Familial syndromes

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Familial hyperparathyroidism can be part of a well-recognised endocrine disorder, but it may also occur in isolation in a non-syndromic form. PHPT occurs as a central facet in multiple MEN type 1, type 4, type 2A, HPT-JT , autosomal dominant mild hyperparathyroidism and FHH. Familial isolated hyperparathyroidism Familial isolated hyperparathyroidism occurs when patients have PHPT without any other associated endocrinopathies. The underlying genetic abnormality has yet to be fully elucidated, but the syndrome has been linked to known mutations in the MEN1 gene, the HRPT2 gene as well as the calcium-sensing receptor gene. A significant proportion of patients will belong to the MEN /uni00A0 1 family , with documented recognised mutations but without expression of other endocrinopathies. Hyper parathyroidism should be treated with a formal bilateral neck exploration and management as per patients with MEN. MEN type 1-associated hyperparathyroidism MEN type 1 is a rare autosomal dominant syndrome consisting of tumours of the parathyroids, endocrine pancreas–duode num and the pituitary (the three Ps). It occurs in approximately 1 per 30 /uni00A0 000 individuals. It can also be associated with adrenal adenomas or carcinoma, foregut carcinoids and lipomas. Mutations, of which there are o ver 1000 identified in di ff erent families, occur in the MEN1 gene, which encodes the protein menin. Menin acts as a tumour suppressor. Patients typically present with young onset (20–30 years of age) of symptomatic hyperparathyroidism and over 95% of patients will have PHPT before the age of 40 years. Surgical intervention in MEN type 1 aims to obtain and maintain normocalcaemia for the longest time possible. In gen eral, it is associated with the presence of multig land parathyroid disease and as such has mandated a bilateral cervical explora tion with at least a subtotal parathyroidectomy and cervical thymectomy . A subtotal parathyroidectomy r emoves three and a half glands with half of the most normal-appearing para th yroid left in situ with a marking stitch to facilitate reoperative intervention. A total parathyroidectomy and forearm auto transplantation is an acceptable alternative. Detailed intra operative notes, including diagrams, should be kept. Despite meticulous and extensive surgery , the rates of both persistent and recurrent disease remain high in this group of patients (up to 62%) regardless of the type of surgery performed. Unfor tunately , the rates of postoperative permanent hypocalcaemia are also high, with published rates up to 47%. Max Wilms , 1867–1918, Professor of Surgery , University of Heidelberg, Germany . MEN type 4 is an autosomal dominant syndrome that comprises the same combination of tumours as MEN type 1 but is a rarer cause of hereditary PHPT . It arises as a result of an inactivating pathogenic variant in the cyclin-dependent kinase inhibitor CDKN1B gene. It should be managed in the same fashion as MEN type 1. MEN type 2A-associated hyperparathyroidism MEN type 2A consists of medullary thyroid carcinoma (MTC), unilateral or bilateral phaeochromocytomas and PHPT . PHPT occurs in approximately 20% of patients and is associated with mutations in codon 634 in the RET proto-oncogene. The majority of patients will be asymptomatic, with a mild elevation in calcium and asymmetrically enlarged parathyroid glands. It is extremely important that the presence of a phae - ochromocytoma is excluded prior to surgical intervention. Surgery is usually performed for MTC, with the parathyroid enlargement often being a coincidental

intraoperative finding (see Chapter 55). In this setting, with extensive surger y for MTC, the primary aim of treatment is to avoid hypoparathy - roidism. A conservative stance is adopted with resection of grossly enlarged glands, but with preservation of parathyroid tissue where possible and identification with a mar king stitch - in the neck. Hyperparathyroidism–jaw tumour syndrome HPT-JT is a rare cause of PHPT . It arises as a result of inactivating mutations in the HRPT2 / CDC73 gene on chromosome 1q21–q31, encoding parafibromin. It classically - presents with early-onset PHPT (mean age of 32 years), the aetiology of which can be either single- or multigland disease but is predominantly cystic in nature. It presents with severe hypercalcaemia and is associated with an increased risk of an underlying parathyroid carcinoma. Approximately 40% of patients will have the pathognomonic ossifying jaw fibromas of the maxilla or mandible. Other associated abnormalities include renal pathology (hamartomas, polycystic kidney disease and adult Wilms' tumours) and female patients may have uterine malignancies. Surgical intervention involves removal of all enlarged parathyroid glands. - Where there is concern for a parathyroid carcinoma, great care must be taken to avoid tumour spillage. Whether or not - an en bloc resection of the enlarged suspicious parathyroid and the adjacent thyroid lobectom y is required remains con - troversial. - Autosomal dominant mild - hyperparathyroidism - This is a rare autosomal dominant syndrome presenting with hypercalcaemia and hypercalciuria. It is associated with a mutation in the calcium-sensing receptor gene. It typically - presents in patients who are over 40 years of age and all patients have PHPT . Surgical intervention requires a bilateral neck exploration as it is associated with multigland disease. FHH is not a surgical disease and therefore preoperative diag nosis is imperative for the surgeon. FHH arises as a result of heterozygous mutations in the calcium-sensing receptor gene on chromosome 3. Benign FHH typically presents with hypercalcaemia in young (<10 years of age) asymptomatic patients. Patients with FHH have a normal or slightly elevated PTH level, increased serum magnesium levels and hypocalci uria. A low urinary calcium–creatinine clearance ratio is used to discriminate between FHH and mild PHPT . Patients rarely require intervention and surgical intervention is not indicated. Criteria for genetic testing In clinical practice, specific criteria can be employed to deter mine which patients are at the highest risk of hereditary PHPT . The current NHS England National Genomic Test Directory testing criteria from March 2019 for familial hyperparathy r oidism state that testing should be considered for patients with PHPT and a creatinine clearance ratio >0.02 who meet of the following criteria: 1 presenting before the age of 35 years or 2 presenting before the age of 45 years with one of: a proven multigland involvement or b hyperplasia on histology or c ossifying fibroma(s) of the maxilla or mandible d at least one first-degree relative with unexplained hyperparathyroidism. The testing criterion for FHH is a creatinine clearance ratio <0.02. Summary box 56.1 Primary hyperparathyroidism /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF

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