

Solid Tumour Section

Mini Review

Endocrine/neuroendocrine glands: Pituitary Adenomas

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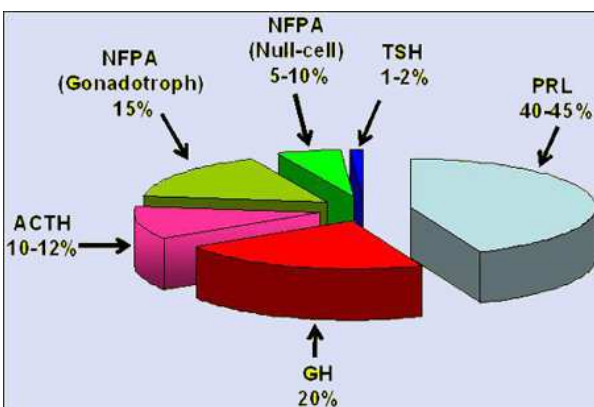
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Identity

Note

Pituitary adenomas are common benign monoclonal neoplasms accounting for approximately 15% of intracranial tumors, while occult adenomas are discovered in as many as 25% of unselected autopsies. Pituitary tumors are usually benign, but cause significant morbidity due to their critical location, expanding size, and/or inappropriate pituitary hormone expression. True malignant behaviour with metastatic spread is very rare.

Classification



The relative incidence of the different pituitary adenomas subtypes is diagrammed in Fig.1

Various subtypes have been recognized on the basis of clinical presentation, as well as immunocytological and ultrastructural characteristics. About one-third of

pituitary adenomas are not associated with clinical hypersecretory syndromes, but with symptoms of an intracranial mass such as headaches, hypopituitarism, or visual field disturbances, and are classified as nonfunctioning pituitary adenomas (NFPAs). Clinically non-functioning adenomas (NFPA) are actually a diverse group of tumors that include LH-, FSH-secreting adenomas, null cell adenoma and oncocytoma. The clinical features of all other pituitary adenomas are linked to the hypersecreted hormone(s) which mark the specific cell origin, allowing the tumors to be classified as:

Prolactinomas or PRL-secreting PA, the most common of all functional pituitary adenomas. The patients usually present with amenorrhea, infertility, and galactorrhea (females), impotence or infertility (males). Tumors expressing both PRL and GH are thought to originate from a common mammosomatotroph precursor cell.

Somatotropinomas or GH-secreting PA, which cause acromegaly in adults, with bony acral changes in soft tissues and bone, and increased risk of hypertension, cardiac disease, and diabetes.

Corticotropinomas or ACTH-secreting PA, leading to Cushing disease and adrenal steroid overstimulation. Features of hypercortisolism include truncal obesity, striae, muscle wasting, hirsutism, cardiovascular complications, osteoporosis, and psychiatric disturbances.

Pure gonadotropinomas secreting intact FSH or LH are rarely encountered and may cause sexual dysfunction and hypogonadism.

Thyrotropinomas cause a mild increase in thyroxine levels with inappropriate TSH levels.

Clinics and pathology

Treatment

PRL: medical therapy to reduce prolactin secretion and tumor size by using dopamine agonists such as bromocriptine, cabergoline and quinagolide. Trans-sphenoidal surgery may be required for drug resistant tumours or drug-intolerant individuals.

NFPA: in the presence of clinical signs, the primary treatment is trans-sphenoidal surgery. Medical and radiation therapy are considered following incomplete tumor resection. Patients without clinical signs are followed-up by MRI scans and visual field checks.

GH: treatment depends on the adenoma size/activity and patient's age. Trans-sphenoidal surgery is the treatment of choice in most cases and can be dramatically effective, especially for microadenomas. Following surgery some patients may need radiotherapy and medical treatment with bromocriptine or somatostatin analogues to reduce prolactin secretion or inhibiting GH release from the pituitary.

ACTH: the usual treatment is trans-sphenoidal surgery which leads to rapid disappearance of cortisol from the blood. When surgery is unsuccessful, radiotherapy is administered. Drugs such as metyrapone, ketoconazole and o,p'DDD are used to control cortisol levels, particularly before surgery.

Evolution

Is dependent on adenoma subtype. A significantly higher frequency of multiple allelic deletions were found in invasive tumors compared to non-invasive tumors.

Prognosis

Usually favourable. Truly malignant metastatic behaviour is extremely rare. The unresponsiveness to pharmacological treatment is associated with more aggressive behaviour.

Genetics

Note

Little is known about the genetic defects leading to pituitary tumor formation, which likely involves multiple initiating and promoting factors.

With the exception of activating mutations of *GNAS1* which have been associated with 40% of somatotrophic adenomas and 10% of NFPA, none of the candidate cell cycle, receptor, second messenger or related genes examined thus far appears to be responsible individually for more than a few percent of sporadic pituitary adenomas.

Inactivation of *p27kip1* and *RB1* has been associated with the development of pituitary adenomas in mice, but no similar evidence has been achieved in human.

MEN1A mutations, commonly found in patients

affected by the MEN-1 syndrome, are rarely found in sporadic pituitary adenomas, despite a *menin* variably diminished expression has been demonstrated.

Increased expression of pituitary tumor transforming gene (PTTG) has been found in sporadic pituitary adenomas, and a role for this gene in pituitary cell proliferation is supported by development of multifocal plurihormonal focal pituitary adenomas in transgenic male mice overexpressing PTTG.

A role for *HMGA2* gene in pituitary oncogenesis has been pointed out by development of PRL adenomas in *HMGA2* transgenic mice and the finding of *HMGA2* expression, which is switched off in the adult pituitary gland, in human prolactinomas. Amplification and/or rearrangement of the *HMGA2* gene, mapping to 12q14, was observed in most of the PRLs analyzed. Increased dosage of chromosome 12 appears to be a condition predisposing to selective overrepresentation of the 12q14 region and/or rearrangement of the *HMGA2* gene.

Expression of *HMGA2* has been recorded also in human NFPA, which rarely harbor trisomy 12, suggesting a mechanism of activation different from that mainly operating in PRLs (Figure 2).

It remains to be determined which of the many oncogenes/growth factors and oncosuppressors reported overexpressed or underexpressed contribute to pituitary oncogenesis to identify the pathogenetic pathways which are altered in pituitary adenomas.

Cytogenetics

Note

Cytogenetic analysis failed for some time to identify recurrent chromosomal anomalies which might correlate with a clinical adenoma subtype or with a defined tumor stage.

Technical difficulties related to the size of the samples available after surgery and the low proliferative rate of pituitary cells account for the limited cytogenetic findings. Despite these constraints a small fraction of pituitary adenomas showed an abnormal karyotype characterized by hyperdiploid or near triploid modal chromosome numbers and rare random structural abnormalities. Microsatellite and interphase FISH studies indicated that trisomy of chromosome 12 is pathogenetically important, and represents the most frequent cytogenetic alteration in human PRL. Chromosomes 5, 8 and X were also found to be preferentially overrepresented (Figure 3). Combined gains of the above chromosomes appear a non random pattern in pituitary adenoma. Comparative genomic hybridization (CGH) studies confirmed the cytogenetic and FISH evidence, but did not provide significant clues to specific subchromosomal regions.

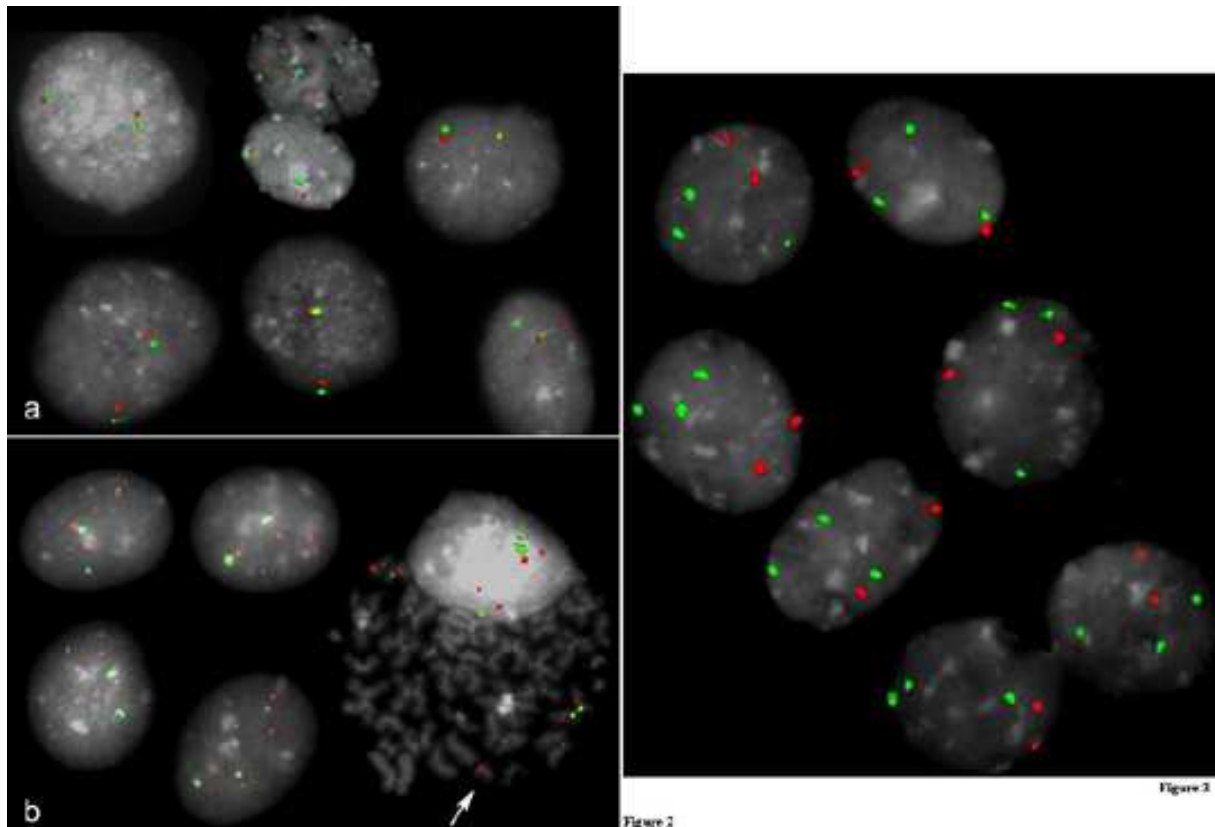


Figure 2. Interphase and metaphase FISH of HMGA2 dosage in human pituitary adenomas. Dual-color FISH of 669g18 +698i6 BACs (targeting the entire HMGA2 genomic region, red) and pBR12 (alphoid-specific probe of chromosome 12, D12Z3 locus, green) showing: (a) disomy of both regions in a NFPA tumor expressing HMGA2 and (b) increased number of signals given by HMGA2-specific BACs as compared to that given by the alphoid probe on a NFPA expressing HMGA2. Note one HMGA2 signal on a marker chromosome (arrowed). Figure 3. Interphase dual-color FISH of probes pBR12 (D12Z3 locus, green fluorescence) and pDMX1 (DXZ1 locus, red) showing trisomic and disomic dosage of chromosomes 12 and X respectively, in a PRL pituitary adenoma.

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