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Phaeochromocytoma

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Introduction:

Background :
The World Health Organisation defines phaeochromocytomas as rare tumours arising from catecholamine producing cells in the adrenal medulla[1] .

Although chromaffin tissue is also present elsewhere in the body, such as in the mediastinum, along the aorta, and in the pelvis, the term phaeochromocytoma is reserved for tumours that arise from the adrenal medulla. Chromaffin cell tumours at other locations are called paragangliomas, although the term extra-adrenal phaeochromocytoma is still applied.

The tumour was first described in 1886 by Frankel[2]. In 1912, a pathologist named Pick derived the term phaeochromocytoma after the Greek words "phaios", meaning dark or dusky, and chroma, meaning colour to describe the chromaffin reaction seen in adrenomedullary tumours.

Catecholamine producing tumours

1. Phaeochromocytoma
2. Paraganglioma (extra-adrenal phaeo)
3. Ganglioneuroma – Tumour of sympathetic nerve fibres arising from neural crest cells. Composed of mature ganglion cells and are benign tumours.
4. Neuroblastoma – Malignant neuroendocrine tumour arising from any neural crest element of the sympathetic nervous system. It is the commonest extra-cranial solid malignancy in childhood.
5. Chemodectoma – Benign chromaffin negative tumour of the chemoreceptor system. Eg. carotid body tumour, aortic body tumour, glomus jugulare tumour. Glomus Jugulare tumours – rare, slow growing paraganglioma. Derived from neural tissue of the jugular foramen of the temporal bone. Occur at sites such as the carotid body, vagus nerve, middle ear.

Incidence

Phaeochromocytomas are rare tumours with an annual incidence of 1-4/10^6. 0.5% of patients with hypertension and 4% of patients with an adrenal mass harbor a phaeochromocytoma[3]. However we must appreciate that 18-60% of these tumours remain undiagnosed during life. Peak age for diagnoses of phaeo is between the 3rd to 5th decade of life, with an almost equal Male/Female ratio.

"Rule of 10's" – An Outdated Axiom

Health care providers frequently learn that phaeochromocytoma is the "tumour of tens". However, this is an outdated axiom. The current paradigm is in flux. The recent description of mutations of the succinate dehydrogenase gene (*SDH*) has demonstrated a much stronger hereditary component than formerly thought. Currently, up to 24% of phaeochromocytomas may have a genetic predisposition[2]. In addition, 13-26% are now thought to be malignant. Furthermore 98% of phaeo is found in the abdomen and pelvis[3].

Table 1. Most Common Hereditary Disorders Associated with Pheochromocytoma

Syndrome	Gene	Clinical Features
MEN2	RET	
Type A		Medullary thyroid carcinoma, primary hyperparathyroidism
Type B		Medullary thyroid carcinoma, ganglioneuromas, marfanoid habitus
VHL disease	VHL	
Type 2A		Hemangioblastoma, low risk of renal cell carcinoma
Type 2B		Hemangioblastoma, high risk of renal cell carcinoma
Type 2C		Pheochromocytoma only
NF1	NF1	Neurofibromas, café-au-lait spots, axillary or inguinal freckling, optic nerve glioma
PGL1/PGL4	SDHD/SDHB	Skull base tumors

Adapted from Elder EE, Elder G, Larsson C. Pheochromocytoma and functional paraganglioma syndrome: no longer the 10% tumor. J Surg Oncol 2005;89:193–201; *and* Kim WY, Kaelin WG. Role of VHL gene mutation in human cancer. J Clin Oncol 2004;22:4991–5004.

MEN2 = multiple endocrine neoplasia II; NF1 = neurofibromatosis type 1; PGL = paraganglioma; SDHB = succinate dehydrogenase subunit B; SDHD = succinate dehydrogenase subunit D; VHL = von Hippel-Lindau.

Mortality/Morbidity

Although rare, phaeochromocytomas can, if unrecognised, result in serious morbidity or in mortality.
The most severe complication is phaeochromocytoma crisis, which includes any manifestation of obtundation, shock, disseminated intravascular coagulopathy, seizures, rhabdomyolysis, acute renal failure, and death.
Other complications include the reactivation of Graves disease or transient thyrotoxicosis, as well as hypercalcemia as a result of tumour secretion of a parathyroid hormone – related protein, non-cardiogenic pulmonary oedema, acute abdomen, and renal infarction, among others. The high risk of provoking a hypertensive crisis during the manipulation of an adrenal gland is well known.

Familial Phaeochromocytoma [2]

Previously, it was generally accepted that 10% of phaeochromocytomas were associated with familial syndromes; however, it is now recognized that the frequency of germline mutations in apparently sporadic presentations is as high as 15%–24%. Familial phaeochromocytomas are often multifocal or bilateral and generally present at an earlier age than sporadic phaeochromocytoma . Germline mutations in six genes have been associated with familial phaeochromocytoma, namely, the von Hippel-Lindau gene (*VHL*), which causes von Hippel-Lindau (VHL) syndrome, the *RET* gene, leading to multiple endocrine neoplasia type 2 (MEN-2), the neurofibromatosis type 1 gene (*NF1*), associated with neurofibromatosis type 1 (NF1) disease, and the genes encoding subunits B and D (and also rarely C) of mitochondrial succinate dehydrogenase (*SDHB,SDHD*, and *SDHC*), which are associated with familial paraganglioma/phaeochromocytoma.

VHL Syndrome

VHL syndrome is characterised by the development of retinal and central nervous system (CNS) hemangioblastomas, renal cell carcinoma, phaeochromocytoma, pancreatic and renal cysts, endolymphatic sac tumours, and papillary cystadenoma of the epididymis or broad ligament. *VHL* germline mutations are inherited in an autosomal dominant manner. 7%–18% will develop phaeochromocytomas at a mean age of 30 years. From 3% to 11% of patients presenting with an apparently sporadic phaeochromocytoma will have a *VHL* germline mutation. VHL-associated phaeochromocytomas frequently occur as bilateral adrenal lesions but can also be extra-adrenal in location, and frequently secrete norepinephrine but generally do not produce epinephrine.

MEN-2

Activating germline mutations of the *RET* proto-oncogene result in MEN-2. Medullary thyroid carcinoma (MTC) is the most common presenting feature of MEN-2. Phaeochromocytoma occurs in approximately 50% of patients with MEN-2. Extra-adrenal disease is rarely seen with MEN-2. Adrenal phaeochromocytoma can present as either unilateral or bilateral disease. MEN-2–associated phaeochromocytomas generally secrete epinephrine, in contrast to VHL-associated tumours.

NF1

The diagnosis of NF1 is usually made on the following clinical criteria: greater than six café-au-lait spots, more than two neurofibromas, and axillary freckling. NF1 is associated with a greater incidence of a variety of neuroendocrine tumours, including phaeochromocytomas, but the occurrence of phaeochromocytoma is relatively uncommon, with an estimated lifetime incidence of 0.1%–5.5%.

Presentation

Increased catecholamine production by a phaeochromocytoma results in hypertension, which may be episodic as classically described, or sustained. Not uncommonly, patients are entirely normotensive between episodes. A **triad of headaches, palpitations, and sweating** is described in phaeochromocytoma and is seen in most patients. Patients with familial syndromes may be asymptomatic.

Patients who may be referred for imaging of the adrenal glands include those with new or worsening diabetes mellitus (owing to impaired glucose regulation) and those with hypertensive crisis after anaesthesia, surgery, or treatment with medications. Phaeochromocytoma is diagnosed when a combination of clinical signs and symptoms and elevated catecholamine levels are present.

Clinical symptoms and signs

The classic history of a patient with a phaeochromocytoma includes spells characterised by headaches, palpitations, and sweating in association with severe hypertension. These characteristics together are strongly suggestive of a phaeochromocytoma. In the absence of these 3 symptoms and hypertension, the diagnosis may be excluded. The spells may vary in occurrence from monthly to several times per day, and the duration may vary from seconds to hours. Typically, they worsen with time, occurring more frequently and becoming more severe as the tumour grows.

- Symptoms + signs include the following:
    - Hypertension (pressure)
    - Headache (pain)
    - Sweating (perspiration)
    - Palpitations
    - Pallor
    - Paroxysms
    - Nausea, vomiting
    - Abdominal pain
    - Constipation
    - Angina – coronary vasospasm
    - CCF
    - Cardiac dysrhythmias and conduction defects
    - Cardiomyopathy

Cardiomyopathy in phaeochromocytoma

Patients may present with both systolic and diastolic dysfunction. Hypertrophic cardiomyopathy may be as a result of norepinephrine induced hypertension[6] and results in diastolic dysfunction. Prolonged exposure to increase concentrations of circulating catecholamines may result in a form of dilated cardiomyopathy aka

catecholamine induced myopathy. This essentially presents as systolic dysfunction and is usually reversible. It is not clear whether this results from α or β- adrenoceptor activation[6].

Catecholamines and adrenoceptors [1]

The adrenoceptors are the final targets for catecholamines that are found in excess in most patients with pheochromocytoma. Both epinephrine and norepinephrine have overlapping but different effects on α- and β-adrenoceptors on various organs and systems. In particular, epinephrine has a more potent effect on β2-adrenoceptors than norepinephrine, whereas norepinephrine is a more potent β1 -adrenoceptor agonist than epinephrine. Epinephrine is also a more potent α -adrenoceptor agonist than norepinephrine. However, the proximity of sites of norepinephrine and epinephrine release to adrenoceptors and the resulting concentrations at effector sites are also important determinants of adrenoceptor-mediated responses to these two catecholamines. In patients with pheochromocytoma, both norepinephrine and epinephrine behave as hormones as they are released into circulation. As a circulating hormone, epinephrine (more than 95% derived from the adrenal medulla) acts potently on β2 adrenergic receptors of the skeletal muscle vasculature causing vasodilation that results in hypotension. In contrast, norepinephrine released locally from sympathetic nerve endings within the vasculature causes α1-adrenoceptor-mediated vasoconstriction resulting in hypertension. Both catecholamines, although norepinehrine to a higher degree, stimulate β1-adrenoceptors resulting in an increased heart rate. Furthermore, epinephrine is important as a metabolic hormone. In particular, epinephrine stimulates lipolysis, ketogenesis, thermogenesis, and glycolysis, and raises plasma glucose levels by stimulating glycogenolysis and gluconeogenesis. Epinephrine also has potent effects on pulmonary function, causing β2-adrenoceptor-mediated dilation of airways. Thus, patients with epinephrine-secreting pheochromocytomas more frequently show episodic symptoms and signs with palpitations, light-headedness or syncope, anxiety, and hyperglycemia than patients with tumors that secrete mainly norepinephrine, who more often have continuous symptoms and signs including hypertension, sweating, and headache. These catecholamine-specific effects on adrenoceptors explain the wide range of clinical presentations of patients with pheochromocytomas and serve as the basis for appropriate preoperative adrenergic blockade.

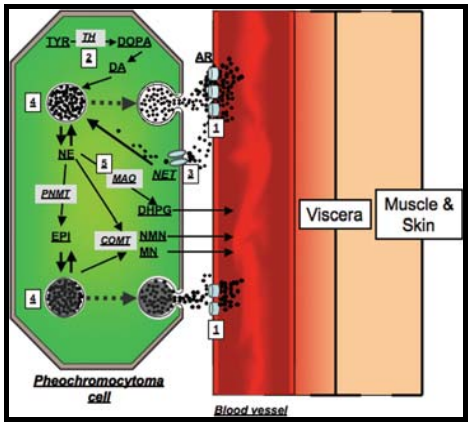

Figure 1 : Diagram illustrating the main pathways in catecholamine synthesis, release and metabolism in phaeochromocytoma.

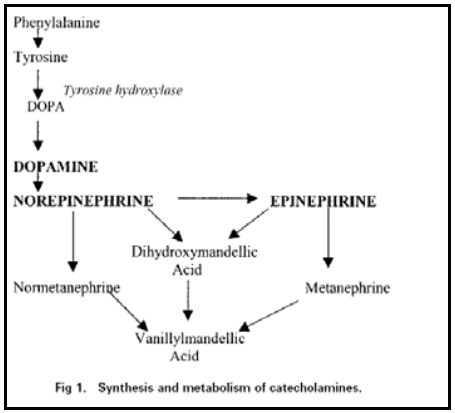

Fig 1. Synthesis and metabolism of catecholamines.

Biosynthesis of catecholamines [11]

The principal catecholamines (epinephrine, norepinephrine and dopamine) are formed by hydroxylation and decarboxylation of the amino acid tyrosine. Some of the tyrosine is formed from phenylalaline but most is of dietary origin. Phenylalaline hydroxylase is found primarily in the liver. Tyrosine is transported into catecholamine-secreting neurons and adrenal medullary cells. It is converted to dopa and then to dopamine in the cytoplasm of the cells by tyrosine hydroxylase and dopa decarboxylase respectively. Dopamine then enters the

granulated vesicles where it is converted to norepinephrine by dopamine-β-hydroxylase (DBH). The rate limiting step is the conversion of tyrosine to dopa (tyrosine hydroxylase catalyzes this reaction). The co-factor for TH is tetrahydrobiopterin. Some neurons and adrenal medullary cells contain the cytoplasmic enzyme PNMT (phenylethanolamine- N-methyltransferase), which catalyzes the conversion of norepinephrine to epinephrine. The catecholamines are transported into granulated vesicles.

Metabolism of catecholamines[11]

Epinephrine and norepinephrine are metabolized to biologically inactive products by oxidation and methylation. The former reaction is catalyzed by monoamine oxidase (MAO) and the latter by catechol-O-methyl-tranferase(COMT). Extracellular epinephrine and norepinephrine are mostly O-methylated and their derivatives are normetanephrine and metanephrine. These derivatives are largely oxidized to vanillylmandelic acid (VMA). In noradrenergic terminals some norepinephrine is converted to 3,4- dihydroxymandelic acid (DHMA). These are subsequently converted to VMA.

Biochemical evaluation [10, 4, 1]

All patients with suspected phaeo should undergo biochemical testing. These include patients with paroxysmal signs and symptoms suggestive of phaeo; patients with recent therapy resistant hypertension; patients with paradoxical blood pressure response during surgery and anaesthesia; patients with a hereditary predisposition for phaeo; patients with adrenal incidentalomas. Because of the low prevalence of phaeo, biochemical testing for the tumour in asymptomatic patients with hypertension is not indicated.

Biochemical presentation of excessive production of catecholamines is an essential step for the diagnosis of phaeo. Traditional biochemical tests include measurements of urinary and plasma catecholamines, urinary metanephrines, and urinary vanillylmandelic acid (VMA). Measurements of plasma free metanephrines is a more recently available test.

The potentially fatal consequences of a missed diagnoses justify the need for a high level of reliability of a positive test result in a patient with the tumour. The initial examination of a patient with suspected phaeo should therefore include a suitably sensitive biochemical test. Either blood or urine testing can be used with each having its own advantages and disadvantages. The evidence suggests that measurements of plasma free metanephrines or urinary catecholamines+metanephrines are the most sensitive tests for diagnoses, and more suitable for reliable exclusion of phaeo.

	SENSITIVITY	SPECIFICITY
$U_{catechols}$	86%	88%
$U_{total\ metanephrines}$	77%	93%
$U_{catechols+metanephrines}$	90%	98%
U_{VMA}	64%	95%
Plasma catecholamines	84%	81%
Plasma metanephrines	99%	89%

As with all biochemical tests of catecholamine excess, a remaining difficulty is that a positive result for plasma or urinary metanephrines does not always reliably indicate a phaeo. The many physiological stimuli, drugs and clinical conditions that cause increases in circulating catecholamines and metabolites compound this problem. Some causes of false positive results include tricyclic antidepressants, phenoxybenzamine, radiographic contrast, CCF and major depression.

The clonidine suppression test can be useful to distinguish false positive results from true positive results. The centrally acting alpha2 agonists is unable to suppress the secretion of epinephrine and norepinephrine in phaeo, and it has a reported diagnostic accuracy of 92%. However its routine use is not recommended because of its reliability and ease of use of other tests.

Imaging[2]

Imaging tests should be used for localization after a biochemical diagnosis is confirmed . With the exception of the smaller tumours seen in hereditary disease, CT and MRI are sensitive enough to localize most phaeochromocytomas . Ninety-five percent of extra-adrenal phaeochromocytomas are found in the abdomen and pelvis. Both CT and MRI have a sensitivity of 98%–100% for adrenal phaeochromocytomas, but MRI is more sensitive for extra-adrenal phaeochromocytomas . Unfortunately, these tests have a specificity of approximately 70% because of the high incidence of adrenal incidentalomas. If a solitary tumour is localized, confirmatory studies may be done but are not essential if there is no suggestion of familial disease. The most commonly used studies are either iodine-123–labelled metaiodobenzylguanadine (^{123}I-MIBG) or ^{131}I-MIBG scintigraphy, which use a norepinephrine precursor compound to localize the hypersecretory adrenergic tissue. When a phaeochromocytoma is confirmed both biochemically and by CT or MRI, scintigraphy has been shown to be unnecessary for benign sporadic or familial phaeochromocytoma . ^{123}I-MIBG is superior to ^{131}I-MIBG scintigraphy for the evaluation of metastases, but it is not widely available . Both have a specificity of approximately 95%, but the sensitivity ^{123}I-MIBG is higher (90% versus 77%). In contrast to benign tumours, MIBG does have a role in the staging and diagnosis of malignant disease, where it can be used to find metastases too small to be detected by CT or MRI.

In summary, the current recommendation is to first attempt to localize the tumour by CT or MRI. Routine preoperative imaging with MIBG in patients with well-

localized tumours is unnecessary, but may be beneficial in patients with bilateral lesions or a clinical suspicion of malignancy. If the tumour cannot be found and phaeochromocytoma is still strongly suspected, further imaging with MIBG is an appropriate option.

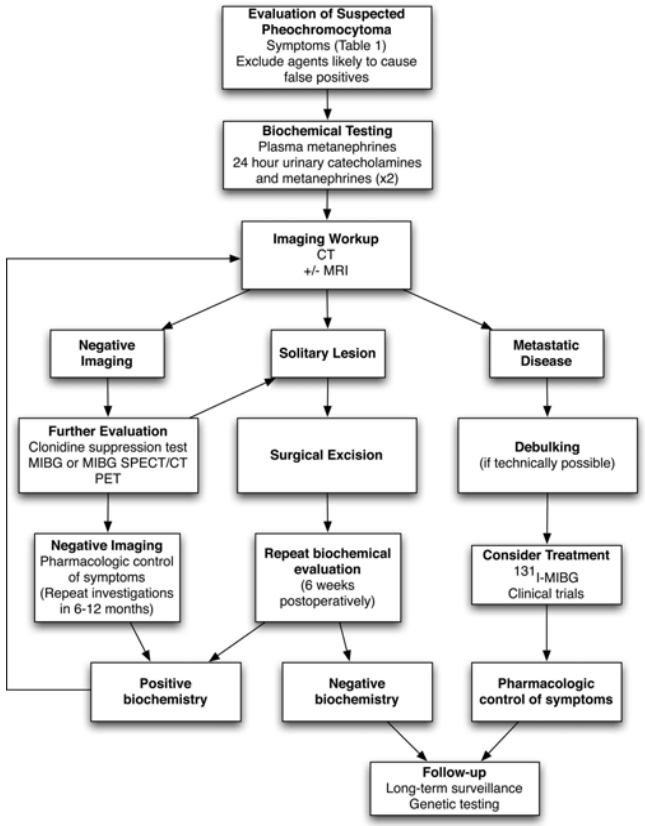

Figure 3 : Flow chart of the diagnosis and management of phaeochromocytoma

Management of phaeo

Prior to 1951, the reported mortality for the excision of phaeo was 24-50%. Currently, after adequate pre-op preparation and adequate α blockade, the operative mortality is < 3% if undertaken by an experienced anaesthetist and a skilful surgeon[4].

The management of anaesthesia and monitoring for surgery depends to some extent on the surgical approach. Adrenalectomy for phaeo has traditionally been performed by open lateral retroperitoneal surgery, although the transabdominal

approach may be necessary in some patients. With the advent of laparoscopy, laparoscopic transperitoneal excision of phaeo has become a feasible alternative. Open surgery is usually quicker, but the patient may require longer post-op hospitalisation. In the absence of complications, patients may be ready to leave hospital 36-48 hours following laparoscopic surgery.

Manipulation of the tumour during open surgery has inevitable haemodynamic consequences. Prys Roberts claims that in his experience, laparoscopic excision requires persistent tissue traction and diathermy which causes haemodynamic consequences over a longer duration than during open surgery[6].

However data from observational studies clearly show that laparoscopic adrenalectomy reduces post-op morbidity, hospital stay and medical expense compared to conventional surgery[4].

Pre-operative management[4]

Once a phaeo is located complications during surgery need to be kept to a minimum with appropriate pre-op medical treatment. With the advent of alpha blockade, periop mortality has fallen to less than 3%. The major aim of pre-treatment is to prevent catecholamine induced serious and potentially life threatening complications during surgery, including hypertensive crises, cardiac arrhythmias, pulmonary oedema and myocardial ischaemia. Even in life threatening conditions eg shock due to haemorrhagic necrosis or rupture due to phaeo, stabilisation with subsequent medical pre treatment and elective surgery is preferred. Emergency tumour resection without proper pre-op preparation results in poor survival.

To ensure adequate pre-op preparation several criteria have been proposed: blood pressure should be below 160/90 mmHg for at least 24hrs. Orthostatic hypotension should be present, but blood pressure in the upright position should not fall below 80/45 mm Hg ; there should be no more than one ventricular extrasystole every 5 min; and the electro-cardiogram should show no S-T segment changes and T-wave inversions for 1 week.

There are **no randomised controlled prospective studies** which are large enough to determine the most effective drug regimen before surgery. Traditional regimens include the blockade of alpha adrenoceptors with phenoxybenzamine, prazosin, doxazosin. Phenoxybenzamine is often preferred because it blocks alpha adrenoceptors non-competitively.

However several groups have advocated pre treatment with doxazosin based on a so-called increased risk of post op hypotension with the extended non-competitive alpha blockers. Several retrospective non-randomised clinical trials comparing phenoxybenzamine with prazosin or doxazosin have provided conflicting results.

Other alternative drugs for pre-op management are beta blockers and calcium channel blockers. **Blockade of beta adrenoceptors should never be initiated before blockade of alpha-adrenoceptors**, since the loss of beta adrenoceptor mediated vasodilation leaves alpha adrenoceptor stimulation unopposed, which could result in a hypertensive crisis. B-blockers may be used to control reflex tachycardia and prophylaxis against arrhythmias during surgery. Kinney et al claims that pre treatment with a beta blocker is not routinely necessary in the absence of arrhythmias[5]. Labetalol is a combined alpha and beta adrenoceptor blocker with stronger actions on beta adrenoceptors.

Prof James vs Prys Roberts:

Few would have believed that a topic such as phaeo would stir such debate and controversy as it has over the years. The well renowned difference of opinion between Prof James and Prys Roberts came to the fore in the BJA 86(4) 2001.

In a letter to the editior, Prof James remarked that the Prys Roberts article in BJA 2000 " Phaeochromocytoma – recent progress in its management" raised many 'contentious issues'.

Prof James defends the use of phenoxybenzamine stating that the non-competitive nature of the block, which Prys Roberts cited as being a disadvantage, is precisely the reason why many find the agent useful. In phaeo where there is an episodic release of vast quantities of catecholamines, the non-competitive blockade will remain effective regardless of the concentration of circulating catecholamines.

Prys-Roberts claimed that hypotension occurred in patients treated with phenoxybenzamine following tumour excision. James refutes this, adding that in his personal experience of over 40 phaeo managed with phenoxybenzamine, "hypotension is never a clinical problem provided that appropriate therapy with crystalloids, colloids, and blood is maintained".

Prof James questioned whether the hypertension and oedema referred to by Prys-Roberts is not a consequence of his personal preferences in anaesthetic management.

James opts not to use epidural anaesthesia stating that it may add to the problems of fluid balance management, and that it does not contribute to the control of catecholamine release since this is due to tumour handling and NOT adrenergic stimulation.

He advocates the use of magnesium sulphate for haemodynamic control in phaeo anaesthesia, highlighting that magnesium has a wide range of pharmacological effects. He re-iterates the mechanisms of action of magnesium sulphate as follows ; inhibition of release of catecholamines from the adrenal medulla ;

inhibition of release from pheripheral adrenergic nerve endings ; direct blockade of catecholamine receptors ; vasodilatation by direct effects on vessel walls ; antiarrhythmic actions; and myocardial protection[12].

Anaesthetic techniques – Prys-Roberts

In his BJA article of 2000, Prys Roberts highlighted the techniques that he adopts in the management of over 50 patients with phaeochromocytoma. Firstly he comments that one should employ a rational anaesthetic technique and it should be based on sound pharmacological principles. He advocates a combined regional + general anaesthetic. He does not favour the use of phenoxybenzamine. Instead he uses a selective competitive α1 blocker, doxazosine. Since doxazosine does not block the presynaptic α2- as adrenoceptors which regulate norepinephrine release, it is unnecessary to administer beta blockers until the patient has a epinephrine secreting tumour. Prys-Roberts conducted a sequential trial over a 12 year period comparing phenoxybenzamine versus doxazosine and claimed that the evidence favoured doxazosine[13]

Summary of intra-op anaesthetic considerations : Kinney et al[5]

- Administer an anxiolytic
- Place an intra-aterial catheter before induction
- Place a dedicated intravenous catheter for antihypertensive administration before induction
- Placement of central venous catheter
- Treat haemodynamic fluctuations with antihypertensives and β-blockers
- Monitor for hypotension and hypoglycaemia after tumour isolation

Post operative Management[4]

After surgery, patients need to be under close surveillance for the first 24 hours in an intensive care or high care unit. The two major post operative complications are hypotension and hypoglycaemia. Post operative hypotension is due to the abrupt fall in circulating catecholamines after tumour removal in the continuing presence of α-blockade (due to phenoxybenzamine). Treatment consists of fluid replacement and occasional iv ephedrine. The risk of hypoglycaemia is related to rebound hyperinsulinaemia due to the recovery of insulin release after tumour removal.

Phaeochromocytoma crisis and the role of magnesium sulphate

The clinical picture of phaeo crisis may be extremely variable , ranging from severe hypertension to circulatory failure and shock. This is due to massive catecholamine release. Acute myocardial infarction, cardiac arrhythmias pulmonary oedema, encephalopathy and multi organ failure have all been reported. Phaeo crisis is associated with significant mortality of upto 85%.

Cronje and James reviewed the use of $MgSO_4$ in the management of phaeo crisis[10]. They reviewed 3 cases of life threatening crisis in which $MgSO_4$ was particularly beneficial in controlling symptoms and signs when conventional forms of therapy had failed. 2 patients presented with hypertensive encephalopathy and the 3rd presented with catecholamine induced cardiomyopathy.

All 3 patients successfully underwent tumour excision with $MgSO_4$ used as the sole drug for the control of haemodynamic disturbances during surgery.

Conclusion

There has been much attention devoted to phaeo in recent times. Advances in molecular genetics will continue to improve our understanding of the tumour. Biochemical diagnostic tests have achieved a high sensitivity and specificity. In addition, newer imaging techniques will undoubtedly surface to assist further in localization of tumours.

However, in view of the inherent problems regarding the lack of evidence and even consensus amongst experts regarding the ideal drug regimens and pre-operative management of these patients, I pose the question: How can we improve patient outcome???

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