion 3 cm in diameter in the right adrenal gland, hypointense in T1 sequences (Figure 1(A,B)), with intermediate-high signals in T2 sequences (Figure 1(C)). Based on the laboratory results in conjunction with imaging and clinical findings, a diagnosis of right adrenal PHEO was formulated. Treatment was immediately started with an α1-adrenergic receptor antagonist (doxazosin up to 14 mg/day), β1-selective adrenergic receptor antagonist (atenolol 12.5 mg/day) and a dihydropyridine L-type calcium channel blocker (nifedipine extended release 30 mg/day). Adequate blood pressure control was thereby attained within few days of therapy. After a multidisciplinary discussion, at 33 4/7 weeks of gestation, the patient underwent a caesarean section with a regular post-operative course (delivery of an infant girl of 2910 g, APGAR score 9 after 1 and 5 min). Three weeks later, a contrast CT abdomen scan confirmed the presence of the right adrenal gland lesion of 3 cm (see Online Supplement Figure 1(A,B)). To investigate the potential metastatic spread of the PHEO, a whole-body ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/CT (PET/CT) was performed, and only focal right adrenal gland was positive (see Online Supplement Figure 2). Thus, seven weeks following the delivery, a videolaparoscopic right adrenalectomy was successfully carried out under treatment with doxazosin (8 mg/day) and atenolol (uptitrated to 25 mg/day one week earlier). The surgery was uneventful, and the patient was discharged with normal blood pressure levels. Histological examination revealed a right capsulated PHEO with a Pheochromocytoma of the Adrenal gland Scaled Score (PASS) of 5, indicating a mildly aggressive histomorphologic behaviour (see Online Supplement for genetic analysis).

With Next Generation Sequencing (NGS) approach (Trusight One Sequencing Panel) a series of predisposing genes were evaluated and two variants of the RET gene, one synonymous and the other missense, respectively c.2071G>A and c.2508C>T, the former a variant of uncertain significance and the latter considered benign or likely benign were found.

The patient is currently in good clinical condition, normotensive and euglycemic (without insulin), and she is scheduled at our outpatient clinic for periodic follow-up visits.

Discussion and conclusion

This patient represents a rare case of an undiagnosed PHEO discovered in a pregnant woman whose catecholaminergic crisis was triggered by the antiemetic drug metoclopramide. In addition, when the severe hypertensive crisis was treated in the emergency room with intravenous labetalol, a paradoxical worsening of blood pressure was observed, strongly confirming the suspicion of an underlying undiagnosed PHEO. The patient had her blood pressure safely reduced when the selective α1-adrenergic antagonist urapidil and magnesium sulphate were infused. Magnesium sulphate infusion is useful in this setting because of its arterial dilatory property and ability to reduce postsynaptic catecholamine release from the adrenal medulla [7]. This case presents several points of discussion concerning practical management of undiagnosed PHEO in pregnancy and the potential risk linked to inappropriate drug use.

First, as a general consideration, a hypertensive emergency which occurs after 20 weeks of gestation could plausibly be due to pre-eclampsia, which can mimic a PHEO hypertensive crisis. Pre-eclampsia/eclampsia-related hypertension can cause a de novo acute rise of blood pressure (or a rise superimposed on a pre-existing chronic hypertension) and associates with proteinuria, oedema and less frequently can progress with elevated liver enzymes, right upper quadrant or epigastric abdominal pain, low platelet count, acute kidney injury, neurological complications, disseminated intravascular coagulation, and haemolysis (HELLP syndrome). Prompt delivery is usually the clear indication in case of pre-eclampsia but it may be life-threatening in case of undiagnosed PHEO, in the absence of adequate drug preparation that must include treatment with α1-adrenergic receptor antagonist to which a β1-adrenergic receptor antagonist can only be subsequently combined. Both antagonists of α1-adrenergic receptor doxazosin (competitive) and phenoxybenzamine (non-competitive and irreversible) have been used in pregnant woman with PHEO and are considered safe even if the former has a foetal/maternal plasma ratio of 0.8 vs 1.6, suggesting a lower accumulation in the foetus [8]. Keeping in mind the possible catastrophic situation of an undiagnosed PHEO, an accurate differentiation with pre-eclampsia is of utmost importance. The measurement of serum concentration of the soluble Fms-like tyrosine kinase 1 and of placental growth factor was not performed and the ratio calculation between these 2 parameters was not available to help in discriminating pre-eclampsia from PHEO hypertensive emergency [9].

But in our case report, the medical history of a pre-existing hypertensive condition, the observed clinical and laboratory parameters (acute rise of blood pressure, mild-moderate proteinuria, no oedema, no coagulation and liver abnormalities), the recent drug history of metoclopramide intake and the paradoxical response to the infusion of labetalol led to the strong suspicion of an undiagnosed PHEO.

Second, it is also important to investigate drugs whose administration may result in an increase of catecholamine release leading to massive vasopressor responses.

As noted in our case, taking metoclopramide likely sparked the catecholamine storm that brought the patient to the emergency room with severe hypertension and headache. *A posteriori*, such a clinical observation raised the suspicion of a PHEO, that was strengthened by the paradoxical rise in blood pressure following the intravenous infusion of labetalol. Both metoclopramide and labetalol have been described as drugs which can potentially exacerbate an acute hypertensive crisis in PHEO [6, see Online Supplement for clinical cases described in literature], but very few in pregnancy [10,11]. The antiemetic agent metoclopramide, a selective dopamine type 2 (D2) receptor antagonist, is frequently used in the treatment of nausea and vomiting associated with neoplastic disease, narcotic analgesics, radiation therapy, gastroenteritis, alcoholism as well as pregnancy. Even if metoclopramide is not licenced for nausea and vomiting during pregnancy, it is the antiemetic drug of choice during pregnancy in several European countries and in Australia [12].

In fact, it is categorised as a Pregnancy Category A drug by the Australia Therapeutic Goods Administration and in the United States it is a Pregnancy Category "Not Assigned" drug by the Food and Drugs Administration. The United States Food and Drugs Administration recently stated that metoclopramide should only be used during pregnancy in cases when benefits outweigh the risks . In 2015, the European Medicines Agency recommended metoclopramide use only for 5 days, because longer courses are more likely to produce side effects for the mother such as oculogyric crises and dystonia, facial and skeletal muscle spasms and dizziness, without concerns about malformations, spontaneous abortions, or decreased birth weight of the infants.

Dopaminergic D2 receptors are expressed in the normal adrenal medulla as well as in PHEO chromaffin cells and their antagonism by metoclopramide can lead to a marked release of catecholamines. Besides the anti-dopaminergic D2 receptor activity antagonism, it has been demonstrated that metoclopramide may act as a partial agonist on 5-hydroxytryptamine 4 receptors, further promoting catecholamine release from chromaffin cells of PHEO [13].

Intravenous labetalol administration in the emergency room brought to blood pressure worsening strengthening the suspicion of an undiagnosed PHEO. Labetalol antagonises α1-, β1-, and β2-adrenoreceptors, but it acts predominantly as a β-adrenoreceptor blocker with weak α1-blocking activity (ratio 7:1 between β-blockade and α-blockade). Therefore, even if most of the health authorities recommend labetalol as first-line alternative along with hydralazine and nifedipine for the treatment of severe, persistent and refractory hypertension during pregnancy [14], its use in our patient precipitated the hypertensive crisis because of the non-selective β-adrenergic blockade

leaving unopposed α1-adrenergic receptor stimulation causing massive vasoconstriction. Several cases have been reported in the literature about labetalol-triggered hypertensive crises and acute cardiovascular and neurological complications in patients with PHEO [15], but just a few pertain to pregnancy [16].

A careful attention to drugs-triggered catecholamine crises, but especially early recognition of PHEO in hypertensive pregnant women, is fundamental and should be always suspected in the differential diagnosis of uncontrolled hypertension in order to aggressively treat this potential life-threatening disease. A missed or delayed diagnosis during pregnancy could result in catastrophic results affecting foetal and maternal outcomes.

Disclosure statement

The authors report no conflict of interest.

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Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study

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