Advances in understanding pituitary tumors
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Abstract
Pituitary tumors are common in the general population. Since neuroimaging techniques have improved, pituitary tumors are more often diagnosed incidentally. About 16.7% of the general population show changes in the pituitary gland. Predominantly, pituitary tumors are benign pituitary adenomas. Pituitary carcinomas or aggressive pituitary tumors are extremely rare. They might develop from benign adenomas. New genetic and epigenetic abnormalities help us to understand pituitary tumorigenesis and might lead to therapeutical targeting drugs in the future. Macroadenomas (>1 cm) can lead to visual field disturbances, compression of cranial nerves, hypopituitarism, and infiltration of the cavernous sinuses. The functional status of the pituitary tumor is important. About half to one third of all pituitary tumors are non-functioning pituitary adenomas. The other pituitary tumors show a specific pattern of hormone secretion. About 25% to 41% of all pituitary tumors are prolactinomas, acromegaly with production of growth hormone represents 10% to 15% of adenomas, Cushing’s disease with production of adrenocorticotropic hormone accounts for 10%, and other hormonal characteristics are less common. Transsphenoidal resection and total adenomectomy are desirable. Radiosurgery has enriched the surgical treatment options. Surgical treatment is the intervention of choice except for prolactinomas, where pharmaceutical treatment is recommended. Pharmaceutical treatment consists of dopamine agonists such as cabergoline and somatostatin analogues that include octreotide and pasireotide; retinoic acid is of theoretical interest while peroxisome proliferator-activated receptor-gamma-ligands are not clinically useful. In acromegaly, pegvisomant is a further treatment option. Temozolomide should be considered in aggressive pituitary tumors. In general, pharmaceutical options developed recently have extended the repertoire of treatment possibilities of pituitary tumors.

Recent advances
Epidemiology
Pituitary tumors are common in the general population. In 16.7%, changes in the pituitary gland can be detected [1]. Since neuroimaging techniques have recently improved, pituitary tumors are more frequently diagnosed incidentally.

Usually, pituitary tumors are assigned as primary tumors of the central nervous system (CNS) and contribute to 5% to 20% of all primary CNS tumors [2]. In 95% of cases, pituitary tumors occur sporadically. Only in 5% may a familial genetic background be assumed, e.g. as part of Multiple Endocrine Neoplasia (MEN) Type 1, Carney's Complex (CNC), or Familial Isolated Pituitary Adenomas (FIPAs). In MEN1 syndrome, pituitary tumors occur alongside (entero-) pancreatic tumors, parathyroid hyperplasia, lipomas, and angiofibromas. This autosomal-dominant syndrome contributes to 2.7% of all pituitary tumors [3].

In most cases, pituitary tumors are benign adenomas. Pituitary carcinomas are extremely rare, and in these cases the assumption is that they are former benign adenomas that have undergone additional genetic mutations [4]. These changes induce an invasive tumor progression and the development of metastasis, mainly into the brain or spinal cord. Distant metastasis can be found in the liver, lung, or lymph nodes.
In childhood, craniopharyngiomas occur with an incidence of 0.5-2/million/year. Survival rates after surgical treatment are rather high: between 91% and 98% [5].

Pituitary adenomas are classified partially depending on their size into microadenomas (<1 cm) and macroadenomas (>1 cm). The size of the adenoma corresponds with compromising effects on the optic chiasm, cranial nerves, and cavernous sinuses, but tumor size does not reflect its clinical importance [6]. This classification is supplemented by immunochemistry and functional status. Pituitary tumors are classified as functioning or non-functioning on the basis of their ability to produce and secrete mature hormones [1,7]. Approximately half to one third of all pituitary tumors are non-functioning pituitary adenomas (NFPAs) (i.e. without hormone secretion detected either by immohistochemistry or by elevated hormonal blood levels). The most common hormone-secreting pituitary tumor is the prolactinoma (lactotroph adenoma – 25%-41%), followed by somatotroph adenomas (10%-15%), corticotroph adenomas (about 10%), thyrotroph adenomas (<1%), and gonadotroph adenomas (<1%) [1,8].

**Pathophysiology and molecular genetics**

Pituitary tumors are mostly monoclonal. Therefore, genetic influences in only one cell might induce tumor transformation. In sporadic tumors, gsp oncogene is the most important one. Mutations in the alpha subunit of G protein gene — which is involved in hypothalamic growth hormone (GH) release — might cause continuous activation of adenyl cyclase [2]. This pattern was observed in 40% of GH-secreting tumors (somatotropinomas). Usually the alpha subunit of the G protein gene is expressed monoallelically, whereas in some cases it is expressed biallelically and this is through a process termed loss of imprinting [9].

About 15% of all FIPA patients show mutations in the aryl hydrocarbon receptor-interacting protein (AIP) gene. This chaperone might act as a tumor suppressor; mutations might induce tumorigenesis [10]. Clinically, patients with FIPA are younger and show bigger pituitary adenomas at diagnosis.

The number of genes and molecular abnormalities involved in pituitary tumorigenesis increased in the last years [11]. In some cases genetic changes were associated with specific types of pituitary adenomas such as the promotion of somatotroph pituitary tumorigenesis through the FGFR4-G388R polymorphism [12]. In spite of genetic changes, pituitary tumors show epigenetic changes as different histone modification and aberrant DNA methylation status [13]. These genetic and epigenetic changes might be of interest for the development of new drugs. Further investigations and studies are therefore necessary.

**Diagnosis**

Since magnetic resonance imaging (MRI) techniques have improved and are used more widely in the general population, pituitary adenomas are more frequently diagnosed incidentally. Pituitary tumors such as NFPAs might not be identified for many years. In contrast, macroadenomas can cause local symptoms such as visual disturbances when the optic chiasm is compressed.

Even small pituitary adenomas might have clinically important consequences through elevated hormonal levels and become apparent as hyperprolactinaemia, GH, or cortisol excess. In these patients, endocrinological disturbances can lead to secondary hypogonadism due to hyperprolactinaemia, acromegaly, or Cushing’s disease (CD). Interestingly, the tumor size in prolactinomas correlates with serum prolactin levels [14]. In most patients with prolactin levels >250 µg/l, a (macro)prolactinoma might be assumed. In acromegaly, patients show a typical facial appearance and acral enlargement. The diagnosis can be confirmed by elevated basal GH levels (>0.4 µg/l), elevated basal insulin-like growth factor-1 (IGF-1) levels (depending on age-related normal values), and a lack of suppression of GH in the oral glucose tolerance test with 75 g glucose load (GH >1 µg/l) [15]. In CD, typical clinical symptoms such as abdominal fat distribution, red striae, and muscle weakness can lead to the suspicion of Cushing syndrome [16]. To verify suspected CD, 24-hour urinary cortisol level or a dexamethasone suppression test (1-2 mg) is recommended [17].

Even when neuroimaging techniques have improved, microadenomas can be difficult to detect in MRI and even later during surgery. Before surgery, coronal and sagittal T1-weighted sections through the sella are required. MRI scans should be performed before and after contrast enhancement [18]. In order to detect small hormonal active pituitary adenomas, selective catheterization of the inferior petrosal sinuses can be conducted [17].

The visual field and cranial nerve function have to be evaluated, especially in macroadenomas. MRI techniques help to identify invasion of the cavernous sinuses or suprasellar tumor growth and this is important for the surgical approach [19].

**Surgical treatment**

Surgical treatment is the first-line treatment in pituitary adenomas — except for prolactinomas, where dopamine agonists are recommended as treatment of choice [20,21].
Two operative techniques exist for resection of pituitary tumors. Transsphenoidal (transnasal) resection is the most common operative technique; only in extracellular tumors is a craniotomy recommended. Intraoperative MRI scans might ameliorate outcome in some patients but are not generally recommended [22,23]. Recently, stereotactic and fractional radiosurgery such as Gamma Knife or Cyber Knife have enriched interventional treatment options [24].

Selective adenomectomy is the treatment of choice in order to preserve pituitary function [18]. In CD, surgical curative therapy is the treatment of choice in adrenocorticotropic hormone (ACTH)-producing tumors [21]. On the first day post-surgery, cortisol levels should be determined. Fasting serum cortisol levels <50 nmol/l (<2 µg/dl) indicate a remission and a low recurrence rate (10% after 10 years). If fasting serum cortisol levels are higher than 140 nmol/l (5 µg/dl) in the first week post-surgery, further evaluation is necessary [21]. In case of postsurgical hypocortisolism, a substitution therapy should be initiated [18]. In recurrent adenomas, irradiation or adrenalectomy should be considered as further treatment options [17].

In pituitary carcinomas, it might be necessary to repeat surgical interventions. In most cases, surgical treatment will be supplemented with pharmacological treatment (dopamine agonists, somatostatin analogues, temozolomide). Furthermore, radiotherapy should be evaluated in patients with aggressive pituitary tumors when surgical and pharmacological treatment options fail.

**Pharmacological treatment**

Hormonal active pituitary adenomas can be treated pharmacologically. In prolactinomas, pharmacological treatment is the treatment of choice.

The dopamine D2 receptor subtype is the pharmacological target of dopamine agonists. Dopamine inhibits prolactin production from the pituitary gland [25]. Since about 80% of all corticotropinomas also express the dopamine D2 receptor [26], a normalization of cortisol levels might be achieved using dopamine agonists such as bromocriptine or cabergoline. Dopamine agonists are also used in Parkinson’s disease where higher dosages are necessary. Since ergotamine derivatives might cause multiple fibrosis (i.e., valvular or pulmonary fibrosis) [27,28], bromocriptine or cabergoline is only administered with clinical controls (i.e., echocardiography). Low-dose cabergoline with its long half-life period of 65 hours is the most frequently used dopamine agonist for pharmacological treatment of prolactinomas and corticotropinomas. Clinical guidelines recommend cabergoline treatment in patients with hyperprolactinaemia [14]. Low-dose cabergoline does not seem to cause cardiac fibrosis [29] even as a long-term treatment strategy. Nevertheless, echocardiography is indicated in long-term treatment with higher dosages of cabergoline >2 mg per week [30]. Cabergoline can also be used in women who have indicated a wish to get pregnant; it should not be withdrawn in these patients [30].

In acromegaly, dopamine agonists can be administered as well as somatostatin receptor ligands or the GH receptor antagonist pegvisomant [43]. The aim of the pharmacological treatment in acromegaly is to normalize IGF-1 levels and to decrease GH by less than 2.5 µg/l or possibly lower.

Besides dopamine agonists, further treatment options are available for corticotropinomas. In general, in CD either the production of ACTH can be lowered or the cortisol production in the adrenal gland can be reduced. New pharmacological targets have been developed recently for the treatment of CD.

Somatostatin analogues such as octreotide reduce ACTH secretion. Dexamethasone and probably high levels of corticosteroids in general reduce mRNA expression of the somatostatin receptor type 2 (SSTR2) [31]. Since octreotide acts via suppression of the SSTR2, octreotide treatment is not always successful in CD. Furthermore, most ACTH-secreting adenomas express predominantly somatostatin receptor type 5 (SSTR5) [32]. Recent experience exists with pasireotide (SOM 230), which has a high affinity for the SSTR5 receptor but also shows affinity for the SSTR1 and SSTR2 receptors. Pasireotide may be a new effective tool in the pharmacological treatment of corticotropinomas [33-35]. A combination of pasireotide with adrenal blocking drugs and glucocorticoid receptor antagonizing drugs might be necessary in the individual patient [36,37].

Furthermore, it has been shown that retinoic acid can reduce ACTH secretion and cell proliferation. The effect is mediated by the nuclear retinoic acid receptor (RAR) and retinoid x receptor (RXR) [38,39] and is limited to tumors with ACTH secretion. Retinoic acid was not only markedly suppressing ACTH secretion in corticotroph adenoma cells in vitro but was also effective in vivo as it strongly reduced urinary-free cortisol in patients with CD, as shown in a recent study [40]. It has to be discussed that only 7 patients were included in this study. Hence, human trials are very limited, and retinoic acid is not at present an accepted therapy.

Peroxisome proliferator-associated receptor-gamma (PPAR-γ) ligands, such as rosiglitazone, were potent suppressors of ACTH in corticotroph cell lines in vitro or in mouse models of CD [41] but were not clinically useful in patients with corticotroph adenomas [42].

In acromegaly, dopamine agonists can be administered as well as somatostatin receptor ligands or the GH receptor antagonist pegvisomant [43]. The aim of the pharmacological treatment in acromegaly is to normalize IGF-1 levels and to decrease GH by less than 2.5 µg/l or possibly lower.
In prolactin-producing carcinomas (malignant prolactinomas), temozolomide can be administered as pharmacological treatment [14,44,45]. In case reports, temozolomide reduced tumor size and prolactin levels in tumors that mainly did not express methylguanine-DNA methyltransferase (MGMT) [46]. Since data on MGMT methylation status and response to temozolomide are inconsistent in the literature, temozolomide should be considered for all pituitary carcinomas [47].

In prolactinomas, dopamine agonists can be discontinued after 2 years of treatment by way of trial [20]. Therefore, serum prolactin levels have to be no longer elevated and no tumor has to be detectable in the MRI scan [17]. Nevertheless, normal prolactin levels will persist in only about 21% of all microprolactinomas and in about 16% of all macroprolactinomas [48].

In nonfunctioning pituitary adenomas, no pharmacological treatment option exists. Surgical treatment is the treatment of choice for NFPA. Recurrence cannot be detected by hormonal abnormalities. In incidental NFPA, 10% of microadenomas and 24% of macroadenomas expand without treatment [49]. Surgical treatment is indicated in case of further growth, development of visual deficits, or hypopituitarism [49]. MRI scans should be performed every year for the first 5 to 6 years after surgery. In some cases (e.g. relevant tumor mass post-surgery or invasion of the cavernous sinuses), radiotherapy is recommended [50].

**Perspectives**

Recently, the new somatostatin analog pasireotide has been established for the treatment of corticotroph pituitary adenomas, and the application of temozolomide was effective in a considerable proportion of patients with pituitary carcinomas. There is evidence that inhibitors of cell signaling cascades in combination with already-used drugs (somatostatin analogs, dopamine receptor antagonists) will further improve the pharmacological treatment of pituitary adenomas. Moreover, recent studies have identified several genetic and epigenetic changes that are associated with the tumorigenesis of pituitary adenomas. The pharmacological correction of these changes will probably open new avenues to the medical treatment of pituitary tumors in the near future.

**Abbreviations**

ACTH, adrenocorticotropic hormone; CD, Cushing’s disease; CNS, central nervous system; FIPA, Familial Isolated Pituitary Adenoma; GH, growth hormone; IGF-1, insulin-like growth factor 1; MEN, Multiple Endocrine Neoplasias; MGMT, methylguanine-DNA methyltransferase; MRI, magnetic resonance imaging; NFPA, non-functioning pituitary adenoma; SSTR2, somatostatin receptor type 2; SSTR5, somatostatin receptor type 5.

**Disclosures**

The authors declare that they have no disclosures.

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