BACKGROUND

Adrenal phaeochromocytomas and extra-adrenal paragangliomas (PGL) have an incidence in unselected patients of 2-8 cases per million per year\(^2\).\(^3\).

The classical symptom triad consists of episodic palpitations, headaches and sweating. Pallor, nausea and panic attacks are other reasonably common symptoms although they may present very non-specifically.

3-8% of all adrenal incidentalomas are thought to be undiagnosed phaeochromocytomas\(^2,3\).\(^2\)

The prevalence of phaeochromocytoma in patients with hypertension is estimated to be 0.1-0.6%\(^4\).

PGLs may arise from extra-adrenal sympathetic (prevertebral, paravertebral, thoracoabdominal, pelvis, reproductive organs, prostate, bladder, liver and organ of Zuckerkandl) or parasympathetic tissue (in the vicinity of major arteries and nerves e.g. carotid body, jugular, vagal, tympanic, pulmonary and aortic PGLs)\(^5\).

Phaeochromocytomas and sympathetic PGLs are typically secretory whereas parasympathetic PGLs are predominantly endocrinologically inactive\(^5\).

Part 1
REFERRAL TO ENDOCRINE TEAM

Medical staff that identify a possible phaeochromocytoma should refer the patient to the Endocrine Team for further investigation.

Referral details should include

- Hospital Registration Number
- Surname
- Forename
- Date of Birth
- Date of diagnostic imaging
- Imaging report number

Part 2
ENDOCRINE TEAM ONLY (overleaf)
Part 2
ENDOCRINE TEAM ONLY

1. INVESTIGATION

A careful endocrine and family history is paramount when assessing these patients.

**Biochemical Diagnosis:**
No single biochemical analysis can provide 100% accuracy. How far you pursue the potential diagnosis is influenced by your clinical suspicion and the pre-test probability of a positive result.

Urinary catecholamines (BRI) or urinary metanephrines (NBT) are the local screening tests for investigating new patients with a possible diagnosis of sporadic phaeochromocytoma / paraganglioma. Two 24hour collections (not on consecutive days) is a reasonable first line approach where exclusion of a phaeochromocytoma is the aim.

Plasma free metanephrines are the only appropriate screening test for individuals with an hereditary phaeochromocytoma risk. Plasma free metanephrines have a sensitivity of 97% in hereditary disease and 99% in sporadic disease. They show a specificity of 96% in hereditary and 82% in sporadic disease\(^6\). Plasma free metanephrines may be appropriate in the investigation of sporadic phaeochromocytomas where there is high clinical suspicion or borderline results have been obtained with urine catecholamines but these cases should be discussed with an endocrine consultant.

Plasma free metanephrines on the BRI site must be requested via the Pathology Day Unit led by Dr Wolf Woltersdorf to ensure that the patient is appropriately rested and sampled.

Interference is less with plasma testing than urine testing but the following should be excluded as much as possible prior to sampling:\(^7\):
- Paracetamol
- Alpha blockers
- Beta blockers
- Tricyclic antidepressants
- SSRIs
- ACE inhibitors
- Calcium channel blockers
- Diuretics
- Caffeine
- Dexamethasone
- Alcohol
- Monoamine oxidase inhibitors
- Nicotine
- Salicylates
- Methyl dopa
- Lithium
- Theophylline
- Tetracyclines
- Vasodilators
- Nuts
- Fruits
- Potatoes
- Beans
**Radiological Imaging:**
Due to the frequency of adrenal incidentalomas in the normal population, imaging should not be requested until a biochemical diagnosis is confirmed.

Appropriate baseline cross-sectional imaging should be obtained. This is typically with a CT adrenal scan.

A baseline MIBG scan should be considered pre-operatively to assess/confirm avidity of the primary lesion and to exclude extra-adrenal disease.

**Other baseline Investigations:**
Ensure an ECG and Echocardiogram are requested and reviewed.

**2. MANAGEMENT OF A CONFIRMED DIAGNOSIS**

All patients should be discussed at the Bristol neuroendocrine (NET) MDT once a diagnosis is made and prior to any surgery. Please refer to the NET MDT co-ordinator and Dr Karin Bradley on the appropriate referral proforma. The medical pre-operative management is the responsibility of the relevant ‘home’ endocrine team – UHB, NBT or regional. The targets are below.

**From clinic:**
Start phenoxybenzamine (PBZ) 10mg bd.

Arrange for the patient (via a home blood pressure monitor) or the practice nurse to do twice weekly postural BP (blood pressure) and heart rate readings. Advise on how to meaningfully measure postural BPs. The patient should lie flat and rest for 5 minutes prior to the lying BP and heart rate readings, then the patient should stand and the BP and heart rate should be rechecked after 1-2 minutes). Seated BPs instead of lying BPs are an alternative option.

As an out-patient, gradually increase the PBZ to control BP and any symptoms. A typical final dosage is around 10-30mg twice or three times daily but some patients may need higher doses.

PBZ is used as the agent of choice as it is an irreversible alpha blocking agent. The patient should be warned of the potential side effects of PBZ e.g. nasal stuffiness, ejaculatory failure etc. and the patient should be promptly discussed with their endocrine consultant if they are intolerant of PBZ. An alternative is Doxazosin starting at a dose of 4mg twice daily, increasing to 8mg am and 4mg pm and then 8mg twice daily. A typical maximum dosage if needed would be 16mg twice daily.

Beta blockade is not routinely required initially unless significant tachycardia or palpitations are noted.

In the weeks prior to planned surgery the PBZ should be titrated to achieve nasal stuffiness (if using PBZ) and a systolic BP resting <120/80 and also a postural drop but ideally not below 80/45. Please advise that postural hypotension is what we are trying to achieve and that they need to get up slowly, not operate dangerous machinery and take care driving (best avoided if possible) etc.

Please note that patients must be on alpha blockade for three weeks at least pre-operatively (to allow sufficient time for circulating volume expansion), and are in addition encouraged to drink sufficient fluids prior to the pre-op preparation period.
A full blood count should be checked with increasing alpha blockade due to potential haemodilution. Consider propranolol if indicated to achieve a resting heart rate of 60-70 bpm sitting.

**Pre-op preparation period:**
The patient will be admitted under the North Bristol endocrine team at Southmead on the day prior to surgery provided that out-patient blockade has met appropriate targets.

Once adequately alpha blocked the main risk is post-operative hypotension so adequate volume expansion is essential. The last dose of PBZ should be given no later than 24 hrs pre-operatively and the last dose of beta blocker on the morning of surgery. Consider normal saline intravenously in the 24 hours prior to surgery if there are any concerns regarding complete volume expansion.

**Post-operatively:**
From theatre the patient returns to HDU and then a surgical bed but on-going shared care with NBT endocrinology is essential. Alpha and beta blockade is not continued. The patient should be carefully monitored for hypotension and hypoglycaemia. Other antihypertensives or agents for diabetes mellitus may need reviewing post-operatively.

**All patients should be listed for discussion at the first available Bristol NET MDT once histology is available.**

A routine appointment for around 3 months post-surgery should be made for the relevant endocrine clinic unless there are particular concerns to prioritise the patient for early review. Repeat urinary catecholamines/metanephrines or plasma metanephrines should be organised for 1-2 months post-operatively (on full recovery) so that the results are available for their clinic appointment.

**Genetic Testing:**
Up to 25% of apparently sporadic lesions will have a germline mutation in one of the phaeochromocytoma susceptibility genes\(^5,8\).
The most common culprits are the SDHB/D and VHL genes. Extra-adrenal lesions (46%) and malignant lesions (60%) have the highest chance of yielding a gene mutation.

Current susceptibility genes:
- VHL
- SDHB
- SDHD
- SDHC
- SDHAF2
- RET
- TMEM127
- MAX
- NF1

The patients should be referred to the Bristol clinical genetics service for appropriate counselling, family case detection and genetic testing. Clinical genetics currently utilise the service in Leeds which offers combined screening for the above genes (not NF1 as the clinical phenotype should be obvious) with the exception of MAX for a total cost of £530. This approach is more cost effective than sequential targeted gene screening. Exeter offer combined screening for all susceptibility genes, including MAX, for £600. Full details
In sporadic phaeochromocytomas current evidence would suggest that mutational analysis should be offered to patients with one or more of the following:
- Multiple tumours
- Previous or current head and neck PGL
- Extra-adrenal location of tumour
- Confirmed malignant phaeochromocytoma/PGL
- Age <46 years (cost-effective cut-off – predicted to miss <5%)

Malignant Phaeochromocytomas/PGLs:
There are no curative options in the management of malignant phaeochromocytoma/PGL – all options are palliative.

Metastatic potential varies with the location of the primary tumour and the underlying genetic risk.

Common sites for metastatic disease:
- Lymph nodes 70%
- Bones 68%
- Liver 46%
- Lung 39%

Median survival after a diagnosis of metastatic disease is 42 months if SDHB mutation positive or 244 months if no SDHB mutation.

No intervention may be the best option in stable disease.

Patients should be monitored with biochemistry, BP and imaging.

- MIBG offers a 50% sensitivity for detection of metastatic disease.
- Somatostatin based scintigraphy is of limited use in phaeochromocytomas – it is occasional helpful in assessing metastatic disease. Sensitivity is around 50% for metastatic disease.
- Consider MIBG or SST based imaging if considering these as therapeutic options.
- FDG-PET is better than MIBG for locating metastatic lesions and is especially good in patients with SDH mutations.
- Consider MRI spine if potential compressive lesions.
- Bone scintigraphy can be useful.

Debulking surgery may be helpful if loco-regional recurrence or isolated distant metastases.

131-MIBG can offer a 30-67% complete or partial response rate but randomised controlled trial data is lacking. This is probably sensible first line therapy on the balance of toxicity/benefit if the lesions are MIBG avid and the therapy is available. With time MIBG non-avid lesions do tend to emerge.

Similarly radiolabelled octreotide may be an option.

Chemotherapy can offer up to a 50% complete or partial response rate. This is probably second line therapy.

The MIBG/chemotherapy cycle can be revisited with further progressive disease.

Sunitinib is not freely prescribable but has shown encouraging early data in a small number of
patients and may be considered via the Neuroendocrine MDT for patients who have failed to respond to other therapies.

REFERENCES


QUERIES

**UHB**
Endocrine Specialist Registrar (referrals) 
bleep 6216
Endocrine Consultants 
via switchboard
Dr K Bradley
Dr B Ahmad
Dr N Thorogood
Prof S Lightman
Prof A Levy
Prof D Wynick

**NBT**
Dr Andrew Johnson 
via switchboard
Dr Fong Chau
Dr Vernon Parfitt
Dr Kathryn Lonnen
Dr Liz Cheyne