Clinical Guideline

PHAEOCHROMOCYTOMA – DIAGNOSIS AND MANAGEMENT

SETTING	Trust-wide and Pan Bristol (UH Bristol and North Bristol Trust)
FOR STAFF	Specialist medical staff within Endocrine Team/Neuroendocrine Multidisciplinary Team (MDT)
PATIENTS	Patients with a suspected Phaeochromocytoma/Paraganglioma

BACKGROUND

Adrenal phaeochromocytomas and extra-adrenal paragangliomas (PGL) have an incidence in unselected patients of 2-8 cases per million per year[1]. The incidence of phaeochromocytoma is rising and increasingly smaller and less symptomatic lesions are being detected, likely secondary to increased diagnostic imaging in healthcare overall[2].

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[3,4].

The prevalence of phaeochromocytoma in patients with hypertension is estimated to be 0.1 – 0.6%[5].

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 or aortic PGLs[6].

Phaeochromocytomas and sympathetic PGLs are typically secretory whereas parasympathetic PGLs are predominantly endocrinologically inactive[6].

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

ENDOCRINE TEAM ONLY

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 metanephrines are the local screening tests for investigating new patients with a possible diagnosis of sporadic phaeochromocytoma/paraganglioma. Two 24 hour collections

(not on consecutive days) is a reasonable first line approach where exclusion of a catecholamine secreting tumour is the aim.

Plasma free metanephrines are the agreed 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[7].

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 sampling but these cases should be discussed with an endocrine consultant.

Plasma free metanephrines on the BRI site should be requested via the endocrine clinical nurse specialists to ensure that the patient is appropriately sampled.

Interference is less with plasma testing than urine testing but the following should be excluded as much as possible prior to sampling[8]:

- 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 then 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 that both an ECG and Echocardiogram are requested and reviewed.

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 on the appropriate referral proforma.

The medical pre-operative management is the responsibility of the relevant ‘home’ endocrine team – UH Bristol, NBT or regional but will be reviewed by the team in the Joint Endocrine

Adrenal clinic at Southmead. The pre-op assessment clinic (POAC) will be coordinated for the same day at Southmead. The targets are below but may be individualised according to age and co-morbidities.

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 blood pressure (BP) and heart rate readings. Advise on how to meaningfully measure postural BPs. The patient should sit and rest for five minutes prior to the BP and heart rate readings, then the patient should stand and the BP and heart rate should be rechecked after one to two minutes). Ask the patient to keep a record of these BP and heart rate readings and to bring them to all clinical consultations.

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. Consider propranolol/alternative beta blocker if indicated to achieve a resting heart rate of 60 – 70bpm sitting.

In the weeks prior to planned surgery the PBZ should be titrated to achieve nasal stuffiness (if using PBZ) and a systolic seated BP <130/80 and also a postural drop but ideally not below a standing systolic BP of 90 mmHg[9]. Target heart rates are 60 – 70 bpm seated and 70 – 80 bpm standing[8]. These targets should be modified in each patient according to age and co-morbidities[9,10]. Please advise that postural hypotension is the intention and that patients 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 at least three weeks pre-operatively (to allow sufficient time for circulating volume expansion), and are in addition encouraged to drink sufficient fluids and eat a high sodium diet to reduce the risk of post-operative hypotension[9].

A full blood count should be checked with increasing alpha blockade due to potential haemodilution.

Pre-op preparation period

The patient will be admitted under the joint care of the North Bristol endocrine and urology teams at Southmead 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 24hrs pre-operatively and the last dose of beta blocker on the morning of surgery. Consider normal saline intravenously in the 24-48 hours prior to surgery if there are any concerns regarding complete volume expansion.

Post-operatively

From theatre the patient returns to ITU and then a urology bed at NBT.

Alpha and beta blockade is typically not continued but will be managed on a case by case basis. 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 home endocrine clinic unless there are particular concerns to prioritise the patient for early review.

Repeat urinary 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 20% of apparently sporadic lesions will have a germline mutation in one of the phaeochromocytoma susceptibility genes[6,11,12,13].

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 known susceptibility genes:

- VHL
- SDHB
- SDHD
- SDHC
- SDHAF2
- RET
- TMEM12
- MAX
- NF1

The patients should be referred to the Bristol (or regional) 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 can be found on their website: www.rdehospital.nhs.uk/prof/molecular_genetics.

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%)[13].

Malignant Phaeochromocytomas/PGLs

Metastatic potential varies with the location of the primary tumour and the underlying genetic risk[14].

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[14].

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[15,16].
- (68)Ga-DOTATATE PET/CT is potentially a highly sensitive alternative[16]
- Consider MRI spine if potential compressive lesions.
- Bone scintigraphy can be useful.

The only curative option is surgery. This is the standard approach for loco-regional recurrence or isolated distant metastases[16].

For surgically unresectable disease all options are palliative with the intention of stabilising tumour growth for as long as possible. No intervention may be the best option in stable disease.

Debulking surgery may be helpful in controlling the clinical syndrome if catecholamine excess.

131-MIBG can offer a 30 – 67% complete or partial response rate but randomised controlled trial data are lacking[16,17,18]. 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[19].

FOLLOW-UP/SURVEILLANCE

For patients with surgically cured presumed sporadic disease follow-up should be life-long in the endocrine clinic. No imaging is routinely recommended but post-operative and then annual biochemistry (urinary metanephrines) plus clinical assessment is indicated. Life-long follow-up also facilitates ongoing genetic reassessment as appropriate as more susceptibility genes may be identified.

For patients whose tumour was non-secretory at baseline one can consider intermittent imaging with CT, MRI or MIBG to try and monitor for recurrence or metastases but evidence is limited and radiation risks must be considered. An individualised approach should be agreed with the patient.

SCREENING FOR DISEASE FREE PATIENTS CARRYING A MUTATION IN A KNOWN PHAEOCHROMOCYTOMA/PG SUSCEPTIBILITY GENE

The data remain few but the current approach is recommended for adults:

RET: See multiple endocrine neoplasia guideline

VHL: Annual plasma metanephrine screening[20]

NF1: Plasma metanephrine screening every one to two years[21]

SD genes: Plasma metanephrine screening every 18 months plus abdominal MRI imaging every 18 months and MRI of neck, thorax and pelvis every threee years[22].

This current approach is standardised across all the SD genes but individualised care should be discussed with patients. Less frequent imaging likely acceptable for SDHD mutation carriers (lower malignancy risk) whereas SDHB mutation carriers have highest malignancy risk (but low disease penetrance)[22,23].

Other genes: Insufficient data – individualised clinical decision making with patient.

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RELATED DOCUMENTS	Management of patients with multiple endocrine neoplasia http://nww.avon.nhs.uk/dms/Default.aspx?sid=0&s2id=403
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