The pathology of pituitary, parathyroids, thyroid and adrenal glands

Maidie Yeung

Fawzia Tahir

Abstract

The pathology of these endocrine organs is generally related to over or underproduction of hormones with resultant biochemical and clinical manifestations or a consequence of mass lesions. Hyperplastic processes and both benign and malignant neoplasms may be associated with hyperfunction. Hypofunction is usually a destructive process. An integrated multidisciplinary approach with morphological findings, biochemical measurements of hormone levels and their regulators is required to diagnose and treat endocrine diseases. Most hyperplasia/neoplasia are sporadic but a significant subset occurs in multiple endocrine neoplasia (MEN) syndromes, a group of inherited disorders of multiple endocrine organs.

Keywords Adrenal; hormones; parathyroid; pathology; pituitary; thyroid

The pituitary gland

Histology

The pituitary gland is composed of the anterior lobe (adenohypophysis), which constitutes about 80% of the gland, and the posterior lobe (neurohypophysis). Both components are morphologically and functionally distinct.

The adenohypophysis is controlled by the hypothalamus through factors carried by a portal vascular system. It contains six terminally differentiated cell types:

- somatotrophs – secrete growth hormone (GH)
- mammosomatotrophs – secrete GH and prolactin
- corticotrophs – secrete adrenocorticotropic hormone (ACTH) and melanocyte-stimulating hormone (MSH)
- thyrotrophs – secrete thyroid-stimulating hormone (TSH)
- lactotrophs – secrete prolactin (PRL)
- gonadotrophs – secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

The neurohypophysis is composed of unmyelinated axons and modified glial cells that extend from the hypothalamus. It stores and releases oxytocin and antidiuretic hormone (ADH)/vasopressin in response to relevant stimuli.

Maidie Yeung *BSc MBBS FRCS FRCPath is a Specialty Registrar in Pathology at the Sheffield Teaching Hospitals NHS Foundation Trust, UK. Conflicts of interest: none declared.*

Fawzia Tahir *MBBS FRCPath is a Consultant Pathologist at the Sheffield Teaching Hospitals NHS Foundation Trust, UK. Conflicts of interest: none declared.*

Clinical manifestations of pituitary disease are attributable to excess secretion or deficiency of hormones or mass effects.

Hyperpituitarism

Pituitary adenomas of the anterior lobe are the most common cause of hyperpituitarism. Other causes include hyperplasia, carcinoma and some hypothalamic disorders.

Pituitary adenomas: pituitary adenomas may be functional and associated with endocrine sequelae or non-functional which typically present with mass effects. They constitute 10–15% of all intracranial neoplasms and are usually found in adults between 35 and 60 years. Radiologically they are designated as microadenomas (≤1 cm) that remain confined to the sellar region or macroadenomas (>1 cm).

All pituitary adenomas are WHO grade 1 tumours.

Pituitary adenomas are classified by hormone production from neoplastic cells which can be detected by immunohistochemical methods. They include:

Lactotrophs – these produce PRL and are the most frequent type accounting for 30% of all clinically recognized cases. Prolactinaemia clinically produces amenorrhea, galactorrhoea, loss of libido and infertility. These adenomas are readily diagnosed in premenopausal women between 20 and 40 years of age. Microadenomas are also capable of causing hyperprolactinaemia. Lactotroph adenomas are commonly treated with a dopamine receptor agonist such as bromocriptine.

- Somatotrophs – these are growth hormone (GH) secreting adenomas and the second most common of the functional adenomas. They cause gigantism in children and acromegaly in adults. Up to 40% of somatotroph cell adenomas demonstrate *GNAS* activating mutations. They are treated either surgically or using somatostatin analogs or GH receptor antagonists.
- Corticotrophs – these cause an excess production of ACTH which leads to cortisol hypersecretion by the adrenals and development of Cushing syndrome.
- Gonadotrophs – these are LH and FSH producing adenomas most frequently found in middle-aged men and women causing decreased energy and libido in men and amenorrhea in premenopausal women.
- Thyrotrophs – TSH-secreting adenomas are a rare cause of hyperthyroidism, accounting for approximately 1% of all pituitary adenomas.
- Bihormonal – mammosomatotroph adenomas synthesize both GH and PRL.
- Plurihormonal – multiple hormones are secreted by plurihormonal adenomas and are usually aggressive. The usual combinations are gonadotroph hormones and GH, PRL and TSH.
- Non-functioning (null-cell) adenomas – these constitute about 20–30% of all pituitary tumours. They typically present with symptoms of mass effects or cause gradual hypopituitarism due to slow enlargement of the adenoma or pituitary apoplexy (due to acute intra-tumoral haemorrhage).

Genetics– while most pituitary adenomas are sporadic, approximately 5% are seen in genetic disorders in the setting of:

- multiple endocrine neoplasia (MEN) type 1 (mutation in MEN1 gene on chromosome 11q13)

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- Carney complex (inactivating mutations of PRKAR1A gene, 17q22-24)
- McCune-Albright syndrome (mutation in GNAS1 gene, 20q13)
- MEN4 (mutation in CDKN1B gene, 12p13)
- familial isolated pituitary adenoma (mutation in AIP gene, 11q13).

Grossly, the typical adenoma is soft and well-circumscribed. Haemorrhage and necrosis are common in larger tumours. Macroadenomas commonly extend upwards into the suprasellar region through the diaphragma sella where they often compress the optic chiasm causing visual field abnormalities. A proportion of the adenomas lack a gross capsule and locally invade into nearby structures such as sphenoid and cavernous sinuses and dura.

Microscopically, cellular monotony with scanty supporting connective tissue distinguishes pituitary adenomas from hyperplasia/non-neoplastic pituitary tissue. The cell cytoplasm may be acidophilic, basophilic or chromophobic depending on the type of the secretory product and subtyped using an immunohistochemical panel of pituitary antibodies. Mitotic activity is usually scanty.

Atypical adenomas: these demonstrate an elevated mitotic index, a Ki-67 proliferation index of >3% and p53 expression on histology. These suggest aggressive clinical behaviour and merit close clinical follow-up.

Pituitary carcinoma: these are rare (<1% of pituitary tumours), usually evolve from pre-existing macroadenomas into aggressive lesions and are functionally active. PRL and ACTH are the most common secreted products. The morphology and initial clinical course is indistinguishable from an adenoma. By definition, carcinomas are characterized by craniospinal dissemination or systemic metastases.[1]

No TNM (tumour, node and metastasis) classification exists for pituitary tumours.

Hypopituitarism

Pituitary hypofunction occurs when approximately 75% of the tissue is lost with most cases attributable to a local destructive process and include the following causes:

- traumatic brain injury and subarachnoid haemorrhage (most common)
- mass lesions including pituitary adenomas, primary and metastatic malignancies
- Sheehan syndrome/postpartum necrosis and ischaemic necrosis due to disseminated intravascular coagulation or shock of any cause
- Rathke cleft cyst
- empty sella syndrome: any condition such as radiation or surgery that destroys the pituitary gland
- hypothalamic lesions
- inflammatory or infectious disorders
- congenital defects.

The clinical manifestations of hypopituitarism depend on the deficiency of the particular hormone, e.g. pituitary dwarfism in children due to lack of GH.

Posterior pituitary syndromes include diabetes insipidus due to deficiency of antidiuretic hormone (ADH) and syndrome of inappropriate ADH secretion resulting from excessive ADH.[1,2]

Parathyroids

Histology

There are four main parathyroid glands (each weighing around 40 mg), surrounded by a delicate capsule and composed of two epithelial cell types: chief cells and oxyphil cells. The chief cells predominate, have pale cytoplasm and produce parathyroid hormone (PTH) which regulate calcium homoeostasis. The oxyphil cells contain numerous mitochondria and increase in number with age. Stromal fat increases with age reaching a maximum of approximately 30% of the gland. Variations in the anatomical positions occur within the neck and mediastinum due to faulty migration during embryonic development. These ectopic parathyroid glands are subject to the same pathology as the normal sited glands.

Parathyroid pathology relates to hyper and hypofunction like other endocrine organs. However, tumours of the parathyroid gland mostly come to light by their excessive secretion of PTH and not due to mass effects.

Hyperparathyroidism

Hyperparathyroidism results from excessive PTH and is classified as primary, secondary and tertiary types.

Primary hyperparathyroidism: primary hyperparathyroidism is autonomous overproduction of PTH, usually caused by a single gland adenoma (85–95%) or hyperplasia (a multiglandular process) (5–10%), and in a minority of cases due to parathyroid carcinoma (~1%). The female to male ratio is 4:1 with most cases occurring after 50 years of age. In the familial syndromes, it is a predominant component of MEN I and occurs occasionally in MEN 2A.

Symptomatic primary hyperparathyroidism is due to combined effects of excessive PTH and hypercalcaemia. Nephrolithiasis and bone disease are directly attributable to hyperparathyroidism whereas fatigue, weakness, pancreatitis, metastatic calcifications and constipation are related to hypercalcaemia.

Secondary hyperparathyroidism: secondary hyperparathyroidism is usually secondary to vitamin D deficiency and renal impairment; severe disease is often seen in the latter. The mechanisms of hyperparathyroidism in renal failure include hyperphosphatemia, hypocalcaemia, lack of active vitamin D and renal resistance to PTH.

Tertiary hyperparathyroidism: tertiary hyperparathyroidism is autonomous and excessive PTH secretion arising from long standing secondary hyperparathyroidism and usually detected after correction of renal failure by means of a renal transplant.

Hypoparathyroidism

Hypoparathyroidism is far less common. In the acquired form, it is almost always a complication of surgical intervention. Other causes are autoimmune hypoparathyroidism and genetic causes

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