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Chapter 6

Pheochromocytoma Crisis

Tanya Castelino and Elliot Mitmaker

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Abstract

Pheochromocytomas are rare tumours of the adrenal gland that secrete catecholamines. The classical presentation of these tumours consists of a clinical triad of headaches, palpitations and diaphoresis. This clinical presentation should not be confused with the potentially fatal presentation of pheochromocytoma crisis, which may include severe haemodynamic instability and collapse, multi-organ failure, hyperthermia and encephalopathy. When patients present in profound shock, supportive care and treatment are initiated. Patients presenting with pheochromocytoma crisis have an underlying adrenal tumour, but the clinical manifestations of this life-threatening condition can mimic other entities. Once diagnosis is made, previous anecdotal evidence has shown that pheochromocytoma crisis is a surgical emergency. However, retrospective study of a larger sample of patients presenting with pheochromocytoma crisis suggests that medical management in the acute setting is appropriate and safe. The ultimate treatment is indeed surgical; however, there is no clear recommendation for the acute management of pheochromocytoma crisis. This chapter will focus on the medical and surgical management of potentially life-threatening pheochromocytoma crisis. An in-depth review of the clinical presentation, pathophysiology, causes and treatments of pheochromocytoma crisis will be provided, including the controversial areas surrounding decision-making and timing for adrenalectomy.

Keywords: management, medical, surgery, adrenalectomy

1. Introduction

Pheochromocytomas are rare tumours of the sympathetic nervous system that arise from the chromaffin cells of the adrenal medulla. These tumours secrete catecholamines either intermittently or continuously. Pheochromocytomas are generally unilateral, in 90% of cases, whereas bilateral disease is found more commonly in the paediatric population and associated with genetic syndromes. Right-sided adrenal tumours are more common and have

a higher preponderance to cause paroxysmal hypertension compared to left-sided tumours that are generally associated with persistent hypertension. These tumours have an estimated incidence of 2–8 cases per million per year [1] and comprise less than 0.1% of the hypertensive population; however, approximately 90% of all patients with pheochromocytoma have associated hypertension [2]. Classic presentation of pheochromocytoma consists of a triad of symptoms, including headaches, diaphoresis and palpitations. The gold standard of treatment for pheochromocytoma is elective surgical resection after an appropriate, usually 1–2 weeks, course of anti-hypertensive therapy.

Pheochromocytoma multisystem crisis (PMC) was a term first described in 1988 [3]. This rare and potentially fatal entity consists of a tetrad of symptoms including haemodynamic instability and collapse, encephalopathy, hyperthermia and multi-organ failure. PMC is not synonymous with hypertensive crisis; patients with PMC typically tend to have very labile blood pressures ranging from severe hypotension to severe hypertension (e.g. 60–250 mm Hg systolic). The treatment of PMC remains controversial, as there is no consensus among clinicians regarding the appropriate timing of adrenalectomy in the specific setting of pheochromocytoma crisis. This chapter will address the clinical presentation of PMC, pathophysiology of pheochromocytoma, causes of PMC and a description of medical versus surgical treatment. Finally, the evidence regarding emergency adrenalectomy to treat PMC compared with medical management will be discussed.

2. Clinical presentation

Pheochromocytoma has been termed the 'great mimicker' because it presents in a non-specific way that may be mistaken for other clinical entities. Patients presented with the classic triad of pheochromocytoma (i.e. headaches, palpitations and diaphoresis) may initially be given the misdiagnosis of migraine headaches or psychiatric conditions such as acute anxiety or panic attacks. This clinical situation can be particularly dangerous because some medications used for treatment (i.e. β-blockers) may induce paroxysms of severe hypertension and subsequent pheochromocytoma crisis. Some clinicians advocate that in cases with anxiety and/or migraines, such patients should undergo formal screening for pheochromocytoma because the treatment of the former conditions may precipitate a crisis [4].

PMC consists of a constellation of symptoms that can also resemble other life-threatening conditions and can be difficult to diagnose if the patient is not already known for pheochromocytoma. PMC, which consists of haemodynamic instability with either severe hypotension or hypertension, labile hypertension, hyperthermia (≥40°C), encephalopathy and multi-organ failure, can be confused with other diagnoses such as septic shock, thyroid storm and malignant hyperthermia. This complex can be deleterious to every organ system, resulting from excess norepinephrine secretion causing extreme vasoconstriction, but also due to vasodilatation from excess epinephrine secretion and volume contraction, with a subsequent low-flow state. Encephalopathy may occur secondary to severe hypertension or direct effects of catecholamines on the brain. Other neurologic manifestations of PMC include cerebrovascular

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accidents and seizures. Cardiac complications are numerous and may include cardiomyopathy, myocarditis, myocardial ischemia and necrosis secondary to coronary vasospasm, congestive heart failure, cardiac arrhythmias and cardiogenic shock. Pulmonary manifestations include pulmonary edema and acute respiratory distress syndrome. Patients with PMC may also present with acute liver failure, acute kidney injury, disseminated intravascular coagulation, lactic acidosis, diabetic ketoacidosis and rhabdomyolysis. Gastrointestinal manifestations include paralytic ileus and intestinal ischemia secondary to vasoconstriction. Vascular complications can include peripheral thrombosis, embolism and vasospasm [5, 6].

3. Pathophysiology

Pheochromocytomas arise from the chromaffin cells of the adrenal medulla. Chromaffin cells produce catecholamines, and pheochromocytomas can produce up to 27 times the synthetic capacity of the normal adrenal medulla. This high rate of production causes accumulation of catecholamines and their metabolites, metanephrines, in the cytoplasm of the chromaffin cells, which then diffuse out of the cells into the vascular system [2]. Tumour size directly correlates with levels of catecholamine secretion with smaller tumours secreting fewer hormones than larger tumours, whereas larger tumours reported to have wider variability of hormone secretion [7]. Most pheochromocytomas produce epinephrine and norepinephrine, which both act on G-protein coupled adrenergic receptors [8].

Norepinephrine acts on α-1-adrenergic receptors that are located on smooth muscle cells within peripheral arteries and veins, causing vasoconstriction; α-2-adrenergic receptors, located on the presynaptic surface of sympathetic ganglia, cause coronary vasoconstriction and peripheral arterial dilatation; and β-1-adrenergic receptors located on cardiomyocytes, cause positive inotropic effects, as depicted in **Figure 1**. Activation of β-1-adrenergic receptors also causes increased secretion of renin, which increases the mean arterial pressure. Epinephrine primarily acts on β-1- and β-2-adrenergic receptors. Activation of β-2-adrenergic receptors leads to vasodilatation of arteries as well as increased secretion of norepinephrine by the sympathetic ganglia.

Depending on the catecholamine secretory profile of the tumour, pheochromocytomas can have different clinical manifestations. Most pheochromocytomas secrete more norepinephrine than epinephrine; however, they can secrete both hormones or secrete epinephrine alone. Severe hypertension may develop because of vasoconstriction from excess norepinephrine secretion whereas severe hypotension may result from widespread vasodilation caused by excess epinephrine secretion. Other mechanisms have been postulated to explain these changes in blood pressure. One of the explanations is that tumour necrosis may cause overwhelming tumour cell death and an abrupt cessation of catecholamine secretion, thereby leading to severe hypotension. However, it has also been postulated that tumour cell death may lead to cell lysis and subsequent massive release of catecholamines and severe hypertension. It is unclear which pathophysiologic mechanisms are responsible for the haemodynamic instability associated with PMC, but each mechanism likely contributes to the overall clinical picture.

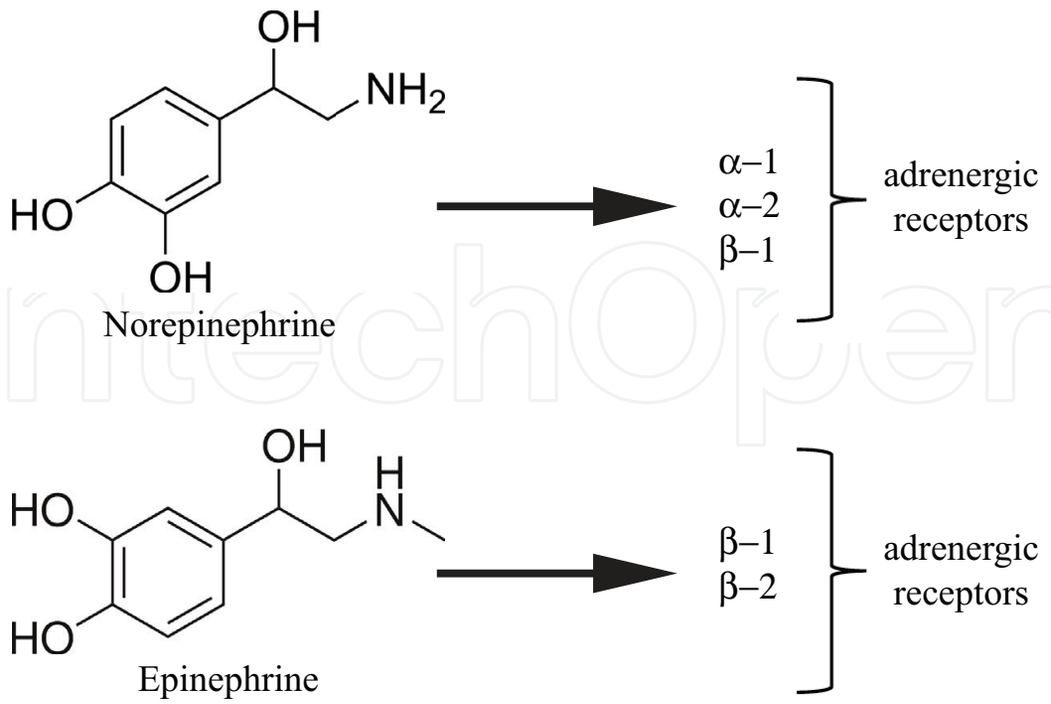

Figure 1. Illustration of catecholamine-receptor interaction.

4. Causes

Pheochromocytomas can cause sustained hypertension if there is continuous secretion of catecholamines, but can also cause paroxysmal hypertension with associated symptoms. If the paroxysm is severe, it may precipitate PMC, as reviewed in **Table 1**. PMC can occur spontaneously, if there is necrosis or haemorrhage of the tumour itself or if there is any source of external pressure on the tumour. Changes in body position, for example, even something as benign as rolling over in bed, may induce PMC [2]. Vigorous exercise, especially if it involves bending and lifting, may also precipitate PMC, as well as any kind of trauma.

PMC may also occur in the perioperative period, in the setting of adrenalectomy or any other operative indication. PMC can be triggered by certain anaesthetic agents upon induction of general anaesthesia, upon incubation, bladder catheterization, surgical skin incision, establishment of pneumoperitoneum and surgical manipulation of the tumour itself [9]. Anxiety and stress may also trigger an episode of PMC. Certain foods, such as aged cheeses, beer, wine, meats, fish, bananas and chocolate, especially those containing tyramine, have been reported to induce PMC [2].

Finally, many medications have been associated with PMC, including β-blockers, glucocorticoids, metoclopramide, various anaesthetic agents, tricyclic anti-depressants, MAO inhibitors, opiates, methyldopa, nicotine, cocaine and certain radio contrast media. The use of non-selective β-blockers causes unopposed activation of α-adrenergic receptors, thus exacerbating vasoconstriction and worsening hypertension. Glucocorticoid administration may cause PMC

Spontaneous	• Tumour necrosis
	• Tumour haemorrhage
	• Patient factors, e.g. anxiety, stress
Related to movement	• Changes in body position, e.g. rolling over in bed
	• Vigorous exercise
	• Trauma
Periprocedural/perioperative	• Induction of general anaesthesia
	• Incubation
	• Bladder catheterization
	• Surgical skin incision
	• Pneumoperitoneum
	• Surgical manipulation of the tumour
Medications	• β-blockers
	• Glucocorticoids
	• Metoclopramide
	• Anaesthetic agents: Intravenous, e.g. ketamine, atropine; inhalational, e.g. halothane, desflurane
	• Paralytics: succinylcholine, pancuronium
	• Antidepressants: Tricyclic agents, monoamine oxidase inhibitors
	• Methyldopa
	• Nicotine
	• Cocaine
Food	• Tyramine-containing: Aged cheeses, wine
	• Beer
	• Meats
	• Fish
	• Bananas
	• Chocolate
Special circumstance	• Pregnancy: Normal foetal movements, compression of the tumour during labour, increased intra-abdominal pressure during labour and delivery

Table 1. Causes of pheochromocytoma multisystem crisis.

by stimulating catecholamine release from the tumour itself and also by potentiating the effects of catecholamines at the level of the endothelial and smooth muscle cells in the peripheral vasculature [10]. Metoclopramide may cause PMC by stimulating catecholamine release by acting

on serotonin type 4 receptors [11]. Any anaesthetic agent that induces catecholamine surges or histamine may precipitate PMC and may include: ketamine, which has sympathomimetic effects; succinylcholine, which can cause catecholamine surges and stimulation of autonomic ganglia, as well as possibly causing mechanical stimulation via muscle fasciculations in close proximity to the tumour; pancuronium, atropine and inhalational anaesthetics such as halothane, which is arrhythmogenic and desflurane, which is a sympathomimetic drug [9].

Special considerations should be made for pheochromocytoma in the context of pregnancy, as there may be adverse effects to both mother and foetus. PMC can be triggered by increased intra-abdominal pressure during gestation and normal labour and delivery, normal foetal movements or tumour compression during labour. PMC almost inevitably occurs with vaginal delivery, and for this reason, pregnant patients with pheochromocytoma in the antepartum period should be delivered by Caesarean section. Depending on when the diagnosis of pheochromocytoma is made, the patient should undergo laparoscopic resection in the first or second trimester, or at time of Caesarean section after delivery. Unrecognized pheochromocytomas have been associated with very high incidences of morbidity and mortality, with reported values of 40% for maternal mortality and 56% for foetal mortality [2]. While maternal catecholamines do not cross the placenta, they can cause uteroplacental insufficiency and subsequent foetal demise [2].

5. Treatment options

Medical management of pheochromocytoma is necessary prior to surgical resection. For PMC, every attempt should be made to control labile blood pressure to reduce or stop the progression of symptoms and thereby stabilize the patient. Many different classes of anti-hypertensive agents can be used to treat hypertension in pheochromocytoma preoperatively before elective adrenalectomy. Intravenous agents such as phentolamine, a parenteral, short-acting α-adrenergic blocker; nitroprusside; nitroglycerin; nicardipine, a calcium-channel blocker; atenolol or esmolol, β-adrenergic blockers and magnesium sulphate have all been shown to effectively treat hypertensive crisis. Intravenous lidocaine is also used to treat cardiac arrhythmias seen in PMC.

The first-line agents are α-adrenergic blockers, the most common of which is phenoxybenzamine, which is a non-selective blocker with a long half-life. Phenoxybenzamine decreases blood pressure, but may also increase the risk of tachycardia and decrease the risk of cardiac arrhythmias; this mechanism of action is achieved by blocking α-adrenergic receptors and not by decreasing the synthesis of catecholamines. Selective α-blockers are also used, including doxazosin and prazosin, which are as effective at treating haemodynamic instability as the non-selective α-blockers. These agents are associated with less reflex tachycardia and less post-operative hypotension than non-selective α-blockers.

Calcium channel blockers (e.g. nifedipine, verapamil or diltiazem) are better tolerated by patients than α-blockers; however, they are less effective therefore not usually a first-line choice. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have also been

used to control hypertension in pheochromocytoma, but not as first-line agents and they usually used in combination with other classes of medications to more effectively control blood pressure. Only β-adrenergic blockers are typically administered after α-blockers have been started, and they are used specifically to treat persistent tachycardia. Non-selective β-blockers should not be used in the treatment of pheochromocytoma because of their effects on β-2-adrenergic receptors, which inhibit vasodilatation and worsen hypertension. Instead, selective β-blockers should be prescribed at low doses as they act solely on β-1-adrenergic receptors, thereby decreasing heart rate. Alpha-methyl-para-tyrosine can also be used to treat hypertension in pheochromocytoma, as it interrupts the first step in the biosynthesis of catecholamines by inhibiting the enzyme tyrosine hydroxylase. However, this drug has severe adverse effects that include psychiatric disturbances, extrapyramidal symptoms, sedation and urolithiasis, and its use, therefore, is generally reserved for patients with malignant or metastatic pheochromocytoma.

Surgical resection remains the definitive treatment for pheochromocytoma. Laparoscopic transperitoneal adrenalectomy is most commonly performed; however, other operations may be used, such as the lateral retroperitoneal, posterior retroperitoneal and transthoracic surgical approaches. Successful adrenalectomy requires close communication between the surgical team and the anaesthesiology team, especially at the time of adrenal vein dissection and division, as the patient may develop profound hypotension once the vein is ligated. Tumour and adrenal gland manipulation should be minimized until after the vein is clipped. Timing of surgical resection in the context of PMC is very controversial, and there is no clear consensus among clinicians as to whether emergency adrenalectomy is indicated and/or is considered safe for PMC. The following section will review the literature pertaining to the treatment options, decision-making and outcomes in PMC.

6. Initial management: when is it appropriate to operate?

The treatment of PMC has traditionally consisted of immediate medical stabilization followed by emergent or urgent adrenalectomy. There are three treatment options in the case of PMC, including: (1) **emergent adrenalectomy**, i.e. once the diagnosis of PMC is made, the patient proceeds directly to surgery; (2) **urgent adrenalectomy**, i.e. the patient's haemodynamic status is first treated medically with a short course of α-blockade prior to adrenalectomy, usually within 7–10 days of presentation and within the same hospital admission and (3) **elective adrenalectomy**, i.e. planned surgery following initial medical stabilization and discharge from hospital. The tendency for emergency adrenalectomy was based on anecdotal evidence from published case reports suggesting that medical management alone led to poorer outcomes. In 1980, one group recommended that only brief attempts should be made to stabilize the patient's haemodynamic and that 'procrastination' prior to operative intervention would lead to 'irreversible shock, renal failure and death' [12]. In their series, two patients who presented with 'acute pheochromocytoma' both died, one in the post-operative period and one in whom the diagnosis of pheochromocytoma had not been established. Another group published a case series that included three cases of PMC [13]. One patient's hypertensive crisis

was successfully controlled prior to operative intervention, however, upon development of a fever of 40°C, a septic workup was initiated and the patient became encephalopathic, leading to respiratory distress and had fatal cardiac arrhythmias while awaiting surgery. The second patient in their series presented with syncope and quickly developed multisystem organ failure despite adequate blood pressure control with multiple α- and β-blocking agents. Urgent adrenalectomy was eventually performed 4 days after hospital admission. The operation was successful, but the patient's post-operative course was prolonged and she was left with long-term sequelae of her encephalopathy, including quadriplegia and dysarthria. The third patient in the case series also presented with hypertensive crisis with rapid deterioration to multisystem organ failure, and underwent emergency adrenalectomy on the seventh day following admission for refractory multi-organ failure. Surgery was successful, and the patient's multisystem crisis resolved post-operatively.

More recently, several case reports have been published that also support urgent operative intervention in the setting of PMC. In 2008, a study described a case of PMC upon induction of general anaesthesia in the context of elective adrenalectomy for a known pheochromocytoma, despite preoperative α-blockade [14]. Surgical resection was aborted, and the patient was transferred to the authors' institution, where he remained in the intensive care unit for 6 days for aggressive medical stabilization followed by urgent adrenalectomy. The patient eventually recovered from his multisystem organ failure and discharged from the hospital 1 month later. In 2010, a reported case of PMC was described that initially presented with acute respiratory failure and encephalopathy, in which surgical resection was performed 11 days after admission because of the patient's progressive and uncontrollable medical deterioration [5]. Post-operatively, the patient's condition improved almost immediately, and the multisystem organ failure resolved except for chronic renal failure requiring long-term haemodialysis. In another case report of a patient who presented with acute heart failure with cardiogenic shock refractory to inotropic pharmacotherapy, insertion of an intra-aortic balloon pump was required, and extracorporeal membrane oxygenation (ECMO) was considered. The treating physicians, however, elected to proceed with emergent adrenalectomy. The patient's haemodynamic and respiratory status greatly improved shortly after surgery [15].

Several other authors have challenged the notion that the only viable option for the treatment of PMC is emergency adrenalectomy. Elective adrenalectomy following intensive medical stabilization has been shown in several case reports. In a 12-year-old child, with severe dilated cardiomyopathy, secondary to excess catecholamine secretion from a pheochromocytoma was treated with anti-hypertensives, specifically phenoxybenzamine and α-methyl-para-tyrosine, for 7 months prior to surgical resection [16]. Cardiac function improved moderately with medical management alone in the preoperative period and normalized completely post-operatively. Another report described two cases of PMC resulting in respiratory failure requiring incubation and ventilation, and acute kidney injury requiring continuous venovenous haemodialysis [4]. Adrenalectomy was performed at least 1 month after initial presentation, following medical stabilization and maintenance.

The case reports above describe the clinical presentation of PMC in detail, but there is very limited data regarding the perioperative management of PMC and whether it is preferable to

proceed with emergency surgery with preoperative α-blockade versus medical management alone in the immediate period of crisis, followed by hospital discharge and elective adrenalectomy. Current review of the literature only reports anecdotal evidence and consequently subject to publication bias. However, a recent retrospective chart review of PMC cases at their institution as well as a literature review of all cases of PMC that underwent adrenalectomy was performed [6]. The authors reviewed medical charts from March 1993 to October 2011 of all patients who underwent adrenalectomy for a diagnosis of pheochromocytoma or paraganglionoma confirmed by pathology. They defined pheochromocytoma crisis as severe hypertension or hypotension resulting in end-organ damage, and found that 25 of 137 patients presented with crisis. None of the patients in their series underwent emergency surgery without initial α-blockade. All but one patient was stabilized with phenoxybenzamine prior to adrenalectomy. Ten patients underwent urgent adrenalectomy during the same hospital admission, whereas the other 15 patients were discharged from hospital and returned for elective adrenalectomy. There were no mortalities in either group, but the major clinical significant difference was that there was an increased use of intra-aortic balloon pumps, higher incidence of preoperative ICU admissions for crisis, higher post-operative complication rate, increased post-operative ICU admissions and longer post-operative length of stay in the urgent surgery group.

In their literature review, the authors found 97 patients who underwent adrenalectomy for PMC. In this group, they identified three different management options: emergency surgery without prior α-blockade, urgent surgery with α-blockade and medical stabilization and elective surgery post-discharge after medical therapy to initially treat the crisis. The combined data for patients undergoing elective and urgent surgery were compared to the emergency surgery group. The most striking significant difference between these groups was the mortality rate, which was found to be 18% in emergency surgery patients compared to 0% in the elective/urgent surgery patients. There were other statistically significant differences, such as increased preoperative diagnosis of pheochromocytoma in the elective/urgent patients, higher incidence of tumour haemorrhage or rupture in the emergency surgery patients, higher incidence and longer duration of preoperative α-blockade in the elective/urgent surgery patients, higher rate of laparoscopy in the elective/urgent surgery patients and increased risks of both intra-operative and post-operative complications in the emergency surgery patients.

Currently, this is the only large-scale study available regarding the management of pheochromocytoma crisis. Based on their experience from their own institutions, it appears feasible and safe to attempt medical therapy and elective adrenalectomy if the patient can be discharged safely from hospital, as outcomes are better for patients undergoing elective compared to urgent surgical resection during the same admission. From the data available in the literature, it is quite clear that emergency adrenalectomy without adequate preoperative α-blockade is associated with high morbidity and mortality in the treatment of PMC. It is therefore recommended to offer urgent adrenalectomy in those patients who are able to partially recover under intensive medical management, while elective adrenalectomy can be reserved for patients who fully recover with medical management and who can safely be discharged from the hospital. Ideally, adrenalectomy should be planned within 4–6 weeks following discharge. This study is limited in that it is a retrospective review, but since PMC is such a rare

clinical entity, it would be very unlikely that a prospective, randomized study could ever be carried out [6]. Nevertheless, it seems clear that emergency adrenalectomy should be discouraged as an initial treatment of PMC and that medical therapy and eventual urgent or elective surgery should be the preferred management if the patient's condition allows it. A flow diagram for decision-making in patients with pheochromocytoma crisis is shown in **Figure 2**.

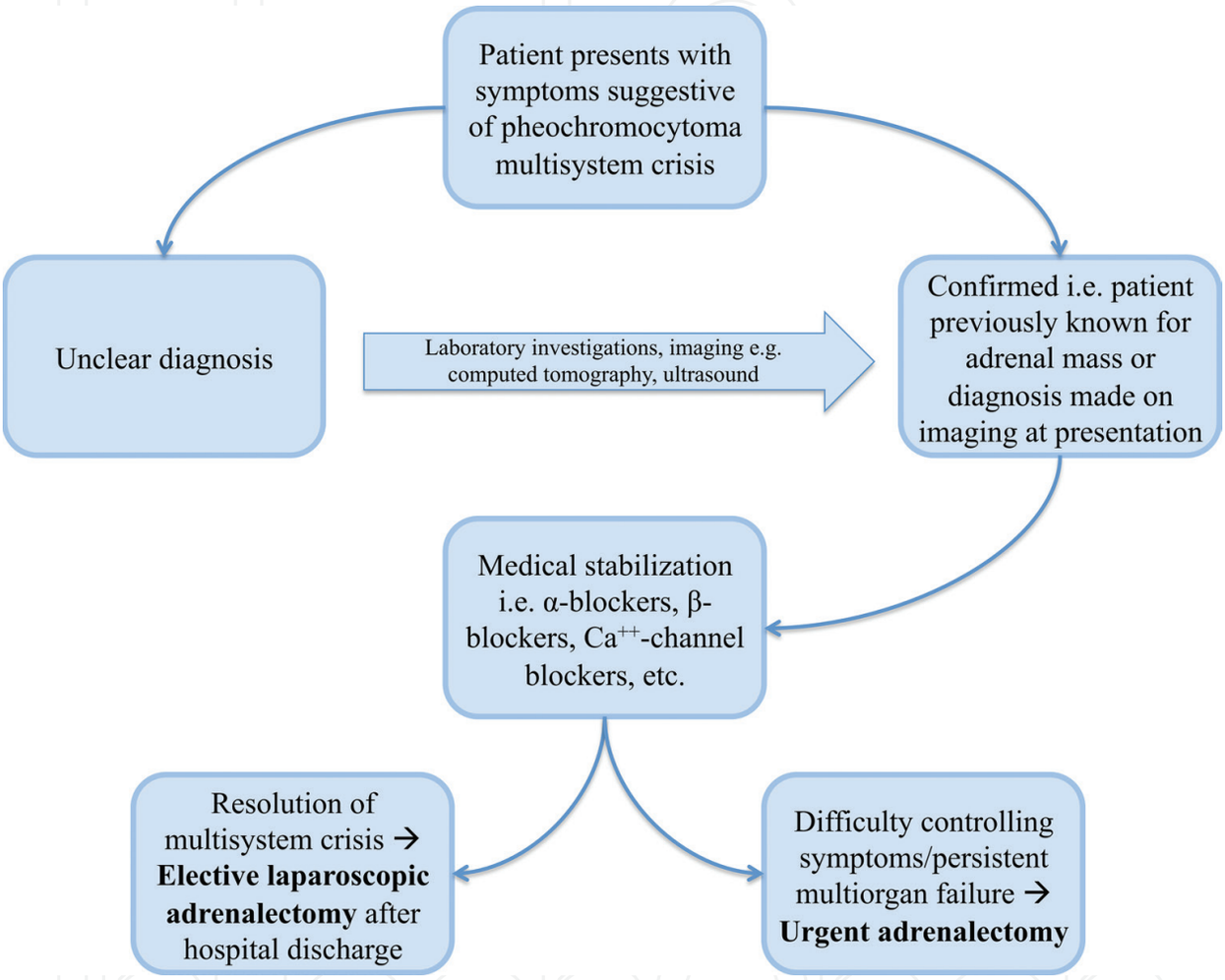

Figure 2. Decision-making flow chart for patients presenting with PMC.

7. Conclusion

There has been a paradigm shift in the surgical management of PMC, from performing emergency adrenalectomy immediately after the diagnosis to now favouring medical stabilization followed by elective adrenalectomy in more controlled and ideal situation, but allowing for urgent adrenalectomy in the same hospital admission if necessary. There are currently no guidelines available or Level 1 evidence to support this change in practice, and randomized studies would be impractical to perform due to the rare presentation of this clinical entity.

Further retrospective studies with larger sample sizes may be helpful in discerning the clinical outcomes of different management strategies and making a stronger recommendation for the preferred treatment of PMC.

Author details

Tanya Castelino and Elliot Mitmaker*

*Address all correspondence to: elliot.mitmaker@mcgill.ca

McGill University Health Centre, Montreal, Canada

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