Functioning Adenomas

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13.1 Introduction

Pituitary adenomas with clinically relevant hypersecretion comprise approximately 40% of all pituitary adenomas. The most frequent is the prolactinoma. For more than 30 years this tumor has been regularly treated primarily by dopamine agonists. Thus, mostly tumor shrinkage and normalization of prolactin plasma levels have been achieved. Intolerance and partial efficacy are indications for a surgical approach. A parallel comparison of medically pretreated and only surgically treated patients showed significant differences that are of importance to the surgeon and pathologist. In acromegaly, specific medications with somatostatin analogues became available more than 20 years ago. In most cases with or, increasingly rarely, without pretreatment, transnasal microsurgery is performed with the option of long-lasting clinical remission. In incompletely resectable adenomas, the discussed indication for surgery involves improvement of the effects of medical treatment and reduction of the radiation field. New pharmaceutical approaches with a GH-receptor antagonist optionally in combination with somatostatin analogues and or dopamine-agonists challenge the surgical options. TSH-secreting adenomas are extremely rare and may also be successfully treated by somatostatin analogues. After shrinkage or without gross invasion and improved microsurgical techniques, long-term results are promising. All these adenomas have tumor markers with a short half-life in plasma and may be checked during or shortly after surgery. Pretreatments influence the assessment, which has to be taken into consideration. In Cushing's disease, measurement of ACTH and cortisol the day after surgery mostly clarifies the effect of surgery. In selected primary failures, early re-operation may be successfully performed.

Nowadays, the diagnosis (late-night cortisol, CRH test) and follow-up can easily be done with salivary cortisol. Medical options with more adenoma-specific ligands (Pasireotide) are under clinical evaluation.

Active adenomas have in common that the results of different treatment options can be compared by exact criteria. Minute nodules or rests of functioning adenomas that are far beyond the detection sensitivity of the best MRI may produce the full clinical syndrome. The diagnostic and therapeutic approaches are so specific that different types of functioning adenomas have to be described separately.

13.2 Prolactinomas

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13.2.1 Epidemiology

By analysis of a stable population around Stoke-on-Trent, UK, with one million inhabitants and a single referral center, R.N. Clayton estimated the incidence and prevalence of prolactinomas during a 10-year period (1988–1998) to be 6–10 cases/million/year and 60–100 cases/million, respectively. Based on clinical endocrine activity, prolactinomas were found to be the most frequent type of pituitary adenomas, accounting for 50.1% of 2,252 patients in Italy and 39.0% of 2,230 surgical cases in San Francisco. Whereas the lower incidence in surgical patients probably reflects the significant percentage treated by medication alone, both studies may overestimate the incidence of prolactinomas because of the inclusion of nonfunctioning adenomas with hyperprolactinemia caused by pituitary stalk disturbance. Using stricter histological criteria, two large studies from North America found true PRL cell adenomas in only 27–27.5% of surgical cases, nearly equal to nonfunctioning adenomas with 25–26%.

13.2.2 Symptoms and Clinical Signs

The clinical features of prolactinomas are composed of the endocrine effects due to the hyperprolactinemic state

and local tumor mass effects [7]. In adult premenopausal women, central hypogonadism may lead to ovulatory dysfunction with anovulation and infertility, as well as menstrual dysfunction with oligo/amenorrhea (>90% of patients). Consequent estrogen deficiency causes vaginal dryness, edema, and osteopenia. Acne, hirsutism, and obesity may result from an imbalance between androgen and estrogen levels. Decreased libido and mood effects are related to estrogen deficiency and hyperprolactinemia. Galactorrhea is a common symptom, being present in approximately 80% of the women. Premenopausal women usually seek medical attention because of their hormonal symptoms long before the tumor has grown large. In the adult postmenopausal woman, the only expression of hyperprolactinemia may be decreased libido and galactorrhea. The most common clinical symptoms in the adult male relate to central hypogonadism and include decreased libido and potency, infertility because of oligospermia, and osteopenia. Gynecomastia and galactorrhea are unusual. Local tumor mass effects include severe headache, visual field abnormalities, and partial or complete hypopituitarism, each being observed in about one third of male patients. Tumors invading into the cavernous sinus may entrap the cranial nerves III, IV, and VI, with the unusual occurrence of ophthalmoplegias. These patients may rarely also develop pain or hyperesthesia in the distribution of the first division of the trigeminal nerve. Extrasellar extension may cause hydrocephalus and temporal lobe epilepsy.

13.2.3 Diagnostics

13.2.3.1 Synopsis

In addition to prolactinomas, various other causes of a hyperprolactinemic state must be considered. The diagnostic steps should include the exclusion of pregnancy, the exclusion of offending drugs, and the exclusion of a variety of functional causes. If hyperprolactinemia persists despite adequate management of a reversible cause, MRI should be performed. In the absence of clinical symptoms, macroprolactinemia should be considered.

PRL is secreted episodically, so that some levels during the day may be above the normal range established for a given laboratory. Furthermore, stress may induce a two- to threefold rise in PRL levels that lasts less than an hour. Once hyperprolactinemia is confirmed,

a number of etiologies have to be considered. In premenopausal women, pregnancy should be excluded. Postpartum PRL levels remain elevated in lactating women. Sexual breast stimulation and breast suckling may also cause a reflex release of PRL in the nonlactating condition. The most common causes of nonphysiological hyperprolactinemia are medications that alter the central bioaminergic pathways. Neuroleptics are dopamine receptor blockers, which uniformly result in elevated PRL levels, generally to less than 100 ng/mL. Tricyclic antidepressants cause modest hyperprolactinemia in about 25% of patients, whereas monoamine oxidase inhibitors may cause only minimal elevations of PRL levels. The antihypertensive drugs α-methyldopa and reserpine may cause a moderate increase in PRL levels. In patients taking verapamil, PRL levels are found elevated in up to 8.5% of patients. Recently, galactorrhea caused by a significant increase of PRL levels was observed in patients treated with protease inhibitors. Chronic abuse of cocaine or opiates has been associated with mild hyperprolactinemia. Hyperprolactinemia is also found in a number of medical conditions. Elevated PRL levels are found in most patients with end-stage renal disease. Furthermore, about one quarter of patients with renal insufficiency not requiring dialysis have PRL levels in the 25–100 ng/mL range. Basal PRL levels may also be increased in patients with alcoholic or nonalcoholic liver cirrhosis. Primary hypothyroidism is associated with hyperprolactinemia, although PRL levels exceed 25 ng/mL in only 10% of patients. Adrenal insufficiency has rarely been reported as a cause of hyperprolactinemia. Elevated PRL levels have also been found after chest wall and cervical cord lesions, after mastectomy and thoracotomy, and after spinal cord injuries. Ectopic production of PRL is exceedingly rare.

A careful history and physical examination, screening blood chemistry, thyroid function test, and a pregnancy test will exclude virtually all causes of hyperprolactinemia mentioned so far. Stimulation and suppression tests give nonspecific results and have largely been abandoned. If a reversible cause of elevated PRL levels is found, its treatment or discontinuation should allow resolution of the hyperprolactinemia. Otherwise, a radiologic evaluation by MRI of the hypothalamic–pituitary region must be performed to detect an underlying prolactinoma. MRI will also reveal hypothalamic or pituitary stalk disease where the hyperprolactinemia is due to a disturbance of the neuroendocrine control of PRL secretion. In these patients with craniopharyngioma, empty sella, Rathke's cleft cyst, or nonfunctioning pituitary adenoma, PRL levels rarely exceed 250 ng/mL, with PRL levels below 100 ng/mL in the majority of cases. In the vast majority of macroprolactinomas, PRL levels are well above 250 ng/mL, with virtually all above 100 ng/mL. Specific caution is needed when two-site immunoradiometric assays or chemiluminometric assays are used [1]. Incubation with extremely high PRL concentrations saturates both antibodies and prevents sandwich formation ("high-dose hook effect"). Patients with macroprolactinomas and very high PRL levels may seem to have only moderately elevated levels. Therefore, confusion with nonfunctioning macroadenomas associated with pituitary stalk disease may arise. When suspected, PRL levels should be remeasured at a 1:100 dilution. In the absence of any clinical symptoms, macroprolactinemia should be considered as a potential cause of increased PRL levels [4]. The major circulating form of prolactin is little PRL with a molecular weight of 23 kDa, the remainder consisting of big PRL (MW 50 kDa) and big-big PRL (MW >150 kDa). However, in 10–26% of hyperprolactinemic populations, a high proportion of big-big prolactin is found in the serum. Several reports suggest that anti-PRL autoantibodies bound to little PRL contribute to big-big PRL and therefore macroprolactinemia. The diagnosis is made mainly by two methods, a polyethylene glycol method and gel chromatography. Repeated hormone or neuroradiological examinations and unnecessary treatments should be avoided in patients with proven macroprolactinemia (Fig. 13.1).

13.2.4 Staging and Classification

13.2.4.1 Synopsis

Prolactinomas are classified into micro- and macroprolactinomas depending on their size. These may represent two different disease entities. Malignant prolactinomas are exceedingly rare.

Microprolactinomas are less than 10 mm in size, whereas macroprolactinomas are at least 10 mm in size. Macroprolactinomas can be intrasellar or can extend into the extrasellar neighborhood and invade the dura, sphenoid bone, cavernous sinuses, suprasellar cisterns, and adjoining parts of the brain. Careful studies of the natural history of patients who refused

Fig. 13.1 Coronal (*upper panel*) and sagittal (*lower panel*) MRI sections of a patient with macroprolactinoma before (*left*) and after (*right*) therapy with a dopamine agonist. Significant tumor shrinkage is observed
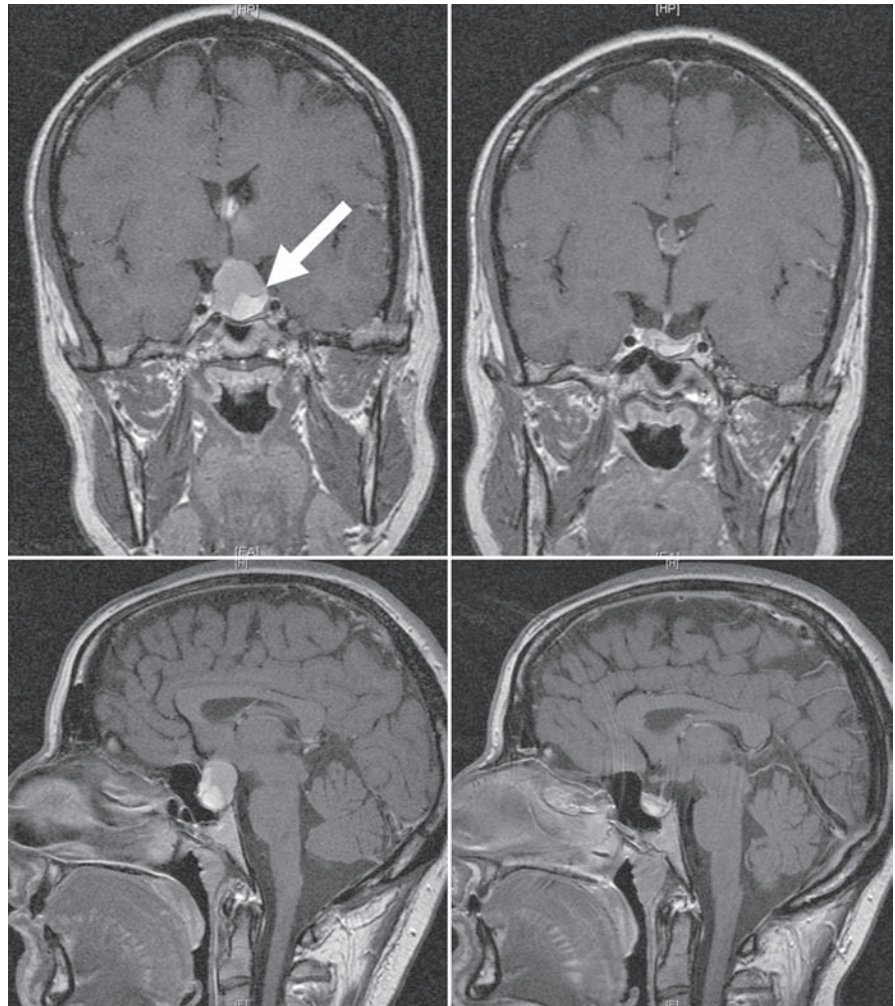
treatment revealed a very low risk of approximately 6.5% for the progression of microprolactinomas into macroprolactinomas. These may therefore be considered two separate disease entities. In agreement, virtually all prolactinomas found at autopsy of subjects not suspected of having pituitary disease while alive were microprolactinomas. True malignant prolactinomas with distant metastasis are exceedingly rare.

By histochemical analysis, frequent sparsely granulated PRL cell adenomas (95% of PRL-producing adenomas) and rare densely granulated prolactin cell adenomas (3%) but also rare acidophil stem cell adenomas (2%) can be differentiated. Prolactin-secreting pituitary carcinomas occur in 0.1–0.5%.

13.2.5 Treatment

13.2.5.1 Synopsis

Observation may be an option in patients with microprolactinomas in the absence of any relevant clinical symptoms. In all other patients with prolactinomas, medical therapy is the initial treatment of choice. Due to its efficacy and tolerability, cabergoline may be the preferred dopamine agonist except for pregnant women, in whom bromocriptine has the most extensive safety record. Transsphenoidal surgery remains an option in patients with resistance to or intolerance of dopamine agonists.

13.2.5.2 Observation

Observation may be considered an option for the treatment of microprolactinomas. Indications for active treatment are tumor progression and symptoms of hyperprolactinemia. However, it has been clearly demonstrated that the vast majority of microprolactinomas will not enlarge. In the absence of specific symptoms, these tumors may be closely followed without any specific treatment. In premenopausal woman, estrogen deficiency should be substituted to prevent the development of osteopenia. Follow-up may be limited to serial PRL levels, as progression of the tumor without an increase in PRL levels is very unlikely. As macroprolactinomas follow a more aggressive course, these tumors should always be treated.

13.2.5.3 Medical Treatment

Medical therapy is employed as the primary therapy of prolactinomas in most centers now. It is based on the use of dopamine agonists. Worldwide, the most experience has been gained with bromocriptine. In several large studies, bromocriptine was able to normalize PRL levels in 70–80% of treated patients. A return of ovulatory menses or normoprolactinemia was observed in 80–90% of patients. The onset of bromocriptine effects is rapid and usually occurs within hours. In premenopausal women, galactorrhea ceases in a few weeks, and ovulatory cycles may return within 2–3 months. In men, restoration of normal sexual/reproductive functions may take 3–6 months. In addition to its effects on PRL levels, bromocriptine often leads to a reduction in lactotroph size and to tumor size reduction. In macroprolactinomas, a significant tumor reduction of at least 25% was found in 68.8% of 112 patients studied in a total of ten studies. Long-term treatment for up to 10 years was well tolerated. Dopamine agonist treatment induces severe alterations of tumor tissue. The cells become dramatically smaller. The cytoplasm shrinks more markedly than the nuclei so that the nuclear:cytoplasmic ratio is increased, and the adenoma appears as a small-cell tumor. The nuclei are irregular and hyperchromatic. In patients with longer term treatment, adenomas develop extensive perivascular and interstitial fibrosis. Single-cell necroses are rarely found. Most series suggest that bromocriptine-induced fibrosis has little effect on later surgical results for microprolactinomas. However, some studies suggest that bromocriptine pretreatment for more than 6–12 weeks may limit complete tumor removal in macroprolactinomas.

Normal PRL levels are maintained in 10–20% of patients stopping treatment. Furthermore, tumor size may remain stable after withdrawal of treatment, especially in patients with marked tumor size reduction during the initial treatment. Substantial visual field improvements were found in 80–90% of patients treated with bromocriptine, with significant changes occurring in some patients within 24–72 h after initiation of therapy. Therefore, even in the patients with macroprolactinomas and visual field abnormalities, immediate surgical decompression is not necessary. The most common side effects of bromocriptine are nausea (50% of patients) and vomiting (10–15%). Other, mostly self-limiting side effects include headaches, orthostatic hypotension, nasal congestion, and constipation. Rare symptoms mostly seen with high doses of bromocriptine are digital vasospasm, alcohol intolerance, and psychotic reactions. Symptoms of the latter include hallucinations, delusional ideas, and mood changes. They usually resolve within 72 h of stopping the drug. Rarely, CSF rhinorrhea is observed, owing to tumor regression. Starting with 1.25 mg once daily with a snack at bedtime minimizes the side effects. The dose is gradually increased to 2.5 mg bid, always taken with meals. Doses higher than 7.5 mg are rarely necessary. In tumors showing an initial response to treatment, regrowth often points to noncompliance.

Second-generation dopamine agonists are currently licensed in many countries for the treatment of prolactinomas. Due to their fewer side effects and ease of application, they may be preferable as the primary treatment in most patients. Cabergoline has a very long half-life and can be given orally (0.25–1 mg) one to three times a week. Treatment should be started with 0.25–0.5 mg weekly, with the dosage gradually being increased. To minimize side effects, cabergoline should be taken at bedtime. In a large prospective, double-blind comparison study, cabergoline was found to be at least as effective as bromocriptine in lowering PRL levels, but with substantially fewer side effects. Furthermore, cabergoline was found to be very effective in reducing tumor size. In a small study of 23 macroprolactinomas without long-term bromocriptine pretreatment, 91% exhibited a greater than 25% reduction in tumor size. In another study of 107 macro- and 97 microprolactinomas, a greater than 30% reduction in tumor size was noted in

71% and 53.6% of patients, respectively. In patients with normalized PRL levels and no evidence of tumor rest, a withdrawal of cabergoline treatment can be safely tried during long-term follow-up. A recent study of 105 micro- and 70 macroprolactinomas found low recurrence rates of 31% and 36%, respectively, during the follow-up of at least 18 months after withdrawal of cabergoline [2]. For inclusion in the study, PRL levels had to be normalized and tumor size reduced by at least 50% during previous treatment. Several studies have demonstrated that cabergoline may be effective in patients who were previously shown to be resistant to treatment with bromocriptine or quinagolide [3]. Quinagolide is a non-ergot, long-acting dopamine agonist. Its efficacy is comparable to bromocriptine, with fewer side effects. It is applied once daily at bedtime in a dose of 75–300 µg. Approximately 50% of patients resistant to bromocriptine were found to respond to quinagolide.

Recently, valvular heart disease has been connected to high doses of dopamine agonists applied in Parkinson's disease. Although such doses are rarely given in prolactinomas and the risk for low-dose treatment of endocrine disease is considered low [5], further long-term analysis is required to determine the cumulative dose associated with an increased risk. It is currently unclear whether the various dopamine agonists used differ in that respect.

13.2.5.4 Surgery

In most centers, surgery is used as an adjunctive therapy for patients who are intolerant of or resistant to medical therapy. In patients who refuse therapy with dopamine agonists or patients with other specific conditions, surgery may also be used as primary therapy. In most patients, transsphenoidal surgery is the surgical procedure of choice [6]. Transcranial surgery is reserved for patients with macroprolactinomas with extensive extrasellar extension. The surgical results depend on the size and the extent of the tumor, but also to a large degree on the expertise of the neurosurgical team. In virtually all cases, prolactin levels fell promptly after tumor removal. In specialized centers, PRL levels may even be measured intraoperatively to check for complete resection of the adenoma. In a large meta-analysis of 34 publications, normalization of PRL levels by 1–12 weeks following surgery was found in 74% of the patients with microprolactinoma and 32% of

those with macroprolactinomas. Tumor recurrence, evidenced by hyperprolactinemia, occurred in 21% and 20% of these cases of microprolactinoma and macroprolactinoma, respectively. Because most recurrences were observed within the 1st year after surgery, they have been attributed to regrowth of tumor remnants. Incomplete tumor removal may be due to invasion of surrounding tissues, as has been found in 69% of microprolactinoma cases. Based on these surgical cure rates and recurrence rates, the long-term cure rates following surgery for micro- and macroprolactinomas were calculated as 58% and 26%, respectively. In patients with giant prolactinomas and those with considerable invasion of the cavernous sinus, surgery is virtually never curative.

13.2.5.5 Radiotherapy

Experience with radiotherapy for the treatment of prolactinomas is limited in comparison to the other two treatment modalities. In most studies, only a small percentage of patients reached normal PRL levels, and then only after a latent period of several years. Hypopituitarism is a major side effect occurring in the majority of patients during long-term follow-up. Other potential side effects include cerebrovascular accidents, neurologic dysfunction, second malignancies, brain necrosis, and optic nerve damage. In most centers, radiotherapy is reserved for the treatment of very aggressive tumors, when treatment with dopamine agonists and surgery has failed. Stereotactic radiotherapy may be more effective and have fewer side effects, but experience is very limited at this point.

13.2.6 Follow-Up/Specific Problems and Measures

13.2.6.1 Pregnancy in Women with Prolactinomas

In an analysis of over 6,000 pregnancies, bromocriptine has not been found to increase the risk of spontaneous abortions, ectopic or multiple pregnancies, trophoblastic disease, or congenital malformations when treatment is stopped at the first sign of pregnancy. Long-term follow-up of children born to mothers

taking bromocriptine in this fashion did not reveal any ill effects. Experience is naturally more limited for cabergoline, with no increased risk of preterm, ectopic, or multiple birth deliveries, or malformations being observed in 265 pregnancies. Most centers still prefer bromocriptine to restore fertility, although pregnant women may be reassured when taking cabergoline prior to conception. The rising estrogen levels during pregnancy have a marked stimulatory effect on the normal lactotrophs. Hypertrophy and hyperplasia result in an up to 1.5-fold increase in pituitary size. Such an increase in size may also occur with prolactinomas, mostly in the second and third trimesters. In a meta-analysis of 19 publications, 1.2% of 363 pregnant women with microprolactinomas and 24% of 82 pregnant women with macroprolactinomas had symptoms of tumor enlargement (headaches and/or visual disturbances). In 69 women with macroprolactinomas treated with surgery or radiotherapy prior to pregnancy, the risk of symptomatic tumor enlargement was considerably attenuated, being 4% in that compilation. Bromocriptine has been used successfully during pregnancy to reduce symptomatic tumor enlargement, with no ill effects on the infant, but experience is limited so far.

In women with microprolactinomas or small infrasellar or inferiorly extending macroprolactinomas, therapy is discontinued following conception and reinitiated only if symptoms of tumor growth develop. In women with larger macroprolactinomas, one should advocate the patient to aim at maximal tumor size reduction by medical treatment prior to pregnancy. At the very least, responsiveness of tumor size to medical treatment should be established. Following conception, treatment with bromocriptine may be stopped or continued during pregnancy, depending on the aggressiveness of the tumor. If symptoms of tumor regrowth develop in the former, therapy may be reinitiated. If medical treatment fails, surgery is recommended. A more conservative approach would be to perform a surgical debulking prior to pregnancy, thereby greatly reducing the risk of symptomatic tumor enlargement during pregnancy. This may be an option especially in patients with tumors unresponsive in size to medical treatment. In patients with macroprolactinomas, once or twice monthly visual field testing is recommended during pregnancy. Postpartum PRL levels and tumor size may be reduced compared with values before pregnancy, possibly due to minor infarctions in the tumor. Breast feeding is possible in women with prolactinomas.

13.3 Acromegaly

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13.3.1 Classification and Epidemiology

Acromegaly is defined by the excessive secretion of growth hormone (GH) into the circulation, leading to its typical clinical features. Most commonly, it is due to a GH-secreting pituitary adenoma [14]. Pituitary carcinoma may be associated with acromegaly, but this is very uncommon. Acromegaly caused by tumors other than a GH cell pituitary tumor accounts for less than 1% of patients. Ectopic production of GHRH may arise from carcinoid tumors of the lung, pancreas, and gastrointestinal tract. Furthermore, entopic GHRH production by intracranial tumors such as hypothalamic hamartomas has been reported. Even more rarely, ectopic GH production by pancreatic tumors, breast and bronchial carcinomas, and ovarian tumors has been demonstrated in a few cases. Rare familial acromegaly syndromes include the multiple endocrine neoplasia 1 (MEN-1) syndrome, McCune-Albright syndrome, Carney syndrome, and isolated familial somatotropinomas of unknown origin.

The prevalence rates of acromegaly reported so far are remarkably similar, being 5.3–6.9/100,000 inhabitants in different countries like the UK, Ireland, Spain, and Sweden. The yearly incidence rates described in these countries were 0.3–0.4/100,000 inhabitants, equivalent to approximately 240–320 new cases in Germany every year. The peak occurrence was observed in the fifth decade. If a GH cell adenoma develops before the epiphyseal growth plates are fused during adolescence, excess growth may result. Therefore, this disease is specifically termed gigantism. Whereas some studies did not find any sex predominance of acromegaly, others reported a female preponderance with a sex ratio of 1.8–2.0:1. Comparisons of the incidence of various types of pituitary adenomas demonstrated GH cell adenomas in 21.4% of 2,252 patients from Italy and 16.4% of 2,230 surgical cases from the USA, based on the clinical activity of the tumors. By immunohistochemical analysis, Terada and co-workers described a similar incidence. They found pure GH cell adenomas and mixed GH and PRL cell adenomas in 13.1% and 6.2% of cases, respectively.

13.3.2 Symptoms and Clinical Signs

Acromegaly is characterized by progressive somatic disfigurement and a wide range of systemic manifestations. Patients generally exhibit coarsened facial features, exaggerated growth of hands and feet, and soft-tissue hypertrophy. Skin changes include skin tags and acanthosis nigricans. Many patients complain about increased "oily" sweating. Cardiovascular features are biventricular hypertrophy, diastolic dysfunction, arrhythmias, hypertension, and endothelial dysfunction, with coronary heart disease and congestive heart failure as possible consequences. Respiratory disease is characterized by macroglossia, upper airway obstruction, and ventilatory dysfunction. Sleep apnea syndrome appears to be common in acromegaly and is probably a cause of major morbidity in these patients. Metabolic changes include insulin resistance, impaired glucose tolerance, and diabetes mellitus, as well as hypertriglyceridemia. Skeletal manifestations are a leading cause of morbidity and functional disability in patients with acromegaly. Acromegalic arthropathy affects both axial and peripheral sites and is generally noninflammatory. Symptomatic carpal tunnel syndrome is a common condition. An increased risk for malignancies in acromegaly is a matter of debate. Acromegaly clearly stimulates the development of benign colonic adenomatous polyps. Such colon adenomas are thought to identify patients at increased risk of developing colon cancer. However, there are conflicting data about the incidence of colon carcinomas in acromegaly. Whereas most studies point to an increased morbidity and mortality, some investigators found similar rates as in their control populations. Obviously, the choice of controls will largely affect the interpretation of the data. We advise patients to undergo routine full-length colonoscopy at the age of 50 years, with further examinations every 3–5 years, depending on the presence of colon polyps. There is no clear evidence for an increased risk of other malignancies. However, the rate of benign tumors in various tissues is increased. Thyroid goiter is considered one typical aspect of the visceromegaly developing in acromegaly. The chance of developing thyroid nodules increases with longer disease duration. Furthermore, acromegaly predisposes to benign prostate hypertrophy and to uterine leiomyomas.

Whereas all the symptoms described above are attributed to the GH and IGF1 excess, others may be due to the mass effects of the pituitary adenoma. These include visual field defects caused by compression of the optic nerve tract or chiasm, cranial nerve palsies, headache, hydrocephalus, and various degrees of pituitary insufficiencies (Fig. 13.2).

13.3.4 Diagnostics

13.3.4.1 Synopsis

Random GH and IGF1 levels may be used as screening parameters in patients with suspected acromegaly. An

Fig. 13.2 Clinical features of acromegaly. The patient exhibits typical coarsened facial features (*left panel*), especially when compared to an old photograph taken 20 years earlier (*right panel*)

adequate age- and gender-matched reference range must be used for interpretation of IGF1 levels. If acromegaly is not excluded by determination of basal levels, an oral glucose tolerance test with measurement of GH levels will help to make the diagnosis.

Current guidelines recommend a fasting or random GH and IGF1 measurement in patients with suspected acromegaly [12]. If GH is less than 0.4 ng/mL and IGF1 is in the age- and gender-matched normal range, acromegaly is excluded in patients with no other intervening disease. Otherwise, an oral glucose tolerance test is recommended with 75 g glucose and subsequent measurement of GH every 30 min over 2 h. GH levels should be suppressed below 1 ng/mL at least at one time-point for acromegaly to be excluded. With the introduction of newer, more sensitive GH assays, it is anticipated that lower cutoff values will be defined in the future. It should be considered that systemic diseases, including catabolic states, hepatic or renal failure, and malnutrition might result in lowered IGF1 levels. However, false-positive results with the failure of normal GH suppression during oGTT may occur in patients with diabetes mellitus, liver disease, renal disease, anorexia nervosa, and during adolescence. Therefore, the evaluation of typical clinical signs and both GH and IGF-1 levels is important, especially in patients with the above-mentioned diseases. Repeat determination of IGF1 may be helpful when IGF1 levels are borderline or clinical and biochemical data are not congruent. Stimulation by TRH, GHRH, or GnRH, measurement of IGF-BP3, and studies of spontaneous GH secretion do not offer additional information for the diagnosis. In the rare case of suspected ectopic GHRH production, circulating GHRH levels may be measured. For follow-up of patients with acromegaly, the same criteria used for the diagnosis are applied to define cure.

The size and extension of an underlying pituitary adenoma are documented by MR tomography. Gadolinium-enhanced coronal and sagittal views in 2-mm slices will give optimal results. In the case of a macroadenoma with a diameter of more than 1 cm, an ophthalmologic examination must be carried out to determine visual field defects. Furthermore, other insufficiencies of the pituitary axis should be investigated in these patients. In contrast, visual field defects or pituitary axis insufficiencies are very rare in patients with microadenomas (diameter of 1 cm). Prior to invasive therapy, co-morbidities should be investigated to determine the individual risk of the patients for the procedure planned.

13.3.5 Treatment

13.3.5.1 Synopsis

Treatment options for acromegaly include surgery, medical therapy, and radiation. Especially in the case of microadenomas, transsphenoidal resection may allow normalization of biochemical parameters in the vast majority of patients. In all other cases, medical treatment may be used as adjunctive therapy. Dopamine agonists are not very effective, but offer oral availability and low costs. Somatostatin analogues have been studied for many years. Long-release formulations effectively lower GH secretion. Furthermore, they may reduce tumor size. GH antagonists are very effective to normalize IGF1 levels. However, tumor growth due to blockade of GH feedback at the pituitary level remains a concern. Both efficacy and side effects of irradiation are a matter of debate. In most centers, irradiation is considered an adjunctive therapy to surgical and medical interventions.

13.3.5.2 Surgery

Selective transsphenoidal surgery is the treatment option offered first to most patients with acromegaly due to a GH-secreting pituitary adenoma [13]. Only very large tumors extending above the sellar region may require a primary or secondary transcranial approach. The aim of the surgical procedure should be complete resection of the GH cell adenoma, with preservation or subsequent restoration of pituitary function. The surgical success rates vary greatly depending on the surgeon's experience. Therefore, especially difficult cases should always be operated on in specialized centers. Criteria suggested for such centers include peer-reviewed publication of surgical results and an annual surgical activity of more than 25 cases/surgeon. Other factors influencing the effectiveness of surgery are size and extension of the tumor mass and preoperative GH levels. Tumor resection generally results in rapid reduction of GH levels. Clinical symptoms improve in >90% of patients and visual field defects in >80%. However, if the rigorous biochemical criteria described above are used to evaluate the success rates of surgery, approximately 80–90% of patients with microadenomas but fewer than 50% of patients with macroadenomas are cured. In patients with surgically accessible residual or recurrent tumor remnants visualized on MRI, reoperation by a specialized

pituitary surgeon may be considered. Intraoperative measurements of GH levels can help to confirm complete resection of the tumor, but experience is limited to a few specialized centers so far. Other techniques introduced recently include neuronavigation, endoscopy, and intraoperative MRI, but definitive data on the impact of these procedures are not yet available. Possible side effects of surgery are newly developed hypopituitarism or visual field defects, permanent diabetes insipidus, hemorrhage, and meningitis. Cerebrospinal fluid leak is treated by lumbar drainage and may require reoperation to seal the sellar defect. Although these complications may occur in up to 10% of patients, experienced pituitary surgeons report significantly lower rates. Intra- or postoperative arterial bleeding may be fatal, but fortunately occurs in very few patients. Altogether, the mortality rate is low at less than 0.5%.

13.3.5.3 Medical Treatment

Drugs currently available for the treatment of acromegaly are dopamine agonists (DA), somatostatin analogues (SA), and GH antagonists. They differ in their efficacy on biochemical parameters and tumor proliferation, in their mode of application, and in their costs.

DAs were the first drugs effectively employed in the medical treatment of acromegaly. In contrast to the physiological stimulation of GH by DA in healthy subjects, a significant suppression of GH may be observed in acromegalic patients. Normalization of IGF1 may be obtained in up to one third of patients. Significant tumor shrinkage is observed in less than 15%. Second-generation DAs like cabergoline and quinagolide demonstrate better efficacy compared with bromocriptine, probably due to better tolerability. Dosages are higher than those required for the treatment of prolactinomas. Side effects include gastrointestinal upset, transient nausea and vomiting, headache, hypotension, nasal congestion, mood disorders, and cold-induced peripheral vasospasm. Due to their significant efficacy in single patients, their oral availability, and their lower cost, we recommend a treatment trial for 3 months in patients with surgically uncontrolled acromegaly.

SAs have been the medical therapy of choice for a considerable time. The two currently available SAs, octreotide and lanreotide, act by binding predominantly to the somatostatin receptor subtype 2, which is especially relevant for suppression of GH secretion. Octreotide is currently available in a short-acting sc-administered form and a long-acting release (LAR) preparation. LAR is usually applied intramuscularly every 4 weeks, but dosing intervals of 6–8 weeks may be sufficient in single patients. Alternatively, lanreotide autogel may be applied every 4–8 weeks by deep subcutaneous injection. New somatostatin receptor ligands with higher affinity to other receptor subtypes are currently under development.

In a large analysis of published reports [11], adjunctive therapy with octreotide LAR over 12–36 months allowed for sufficient GH suppression in 47–75% of patients (average 56%), with IGF1 normalization in 41–75% (average 66%). Tumor shrinkage was observed in about 30% of patients, with a mass reduction of 20–50% in most cases. A bias in some of these studies cannot be excluded, with patients being selected on the basis of their octreotide responsiveness. Interestingly, a recent report demonstrated a significant biochemical improvement in SA-resistant acromegalic patients after addition of cabergoline. Therefore, a combined treatment may be considered in specific patients. Side effects of depot SA therapy include gastrointestinal symptoms like diarrhea, nausea, and abdominal discomfort (≤49% during the early phase of treatment, <10% with persistent symptoms), abnormalities of glucose metabolism (hypoglycemia in 2%, hyperglycemia in 7–15%), injection site pain (4–31%), transient hair loss (3–6%), hypothyroidism (2%), sinus bradycardia, and vitamin B12 deficiency. Biliary tract abnormalities occur in approximately 50% of patients, with development of new gallstones in 4–22% of patients. However, most of these patients remain asymptomatic.

SAs have also been suggested as the primary treatment of acromegaly, considering the low success rates of surgery in patients with macroadenomas. Our review of six studies including 108 patients treated primarily with SA revealed sufficient GH and IGF1 suppression in 62% and 62% of cases, respectively, and significant tumor reduction in 47%. We consider primary therapy with SA an option in patients at significant risk from surgery. However, a randomized study comparing the success rates of surgery and medical treatment has not been presented so far. SA pretreatment in patients destined for surgery may be useful in those with serious medical complications of acromegaly. There are conflicting reports about whether such a pretreatment may also improve the surgical outcome. So far, no

placebo-controlled, randomized trial has been performed to address this issue.

Recently, the GH receptor antagonist pegvisomant became available. Whereas DA and SA function at the level of the pituitary, pegvisomant acts on peripheral GH receptors to block GH action [10]. Therefore, the primary goal of therapy is normalization of IGF1, which has been demonstrated in up to 97% of patients treated for more than 12 months. The fall in serum IGF1 was accompanied by a significant improvement in the signs and symptoms of acromegaly, and notable of insulin resistance. However, a major concern with this very effective drug is its influence on the pituitary tumor volume. In theory, withdrawal of GH feedback at the pituitary level may enhance tumor growth. A recent follow-up on tumor size from 131 patients treated with pegvisomant for a mean of 1 year found relevant tumor growth in two patients. The significance of this observation is currently unknown. Clearly, long-term monitoring of tumor volumes in patients treated with pegvisomant is necessary. Pegvisomant is given as daily subcutaneous injections at doses between 10 and 40 mg. In Germany, it is currently licensed for patients with an inadequate response to or intolerability of other forms of medical treatment. Due to the unknown effect on tumor growth, we do not recommend its use in patients with large pituitary tumors extending near the optic chiasm or tract. Side effects include reversible abnormalities of liver function tests and mild, self-limiting injection site reactions (11% of patients). Due to the former, regular monitoring of liver function is necessary in all patients commencing pegvisomant. Interestingly, recent reports indicate a high efficacy of a combination therapy with somatostatin analogues and pegvisomant. Whereas the former is given in regular doses, the dosing interval of the latter may be reduced to once or twice weekly [15].

13.3.5.4 Radiotherapy

In principle, pituitary irradiation may be applied as fractionated conventional radiotherapy or by stereotactic modalities. The latter include gamma knife, linear accelerators, and particle accelerators, which all offer highly precise, circumscribed delivery of radiation to the target. Radiosurgery is defined as stereotactic radiation in a single session. There are conflicting reports about the efficacy of conventional radiotherapy for the

treatment of acromegaly, administered in fractionated doses not exceeding 1.75 Gy/session, as a slow decrease of GH and IGF1 levels is observed. In a recent study by Biermasz et al. using strict biochemical criteria, normalization of IGF1 was observed in 60%, 74%, and 84% of patients after 5, 10, and 15 years of follow-up, respectively [9]. Normalization of GH suppression during oGTT was found in 65%, 69%, and 71%, respectively. Side effects included pituitary hormone deficiencies, as demonstrated in 29%, 54%, and 58% of patients, respectively. Other possible complications are optic neuropathy, temporal lobe radiation injury, cerebrovascular disease, secondary extrapituitary neoplasms, and neuropsychological disturbances, although causal relations for some of these are controversial. Stereotactic radiosurgery may be an attractive therapeutic alternative because it spares tumor-surrounding tissue. In a recent report by Attanasio et al. with a median follow-up of 46 months (range 9–96 months), IGF1 levels normalized in 23% of patients treated by gamma knife and GH levels fell below 2.5 ng/mL in 37% [8]. Interestingly, tumor shrinkage >25% occurred in 79% of patients at 4 years. Therefore, the gamma knife may be a valid adjunctive tool to control tumor proliferation. However, efficacy and side effects of this new form of irradiation need to be studied in more detail. Overall, radiotherapy modalities are viewed as adjunctive therapies to surgical and medical interventions in most centers. Often, medical therapy is required to bridge the latency period before the onset of radiation effectiveness.

13.4 Thyrotropin-Secreting Pituitary Adenomas, Thyrotroph Adenomas

Takumi Abe, Dieter K. Lüdecke, and Wolfgang Saeger

13.4.1 Introduction and Epidemiology

Thyrotroph adenomas are unusual endocrine lesions that comprise approximately 0.5–2% of all pituitary adenomas [17, 18]. Therefore, such patients are often mistakenly treated for Graves's disease and have long histories of thyroid dysfunction. Consequently, thyrotroph adenomas

often present as macroadenomas with symptoms related to mass effect and hyperthyroidism.

Although thyrotroph adenomas are more easily recognizable as of late due to the wide availability of sensitive and specific thyrotropin assays [17] as well as MRI, they remain uncommon.

In this chapter we briefly describe the clinical features and results of medical as well as transnasal surgically treated patients with thyrotropin-secreting pituitary adenomas since the introduction of improved methods of visualization and microsurgical techniques [16]. For a more detailed description, we refer the reader to consult references [17, 18].

13.4.2 Symptoms and Clinical Signs

The preoperative duration of symptoms ranges from 1 to 15 years (mean 6 years). The patients present with goiter and symptoms of hyperthyroidism, such as tachycardia, palpitations, and diarrhea. Signs of other hormonal abnormalities may be present in relation to tumor size or concomitant hyperprolactinemia, such as amenorrhea, hypogonadism, and gynecomastia. Hemianopsia or visual loss is rarely the leading symptom, though most tumors are macroadenomas.

13.4.2.1 Endocrinological Evaluation

Serum thyrotropin levels (normal range 0.3–3.0 mU/L) are measured by endocrinologists using highly specific thyrotropin assays. The range of TSH in untreated patients with thyrotroph adenomas lies in a wide range between rare normal levels and 568 mU/L. Measurements of serum-free T3 (normal range 2.2–4.7 pg/mL) and free T4 (normal range 0.8–1.8 ng/dL) reveal the hyperthyroidism with non-suppressed TSH. The alpha-subunit of glycoprotein (normal range 0.1–0.3 ng/mL) is also measured nowadays. The alpha-subunit/thyrotropin molar ratio may be calculated to exclude the rare differential diagnosis of resistance to TSH [21].

Other endocrinological findings are assessed on the basis of hormonal levels as described above. Among the endocrine stimulation tests, the thyrotropin-releasing hormone (TRH) stimulation test may be of some value and mostly shows no increase of the already elevated TSH levels. Since there have been reports about tumor bleeding

during this test, the indication has to be carefully considered and explained to the patient. DA and SA should be tested since they may be used as medical treatment.

13.4.3 Classification

13.4.3.1 Radiological Examination

MRI scans are taken before and after gadolinium injections. The tumor classification does not differ from other types of adenomas as described above by E. Laws. Invasion into the cavernous sinus may be sometimes only confirmed or excluded at surgery. Gross nonresectable tumor extension may be classified by MRI and is of great importance for further treatment options [16]. Ectopic sources of TSH hypersecretion except for within the sphenoid, have not been reported so far to our knowledge.

13.4.3.2 Pathological Studies

Histological examination of resected tissue consists of routine staining with hematoxylin and eosin, as well as immunohistological analysis. On light-microscopic studies, adenoma cells are chromophobic. They contain PAS-positive, small, cytoplasmatic granules. Immunohistology reveals TSH within an adenomatous tissue structure, but TSH may be also negative in some. In these cases additional polyclonal TSH antibodies should be used. A large number of thyrotroph adenomas show plurihormonal reactions to prolactin, HGH, gonadotrophins, and even ACTH. Ultrastructurally, thyrotroph adenomas cells are mostly well-differentiated like normal thyrotrophs [23].

13.4.3.3 Medical Treatment

Medical therapy is the first line of treatment in all patients with thyrotroph adenomas. A rare exception is adenomas with rapid deterioration of visual fields and vision where pituitary surgery may be acutely indicated. Regularly, all patients need first medical treatment to achieve normalization of elevated thyroid hormones.

With long-acting SA [17, 19], normalization of TSH and thyroxine as well as considerable adenoma shrinkage has been observed in a high percentage of

macroadenomas. Therefore, nowadays a long-term medical therapy has to be considered, especially if the adenoma is not resectable. Side effects like abdominal discomfort, and diarrhea if persistent, may limit its use. Gallstones should be prevented by additional medication if signs occur during ultrasound investigation.

13.4.3.4 Surgery

Side effects of specific tumor suppressive medication, insufficient response, or the high chance to cure the patient by complete selective adenoma removal are the main present indications for the mostly feasible transnasal surgery.

Direct transnasal, minimally invasive resection of the adenomas is performed according to the described operative technique [16]. At the site of the suprasellar or lateral tumor extension, the pseudocapsule, e.g., of the cavernous sinus is inspected in each case using mirrors and a micro-pressure suction-irrigation, or with endoscopic systems until the site of invasion is detected or excluded. A micro-Doppler instrument is of great value to locate the carotid arteries near or at the adenoma. The main reason for incomplete resection is an overlooked small invasion or a nonresectable adenoma extension. The operative field should at least be completely cleaned at the compressed pituitary site. Microbiopsies of questionable areas may be immediately processed by methylene blue staining of smears or cryohistology of fibrous parts to clarify the border of the anterior or posterior lobe. Thus, in the case of an adenoma rest, the pituitary function may be better preserved by circumscribed localization of radiotherapy.

Intraoperative thyrotropin measurements may be performed using a chemiluminescence assay under continuous anesthesia to calculate the serum half-life of thyrotropin. If the result is less than 60 min, the completeness of adenoma removal is confirmed, and further risky explorations may be avoided. This method as well as the surgical treatment by highly experienced surgeons may improve the results, which have been disappointing in the past [22], to remission rates close to 90%.

Surgery-related deaths are rare, and there were none in our series. Cerebrospinal fluid leakage with revision may occur in up to 8% in these often invasive and firm tumors. Temporary diabetes insipidus was observed at a similar rate. Postoperative isolated transient or even persistent central hypothyroidism may be a result even after selective and radical extirpation of the adenoma, while partial hypopituitarism in experienced hands is rare.

13.4.4 Prognosis/Quality of Life

Criteria for surgical remission [21] not only include total resection of the tumor mass with reduction of serum thyrotropin, free T3, and free T4 levels to normal, but also normalization of the syndrome of inappropriate secretion of thyrotropin (SIST). If thorough endocrinological and radiological examination after at least 4–6 months and a year of follow-up reveals full remission, the prognosis of long-lasting curative effect can be anticipated in about 90% of the patients. A recurrence with both SIST and tumor regrowth, as determined by MRI, may develop in about 10% even several years after surgery.

13.4.5 Future Perspectives

A subtotal thyroidectomy, or subtotal thyroidectomy with either radioiodine thyroid ablation or treatment with antithyroid medication, or radioiodine thyroid ablation have been performed in about half of the patients before the definite causal treatment of the underlying pituitary adenoma was initiated. With a greater awareness and nowadays refined diagnostic tools, the delay before diagnosis might be reduced. With combined medical–microsurgical as well in last instance radiation methods, most patients with thyrotroph adenomas may be cured or at least effectively controlled.

13.5 Cushing's Disease

Jörg Flitsch, Dieter K. Lüdecke, and Wolfgang Saeger

13.5.1 Epidemiology

Cushing's disease is caused by ACTH-secreting (corticotroph) pituitary adenomas. It was first systematically described by Harvey Cushing (1869–1939) in 1932 [27].

In general, Cushing's disease is a rare condition. The estimated prevalence is 2–5 cases per 100,000 with an incidence of 0.25 cases per 100,000 per year. ACTH-secreting pituitary adenomas account for about 10% of all diagnosed pituitary adenomas. Cushing's disease can develop at any age, but signs usually appear between the third and fifth decades. Cushing's disease is predominantly found in women, with a gender ratio of 3:1 to 5:1.

13.5.2 Symptoms and Clinical Signs

The symptoms and clinical signs associated with Cushing's disease are caused by the pathological cortisol production, which results in increased peripheral proteinolysis and lipolysis, as well as glycogenolysis and gluconeogenesis. Consequently, a hyperglycemic (diabetic) state develops, causing increased insulin secretion. This leads to stronger lipogenic than lipolytic effects in the trunk, but rarely in the extremities. This pathomechanism causes the most obvious clinical signs including truncal obesity, buffalo hump, and moon facies. The increased protein catabolism leads to muscle atrophy, osteoporosis, and skin atrophy. The skin atrophy coupled with the stretching of the subcutaneous tissue as well as increased subcutaneous venous plexus results in striae rubrae distensae. A typical complication of muscle atrophy is proximal myopathy, which renders patients incapable of standing up from a squatting position. Impaired bone mineralization and enteral calcium absorption lead to osteoporosis, kyphosis, and pathological fractures. Hypertension is commonly found in Cushing's disease cases. Fatigue, psychological changes (depression), and impaired physical performance are generally found. Patients have an increased risk of thrombosis. Decreased lymphocytes and neutrophil/eosinophil granulocytes cause immunosuppression and thus a higher frequency of (fungal) infections, acne, and impaired wound healing. In children, growth is often impaired. In men, impaired libido, erectile dysfunction, and oligospermia are characteristic due to decreased testosterone levels. In women, oligo- or amenorrhea, hirsutism, and acne are common due to increased adrenal androgen secretion.

13.5.3 Diagnostics

In cases of suspected Cushing's disease, the initial diagnostic step is to prove the state of hypercortisolism. Day profiles of plasma or salivary cortisol levels, 24-h urine sampling of free cortisol or 17-hydroxycorticoids secretion, or the low-dose dexamethasone suppression test (1 or 2 mg) are widely used to prove the hypercortisolemic state. Recently, late-night salivary or plasma cortisol levels (between 10 pm and midnight) have proven to be very reliable in the detection of hypercortisolism. Once the hypercortisolism is established, the etiology of the disease should be determined. The next step is ACTH testing. Normal or slightly elevated ACTH levels are highly suspicious for a pituitary pathology. The combination of the high-dose dexamethasone suppression test (8 mg) and the CRH-stimulation test (1 µg/kg) is generally accepted for the differentiation of pituitary-dependent and ectopic Cushing's syndrome [31, 34]. If both tests are positive, a pituitary origin is found in more than 95% of patients.

After endocrinological testing, MRI of the pituitary is essential (T1WI coronal and sagittal sequences, gadolinium-DTPA enhanced, thin slice technique). Despite advances in imaging techniques, up to 50% of MRIs show no signs of an adenoma. Pituitary exploration using the transsphenoidal approach will reveal the hidden microadenoma in most of these cases [29, 31].

In cases where endocrinological results are ambiguous, invasive catheter studies with venous blood sampling from the inferior petrosal sinus (IPSS) [36] and cavernous sinus (CSS) [30] have been developed to distinguish further between pituitary and ectopic Cushing's syndrome. CSS is also gaining wider acceptance as a localization aid for the mostly lateralized adenomas within the pituitary [30, 40] (Fig. 13.3).
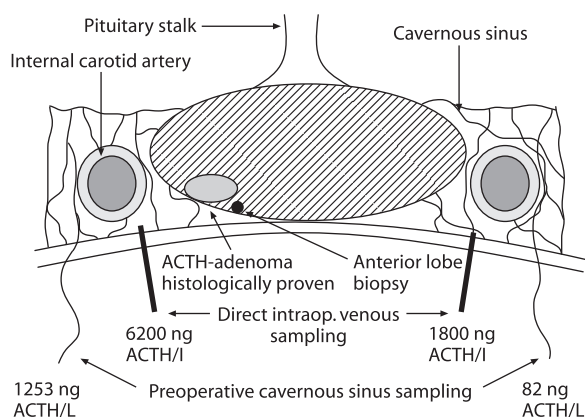
Fig. 13.3 Example of pre- and intraoperative hormone findings using special techniques; preoperative cavernous sinus sampling, intraoperative cavernous sinus sampling

13.5.4 Classification

Pituitary adenomas are generally classified by size and hormone secretion. In Cushing's disease, about 90% of all adenomas are microadenomas of less than 10 mm diameter; 75% of all adenomas are under 5 mm. In older classifications, the tumors were histologically described as basophil or chromophobe adenomas. Using improved techniques including Epon embedding and immunostaining with specific ACTH antibodies, a subdivision into densely or sparsely granulated corticotroph adenomas can be made [38].

ACTH-cell hyperplasias are rarely found to be the source of pituitary-dependent hypercortisolism. For some time, increased hypothalamic CRH secretion was considered a possible cause of Cushing's syndrome (hypothalamic Cushing's syndrome), but this has not been confirmed except in true CRH-secreting tumors [24].

Up to 30% of patients with ACTH adenomas develop Nelson's syndrome after bilateral adrenalectomy [33]. Nelson's syndrome is often characterized by an aggressive growth of the pituitary ACTH adenoma with skull base infiltration. Histologically, the tumors do not differ from other ACTH adenomas. Hyperpigmentation due to ACTH and MSH (melanocyte-stimulating hormone) co-secretion is common.

Pituitary carcinomas, defined by brain invasion and/or proven metastatic tumor spread, are found in only 0.1% of all pituitary tumors [40]. Systemic metastasis is extremely rare. Of over 800 treated Cushing's disease cases in Hamburg over the last 30 years, there were only 2 ACTH-secreting pituitary carcinomas with proven metastatic tumor spread. In these cases, the patients underwent adrenalectomy and pituitary radiation prior to carcinoma development (Fig. 13.4).
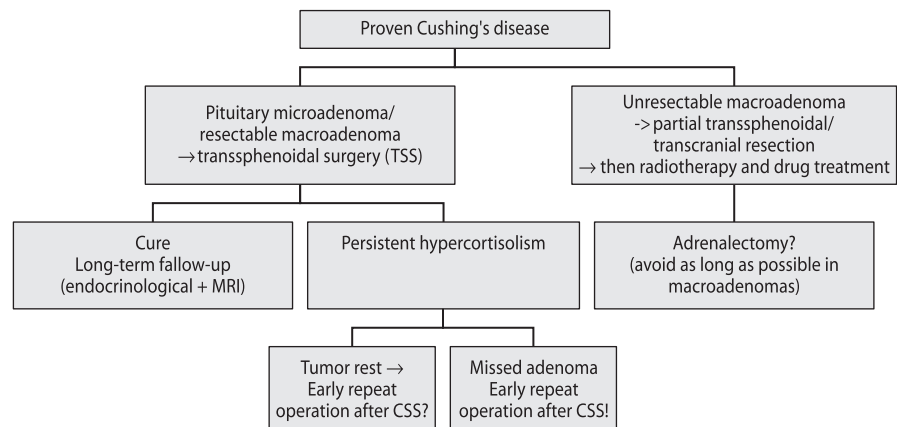
13.5.5 Treatment

A synopsis is provided in Fig. 13.5.
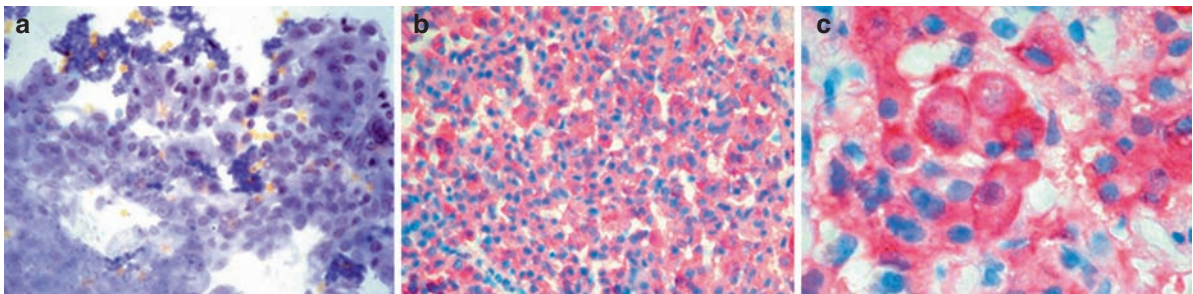
Fig. 13.4 Cushing's disease. Intraoperative cytology (**a** methylene blue staining, 1%; magnification ×100) and postoperative immunohistology (**b** anti-ACTH staining, magnification ×100) of an ACTH-cell adenoma; **c** adjacent anterior lobe tissue with typical changes of hypercortisolism (Crooke cells, ACTH-positive cells with annular intracytoplasmatic hyalinization, paranuclear vacuoles, and sparse mucoid residual granulation), anti-ACTH staining, magnification ×250

Fig. 13.5 Treatment algorithm for ACTH-secreting pituitary adenomas. In special cases, consider transcranial surgery and/or bilateral adrenalectomy

13.5.5.1 Surgery

Transsphenoidal Surgery

Currently, the selective adenomectomy of the ACTH-secreting pituitary adenoma via the transsphenoidal approach (microscopically or, less frequently, endoscopically) is the treatment of choice for Cushing's disease [26]. Only the pathologic tissue and a small rim of the surrounding anterior lobe as a safety zone are resected. Specialized pituitary surgeons, using additional techniques like intraoperative cavernous sinus sampling, cytology, ACTH measurement from tissue samples [30, 31], or intraoperative MRI [29], have published remission rates for microadenomas of 70–96% [29, 31, 37]. In macroadenomas (~10%) remission after surgery is achieved in only about 50–60%. Para- and suprasellar invasive tumor extension may hinder complete surgical resection. Complications following transsphenoidal surgery are rare [29, 39]. The mortality after surgery by experienced hands is approximately 1%. Injuries to the internal carotid artery can occur. CSF leaks are reported in 2–4% of cases; meningitis cases are rare. A transient phase of diabetes insipidus (DI) is found in 10–15%; seldom is it persistent. Oculomotor palsy (mostly transient) occurs in about 1% of patients. Hormonal insufficiencies of the anterior lobe (partial or complete) are reported in 6–19%. Recurrence rates of hypercortisolism range between 9% and 25%, dependent on the surgeon's experience and follow-up time [29, 37].

Transcranial Surgery

The transcranial approach (pterional/frontotemporal) is usually reserved for patients with an extensive para- and suprasellar tumor extension, inaccessible via the transsphenoidal approach. In specialized centers, transcranial surgery for Cushing's disease is performed on less than 5% of all patients. Complication rates are higher than with transsphenoidal surgery and may include damage to the pituitary stalk (complete hypopituitarism), optic nerves/chiasm, or frontal lobe (via retraction).

Bilateral Adrenalectomy

Historically, the surgical treatment of Cushing's disease has progressed from the total bilateral adrenalectomy to the selective, transsphenoidal adenomectomy. The removal of the adrenal glands immediately results in persistent hypocortisolism, requiring life-long glucocorticoid and mineralocorticoid replacement. Surgically, the endoscopic technique is gradually replacing the open approach. Due to the permanent adrenal insufficiency and the risk of Nelson's syndrome, bilateral adrenalectomy is now mostly reserved for persistent Cushing's disease after transsphenoidal surgery and radiation therapy.

13.5.5.2 Radiotherapy

Conventional Radiation Therapy

Conventional radiotherapy usually consists of an overall dosage of 45–50 Gy, applied over 5–6 weeks at 180–200-cGy fractions. The present techniques include the three-field (lateral, opposed, and vertex), 360° rotational field, and moving arcs radiation. Remission rates of 50–60% have been published after radiation therapy for Cushing's disease. Lower overall dosages have led to significantly lower remission rates.

Stereotactic Radiosurgery and Fractionated Stereotactic Radiation Therapy

The development of stereotactic radiation methods has made high-precision radiation of one or more isocenters possible. Local radiation dosages of 20 Gy and more are achieved in one session, with a significantly lower radiation dosage to the border tissue. Possible stereotactic radiosurgery methods include gamma-knife and Linac-based systems. The use of heavy charged particle (protons or alpha) beams has become less common. Successful correction of hypercortisolism after gamma-knife radiosurgery of 63–100% within 1–5 years has been published. Long-term follow-up of gamma-knife radiosurgery reported neither radiation-related deaths nor visual loss. However, anterior lobe insufficiencies occurred in 66% of cases.

The use of multiple convergent radiation beams in 180–200-cGy fractions with a total dose of 50 Gy can reduce the risk of optic system damage [32].

Interstitial Brachytherapy

Stereotactic or transsphenoidal implantation of radioactive labeled seeds (Y-90, J-125, Au-198) was performed

in some specialized centers, either as primary treatment or as secondary treatment for invasive, nonresectable adenomas. Success rates of up to 77% have been reported, but anterior lobe deficits are common. Noninvasive stereotactic radiotherapy methods have essentially replaced interstitial brachytherapy.

13.5.5.3 Pharmacotherapy

ACTH-Release Inhibition

Serotonin antagonists, GABA inhibitors, dopamine agonists, and somatostatin analogues (octreotide, lanreotide) have been tested for the treatment of Cushing's disease due to these drugs' possible effects on CRH or ACTH synthesis or release. All these substances showed insufficient results alone, but dopamine agonists are sometimes used in combination with steroid synthesis inhibitors [35]. A new approach may be the use of a recently developed multiligand somatostatin analogue (parsireotide), which showed promising results in cell culture [25] as well as in a phase 2 study of selected Cushing's disease patients (preliminary, unpublished data).

Inhibition of Steroid Synthesis or Effects at the Receptor

Steroid synthesis inhibitors like metyrapone, ketoconazole, aminoglutethimide, or o,p-DDD act via the direct inhibition of one or more enzymatic steps of cortisol synthesis. At higher doses (>4 g/day), o,p-DDD achieves remission rates of up to 80%. However, side effects, such as adrenal cortex destruction and hepatopathy, are common. At doses of 400–1,600 mg, effective cortisol reduction was reported in 70% of patients treated with ketoconazole [35].

Mifepristone (RU 486) competitively binds to the glucocorticoid receptor and inhibits cortisol effects. Experience is so far very limited, and the substance is available for research purposes only.

Overall, transsphenoidal surgery is currently the primary treatment of choice for Cushing's disease. The available pharmacotherapy and radiotherapy are generally secondary treatment options. Pharmacotherapy at lower doses has limited effects and often has severe side effects at higher doses. The major disadvantage of any kind of radiation therapy is the delay between treatment and the desired effects. Remission after radiation therapy usually takes 2–10 years. Another disadvantage lies in the commonly resulting anterior lobe insufficiencies (24–65% in 5–10 years), especially following conventional radiation therapy. For severely ill Cushing's disease patients who are unable to undergo surgery, stereotactic radiotherapy should nevertheless be considered as a primary option.

13.5.6 Prognosis/Quality of Life

The average time span between the first symptoms of Cushing's disease and consultation of professional help is approximately 1 year. However, the delay between first consultation and diagnosis averages over 4 years. Untreated, Cushing's disease increases the risk of premature death within 5–15 years due to diabetes mellitus, hypertension, and myocardial damage. With symptomatic treatment alone, survival times of 20 years after onset of disease have been reported. About two of three patients with Cushing's disease show significant symptoms of excitability and depression before treatment.

After diagnosis and successful correction of hypercortisolism, most patients notice an increase of physical well-being within 6–8 months [28]. The risk of premature death decreases after successful treatment unless secondary changes have already manifested.

13.5.7 Follow-Up/Specific Problems and Measures

After successful surgery, cortisol levels usually drop to subnormal levels within 20 h, necessitating glucocorticoid replacement. This period of secondary adrenal insufficiency lasts an average of 18 months. In a minority of successfully treated patients, normocortisolism is achieved without an initial period of hypocortisolism. These patients need careful follow-up to rule out recurrence of disease. Proper tools for the initial assessment of surgical results are determination of cortisol and ACTH decrease in plasma (or lately cortisol in saliva) in the early postoperative phase prior to hydrocortisone substitution. Others recommend perioperative glucocorticoid substitution, followed by later assessment of the pituitary-adrenal axis. In either case, the anterior lobe

and posterior lobe function of the pituitary should also be evaluated. Patients should have a careful endocrinological re-evaluation of the corticotroph function twice a year for the first 2 years and annual follow-ups thereafter. MRI of the pituitary is recommended about 6 months postoperatively and should be repeated at 2- to 3-year intervals [31]. After radiotherapy, a normalization of cortisol levels may occur in as soon as 1–2 years. Follow-up should be performed semiannually. Life-long follow-up is important after all therapies to detect recurrences as early as possible. One of the best tools for early detection is late-night salivary cortisol sampling.

13.5.8 Future Perspectives

Due to the success of transsphenoidal surgery in most cases, future research should focus on solutions for "problematic" cases with undetectable, minute adenomas or invasive tumors. Further localization techniques, e.g., improved visualization via MRI and specific contrast enhancement, could improve the preoperative diagnostics of minute adenomas. For invasive (macro-) adenomas unresectable by surgery, advances in pharmacotherapy (e.g., specific receptor-bound drug delivery to adenoma cells) could lead to improved results.

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