Familial paraganglioma syndromes

Key facts

- Phaeochromocytomas and paragangliomas are uncommon tumours that affect between one and eight people per million each year.
- Phaeochromocytomas arise from the medulla of the adrenal gland.
- Paragangliomas are found outside of the adrenal gland, and can arise anywhere, from the head and neck, thorax, abdomen to the bladder.
- Both phaeochromocytomas and paragangliomas can secrete catecholamines (adrenaline and noradrenaline), or can be non-secretory.
- Approximately one in three patients presenting with phaeochromocytomas and/or paragangliomas have a gene mutation associated with familial paraganglioma syndromes.

Clinical features

- Catecholamine-secreting phaeochromocytomas and paragangliomas may present with episodes of headache, sweating and hypertension.
- Phaeochromocytomas are said to occur in 0.1% of patients presenting with hypertension.
- Other phaeochromocytomas and paragangliomas are discovered because of mass effects (for example, deafness, tinnitus, neck lumps in cases of head and neck paraganglia; abdominal distension in cases of abdominal paraganglia).
- Increasingly, these tumours are being discovered as incidental findings on scanning; 10% of incidentally-found adrenal masses are phaeochromocytomas.
- 25% of paragangliomas are malignant, and can present with metastases in bone, liver, lymph nodes and lungs. Malignant phaeochromocytomas are less common.

Diagnosis

- If phaeochromocytoma or paraganglioma is suspected, patients should be referred to endocrine departments or specialist neuroendocrine tumour (NET) units where available.
- Biochemical diagnostic tests rely on detection of metanephrines, which are the stable metabolites of catecholamines. These tests have higher sensitivity and specificity than those testing for catecholamines.
    - » Plasma metanephrine levels: sensitivity 90-95%; specificity 80-90%.
    - » 24-hour urine metanephrines: sensitivity 90%; specificity 75%.
- Once a biochemical diagnosis of phaeochromocytoma or paraganglioma is established, imaging studies can be used to locate and stage the tumours, including:
    - » CT or MRI of the neck, thorax, abdomen (including adrenals).
    - » Nuclear medicine imaging, for example, with 123-I metaiodobenzylguanidine SPECT, 18-F FDG PET or 68-Ga DOTATATE PET.

Genetic basis and genetic testing

- Features that suggest a familial paraganglioma syndrome include: young age of presentation (<50 years), bilateral tumours, a family history of phaeochromocytomas or paragangliomas and presence of metastatic disease. However, even an apparently sporadic presentation may be associated with a familial paraganglioma syndrome.
- Familial paraganglioma syndromes are usually inherited in an autosomal dominant manner. Once the genetic basis of the condition has been established by genetic testing, predictive testing can be offered to the wider family.
- Variants in the following genes are associated with familial paraganglioma syndromes:
    - *SDHB* (succinate dehydrogenase subunit B): more frequently associated with malignancy. May present with paragangliomas and phaeochromocytomas, as well as renal cell carcinomas. Uncommon association with pituitary adenomas reported. Variable age-related penetrance.
    - *SDHD* (succinate dehydrogenase subunit D): associated frequently with head and neck paragangliomas. Uncommon association with pituitary adenomas reported. Tumours less frequently associated with malignancy. Exhibits maternal imprinting (in other words, if a patient inherits a causative variant in *SDHD* from their father, they are more likely to develop tumours than if they inherit the causative variant from their mother).
    - *VHL* (von Hippel-Lindau syndrome): associated with other features of VHL such as renal cysts, renal cell carcinoma, pancreatic cysts and neuroendocrine tumours.
    - *NF1* (neurofibromatosis type 1): associated with other features of the syndrome, including neurofibromas and café-au-lait spots.
    - *MEN2/RET* (multiple endocrine neoplasia type 2): associated with other features of the syndrome, including medullary thyroid carcinoma and hyperparathyroidism.
    - *SDHA* (succinate dehydrogenase subunit A), *SDHC* (succinate dehydrogenase subunit C), *SDHAF2* (SDH assembly factor 2), *FH* (fumarate hydratase), *TMEM127* and *MAX*: rarer causes of familial paraganglioma syndrome.
- Referral for genetic testing, counselling and cascade testing of family members is available via NHS regional genetics centres.

Clinical management

Management of patients with phaeochromocytomas and paragangliomas is best done by a neuroendocrine tumour (NET) multidisciplinary team, which should include endocrinologists, adrenal surgeons, head and neck surgeons and nuclear medicine, medical and clinical oncologists.

Treatment options include:

- surgery to remove tumours;
- chemotherapy for metastatic disease;
- specialist radionuclide therapies for metastatic disease; and
- management of hypertension using adrenoceptor blocking agents.

- If the patient has extreme hypertension (systolic BP >180), chest pain, dyspnoea or haemoptysis, they must be urgently referred to secondary care for management.
- Patients with phaeochromocytoma or paraganglioma who are about to undergo surgery must be referred to the multidisciplinary team for peri-operative management.

- Where carriers of variants in the genes listed above are identified, the individual should be referred to a specialist endocrinologist or specialist NET multidisciplinary team for screening.

Direction to further reading, guidelines and patient groups

- Lenders et al 2014: Pheochromocytoma and Paraganglioma: An Endocrine Society Clinical Practice Guideline
- Society for Endocrinology: You and Your Hormones (https://www.yourhormones.info/endocrine-conditions/phaeochromocytoma/ and https://www.yourhormones.info/endocrine-conditions/paraganglioma/)

This information is intended for educational use and was current in November 2019. For clinical management, it is recommended that local guidelines and protocols are used.

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