DISORDERS OF THE ADRENAL MEDULLA AND DIFFUSE NEURO

DISORDERS OF THE ADRENAL MEDULLA AND DIFFUSE NEUROENDOCRINE SYSTEM
Phaeochromocytoma and paraganglioma

Definition Tumours that arise from the neuroectodermal tissue of the adrenal medulla are termed phaeochromocytomas (PCCs) and those arising from the extra-adrenal parasympathetic and sympathetic ganglia are termed paragangliomas (PGLs). PCCs and PGLs are collectively abbreviated to PPGL. - PGLs are either parasympathetic or sympathetic. Para - sympathetic PGLs are sited mainly in the head and neck (HNPGLs) and 95% do not secrete catecholamines or other hormones. The common types of HNPGL are carotid body , vagal and jugulotympanic. Sympathetic PGLs usually secrete catecholamines. Incidence The incidence of PCC is about 0.6 in 100 /uni00A0 000 and 75% are thought to be sporadic. The incidence of sporadic PGL is not known, but is less common than PCC, and the association with hereditary conditions is more common. Overall, about 70% of PPGLs are sporadic and the rest occur as part of inherited endocrine tumour syndromes, which include: /uni25CF hereditary PPGL syndromes /uni25CF MEN /uni00A0 2 /uni25CF von Hippel–Lindau disease (VHL) /uni25CF neurofibromatosis type 1 (NF1) Hereditary PPGL syndromes These are associated with germline mutations in genes, including succinate dehydrogenase (SDH) subunits, Myc- associated protein X (MAX) and transmembrane protein 127 (TMEM127) (Table 57.2). Loss-of-function mutations in SDH lead to accumulation of Krebs cycle precursors, which act as oncometabolites. Loss-of-function TMEM127 and MAX mutations result in PPGL development through cell death escape and enhanced survival. SDHB gene variants account for the majority of secreting PGLs whereas SDHD mutations account for the majority of non-secreting HNPGLs. A ff ected individuals are regularly surveilled with annual blood tests and 3-yearly MRI (neck and or abdomen). Eugen von Hippel , 1867–1939, Professor of Ophthalmology , Göttingen, Germany . Arvid Lindau , 1892–1958, Professor of Pathology , Lund, Sweden. Sir Hans Adolf Krebs , 1900–1981, German-born British biologist, physician and biochemist, his discovery of the citric acid (Krebs) cycle earned him the Nobel Prize in Physiology or Medicine in 1953. Karl Lisch , 1907–1999, Ophthalmologist, Wörgl, Austria. von Hippel–Lindau disease An autosomal dominant disease characterised by central nervous system and retinal haemangiomas (60–80%), renal cysts (50–70%), clear cell renal cell carcinoma (30%), pancre - atic neuroendocrine tumours (P-NETs) (8–17%), PPGL (20%), endolymphatic sac tumours (6–15%) and epididymal/broad ligament cyst adenoma (50%). VHL is defined by its genotype as type I (deletions) without PPGL and type II (missense muta - tions), which is associated with PPGL. P atients develop PCC much more frequently than PGL. VHL tumours overproduce only noradrenaline. Neurofibromatosis type 1 This

is a syndrome characterised by the development of café- au-lait spots (100%), axillary freckling (90%), neurofibromas (84%), Lisch nodules of the iris (70%), typical osseous lesions (14%) and optic glioma (4%). PPGL (PCC 96%) are found in 7% of a ff ected patients. NF-1 is a tumour-suppressor gene and loss-of-function mutations lead to cell proliferation and cancer development. Pathology PCCs are greyish-pink on the cut surface and are usually highly vascularised. Areas of haemorrhage or necrosis are often observed. Microscopically , tumour cells are polygonal but the configuration varies considerably . Approximately 10% of

Figure 57.9 (a) Massive left retroperitoneal haematoma (edges outlined by wide white arrows) secondary to left adrenal haemorrhage (contrast extravasation marked by thin white arrow). (b) Selective catheterisation of the left middle adrenal artery demonstrating extravasation (seen in (a)). The bleeding was arrested with injection of gel foam and coils.

/uni25CF /uni25CF /uni25CF /uni25CF /uni25CF PCCs are malignant. The di ff erentiation between malignant and benign tumours is di ffi cult, except when metastases are present. An increased PASS (phaeochromocytoma of the adrenal gland scale score), a high number of Ki-67-positive cells, vascular invasion or a breached capsule all lean more towards malignant rather than benign. PCCs may also produce calcitonin, ACTH, vasoactive intestinal polypeptide (VIP) and parathyroid hormone-related protein (PTHrP). In patients with MEN /uni00A0 2, the onset of PCC is preceded by adrenomedullary hyperplasia, sometimes bilateral. PCC is rar ely malignant in MEN /uni00A0 2 (3–5%) but often malignant with SDHB mutations (50%). Clinical presentation Functioning PPGLs typically present with symptoms and signs of catecholamine excess, and these are typically intermittent (Table 57.3). In total, 90% of patients with the combination of headache, palpitations and sweating in the presence of an adrenal tumour have a PCC. Paroxysms may be precipitated by physical training, induction of general anaesthesia and numerous drugs and agents (contrast medium, tricyclic anti depressant drugs, metoclopramide and opiates). Hypertension may occur continuously , be intermittent or absent. HNPGLs present with the side e ff ects arising from their local mass e ff ect (e.g. neck mass, dysphonia or tinnitus). Diagnosis Biochemical The diagnosis of PPGL is confirmed by elevated catecholamine metabolites (metanephrines) in plasma and/or raised 24-hour urinary excretion of fractionated metanephrines. Metanephrines are produced as a result of intratumour conversion of catecholamines by the enzyme catecholamine- O -methyltransferase. Measurement of plasma and urinary metanephrines is more sensitive (99% and 97%, respectively) than plasma and urinary catecholamine measurement (86% and 84%, respectively). Measurements of one or more of these substances that are four times greater than the upper limit of - the reference range are 100% diagnostic. Plasma dopamine can be regarded as a marker of tumour burden in malignant PPGL. Radiological Once a biochemical diagnosis is established, imaging by CT or MRI is undertaken to determine tumour location and assess its size and risk of malignancy . Size is not a predictor of malignancy for PCC. Malignant PPGLs are diagnosed by the presence of local invasion or metastatic disease. Tumours appear vascular and frequently possess cystic areas or central necrosis (Figure 57.10). If initial imaging is negative or reveals extra-adrenal disease, functional investigation with 123 I-MIBG (meta-iodobenzylguanidine; 80–90% sensitive) 111 or In-octretide scanning (50–70% sensitive) is undertaken

Gene Distinguishing clinical features PGL versus PCC Bilateral PCC or multiple PGL MAX PCC 60% bilateral SDHA PGL, PCC Single SDHAF2 HNPGL 90% multiple SDHB PGL 20% multiple SDHC PGL 20% multiple SDHD HNPGL and PGL 50% multiple AD, autosomal dominant; HNPGL, head and neck

paraganglioma; PCC, phaeochromocytoma; PGL, paraganglioma; PPGL, collective term for PCCs and PGLs. a Only mutations inherited from the father will result in the development of tumours. Mode of inheritance Biochemical phenotype Malignancy risk Possibly paternal Mixed 25% AD Low Mixed a Paternal Low Unclear 34–97% Noradrenaline/ AD normetanephrine Low Noradrenaline/ AD normetanephrine a <5% Paternal Noradrenaline/ normetanephrine, often silent TABLE 57.3 Range and incidence of symptoms from PPGL. Symptoms Prevalence (%) Hypertension 80–90 Paroxysmal 50–60 Continuous 30 Headache 60–90 Sweating 50–70 Palpitation 50–70 Pallor 40–45 Weight loss 20–40 Hyperglycaemia 40 Nausea 20–40 Psychological effects 20–40 PPGL, collective term for phaeochromocytomas and paragangliomas.

adrenal lesions. More recently , 6-[F]fl uorodopamine PET scanning has shown promise, particularly in the setting of PGLs, where conventional imaging and MIBG scanning are negative. Medical management Biochemical diagnosis and localisation of PPGLs should be followed by medical preparation to control blood pressure and prompt surgical excision. Preoperative control of blood pressure Once a PCC has been diagnosed, an α -adrenoceptor blocker (phenoxybenzamine) is used to block the e ff ects of catechol - amine excess and its consequences during surgery . With adequate medical pretreatment, the perioperative mortality rate has decreased from 20–45% to less than 3%. A dose of 20 /uni00A0 mg of phenoxybenzamine initially should be increased daily by 10 /uni00A0 mg until a daily dose of 100–160 /uni00A0 mg is achieved and the

Figure 57.10 A cross-section computed tomography scan of a large phaeochromocytoma showing characteristic central necrosis (arrow). (a) (b) Figure 57.11 (a) A cross-section computed tomography scan showing a paraganglioma anterior to the abdominal aorta (white 111

arrow) and an In-octretide scan demonstrating uptake by the tumour (black arrow). Operative photographs before (b) and after (c) extraction of the tumour. AA, /uni00A0 abdominal aorta; IVC, inferior vena cava; K, right kidney; P , para

ganglioma. (c)

β -blockade is required if tachycardia or arrhythmias develop; this should not be introduced until the patient is α -blocked. Other regimens have been described, e.g. α -blockade with doxazosin or prazosin, with and without β -blockade, using calcium channel blockers alone and using the catecholamine synthesis blocker metyrosine in the setting of cardiac failure. However, familiarity and experience with a particular pharma cological regime are probably more important than the regime itself. At this point surgery is safe to proceed . With adequate α -blockade preoperatively , anaesthesia should not be more hazardous than in patients with a non- functioning adrenal tumour; however, in some patients, dramatic changes in heart rate and blood pressure may occur and require sudden administration of pressor or vasodilator agents. A central venous catheter and invasive arterial monitoring are used. Special attention is required when the adrenal vein is ligated as a sudden drop in blood pressure may occur. The infusion of large volumes of fluid or administration of noradrenaline can be necessary to correct postoperative hypotension in the presence of unopposed α -blockade. Postoperative care Patients should be observed for 24 hours as hypovolaemia and hypoglycaemia may occur. Lifelong yearly biochemical tests should be performed to identify recurrent, metastatic or metachronous PCC. Surgical treatment PPGLs are excised by either laparoscopic or open surgery . Adrenalectomy for phaeochromocytoma Laparoscopic resection is now routine in the treatment of PCC. If the tumour is larger than 10 /uni00A0 cm or radiological signs of malignancy are detected, an open approach should be considered. Surgery for paraganglioma Tumours along the sympathetic chain can be technically chal lenging owing to their posterior relationship to the great vessels and visceral arterial branches,

which may hide smaller lesions. Furthermore, hereditary PGLs are associated with increased risk of local recurr ence. For this reason, minimally invasive surgery may not be feasible; open surgery is the preferred option. Special circumstances Surgical excision is the only chance for cure. If there is direct invasion, laparotomy and en bloc excision of involved adjacent organs o ff ers the best chance of cure. In the presence of metastases, excision of the primary tumour is still recommended to improve symptom control and improve the e ffi cacy of adjuvant radiolabelled MIBG and octreotide therapy . The natural history is highly variable with a 5-year survival rate of less than 50%. PCC in pregnancy may be silent and present as a hypertensive emergency or it Without adequate α -blockade, mother and unborn child are thr eatened by a hypertensive crisis during delivery . In the first and second trimesters the mother should be scheduled for laparoscopic adrenalectomy after adequate α -blockade; the risk of a miscarriage during surgery is high. In the third trimes - ter, elective caesarean with delayed consecutive adrenalectomy - 6 weeks later should be performed. The maternal mortality rate is 50% when a PCC r emains undiagnosed.

Malignant phaeochromocytoma. Phaeochromocytoma in pregnancy.

Revision #1
Created 2025-12-31 15:21:16 UTC by Omar Ayman
Updated 2025-12-31 15:21:16 UTC by Omar Ayman