Hyperprolactinemia

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Pathophysiology

PRL is secreted by the lactotrophs, present in the anterior pituitary gland, and its secretion is under the inhibitory control of hypothalamic dopamine that reaches the anterior pituitary gland through the portal circulation via the pituitary stalk. Sellar and suprasellar tumors, as well as inflammatory and infectious diseases evolving pituitary stalk, prevent the inflow of the dopamine to lactotrophs, increasing PRL secretion. Moreover, there are several factors releasing PRL secretion, as estrogens, serotonin, thyrotropin-stimulating hormone (TRH), and vasoactive intestinal peptide (VIP) [1].

Hyperprolactinemia, defined by elevated serum PRL levels above the normal range, is the most common hypothalamic-pituitary dysfunction and can result from several causes, as physiological conditions (pregnancy, breastfeeding, stress); pharmacological and pathological status, like kidney and liver failure, hypothyroidism, pituitary adenomas, tumors, or other inflammatory diseases of the hypothalamic-pituitary region; and macroprolactinemia. Prolactinomas, adenomas with autonomous secretion of PRL, are the most common pituitary tumors, with a prevalence of 100 cases per million, more often reaching young women, being ten times more frequent in females aged 20–50 years old than in males. Nevertheless, the prevalence becomes similar between genders in adults over 60 years old [1]. The differential diagnosis of hyperprolactinemia is essential for its proper treatment.

Secretion and pulsatility of gonadotropin-releasing hormone (GnRH) is impaired in hyperprolactinemia, probably via kisspeptin [2], leading to gonadotropin deficiency and consequent hypogonadism. The classic manifestations are sexual dysfunction, infertility, menstrual irregularities, and bone mass loss [1]. Galactorrhea, often found among women with hyperprolactinemia, is not a mandatory or specific sign. Batrinos et al. evaluated 404 women with galactorrhea, with and without irregular menses, and the prevalence of hyperprolactinemia was 42% and 15%, respectively [3]. Mass effects as headache and visual disturbances are often found [1] in macroprolactinomas and other tumors of the hypothalamic-pituitary region.

Key Points for Diagnosis

Hyperprolactinemia is defined when serum PRL levels are above the normal reference value (usually 20–25 ng/ml in females, 15–20 ng/ml in males) [4]. The stress of venipuncture can increase PRL secretion, frequently at levels slightly above the normal value. When blood collection is performed after rest, about 30% of asymptomatic individuals with mild hyperprolactinemia present with normal hormonal levels [5]. Nevertheless, rest for blood withdrawal is not routinely recommended.

Serum PRL evaluation should be performed only when clinically indicated [1].

Differential Diagnosis

After confirming the diagnosis of hyperprolactinemia, the following etiologies should be evaluated [6]:

- Physiological: pregnancy and lactation and mammary stimulation.
- Pharmacologic: neuroleptic and antipsychotic medications (sulpiride, chlorpromazine, risperidone, haloperidol), antidepressants, opioids, cocaine, antihypertensive medications (verapamil, methyldopa), drugs that act in the gastrointestinal tract (metoclopramide, domperidone), protease inhibitors for AIDS treatment, and the use of estrogens.
- Associated with systemic diseases: kidney and liver failure.

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- Associated with endocrinological diseases: primary hypothyroidism, polycystic ovarian syndrome (PCOS), and Addison's and Cushing's diseases.
- Other tumors of the hypothalamic-pituitary region or infectious/infiltrative disorders compromising the pituitary stalk [7], as pituitary nonfunctioning macroadenomas, craniopharyngiomas, metastasis, lymphocytic hypophysitis, sarcoidosis, and tuberculosis; in addition post-surgery or radiotherapy status can also lead to hyperprolactinemia.
- Intercostal nerves stimulation.
- Autonomous PRL secretion by pituitary adenomas: prolactinomas, mixed PRL and GH secretion tumors.
- Macroprolactinemia.
- Mutant prolactin receptor.
- Idiopathic.

In pharmacological hyperprolactinemia, a new serum PRL evaluation should be performed after 3 days of withdrawal of the suspected drug, if possible. Otherwise, the patient should undergo magnetic resonance imaging (MRI) of the pituitary to rule out pathological causes [8].

In primary hypothyroidism, increasing PRL secretion is attributed to TRH, and serum PRL levels should decrease and become normal after appropriate levotiroxine replacement [9].

Regarding polycystic ovarian syndrome (PCOS), more recent studies did not confirm any pathophysiological relationship with hyperprolactinemia, and the coexistence of these two conditions could just be a random association [10]. Therefore, in patients who remain with irregular menses after reaching normal serum PRL levels, it is important to exclude other causes for the symptoms, such as PCOS.

Mammary stimulation in nonpregnant women, as chest wall disturbances (herpes zoster, mechanical or chemical trauma), can lead to increased levels of PRL due to neurogenic reflex [11]. Breast clinical examination, mammography, and ultrasound have minimal effect on serum PRL levels [12].

Macroprolactinemia is characterized by the predominance of the PRL isoform big-big-PRL (macroprolactin), which occurs in about 25% of hyperprolactinemic individuals. According to its molecular weight, PRL is classified as monomeric, dimeric, and macroprolactin. Monomeric PRL corresponds to more than 50% of total circulating PRL, and it is considered the biological active isoform, while macroprolactin has low biological activity [13]. In an individual with macroprolactinemia and normal serum concentrations of monomeric PRL, symptoms related to hyperprolactinemia are not expected [14, 15]. Macroprolactinemia is an important cause of dissociation between clinical and laboratory findings, and its screening should be performed in asymptomatic hyperprolactinemic individuals in which the request for the initial PRL evaluation is debatable. However, symptomatic hyperprolactinemia can occur in macroprolactinemic patients when monomeric isoform is also elevated [15].

Dealing with a patient with symptomatic hyperprolactinemia, when pregnancy, use of medications that may cause hyperprolactinemia, kidney failure, liver failure, and hypothyroidism are excluded, sellar MRI should be performed in order to identify a pituitary tumor with autonomous PRL secretion (prolactinoma), or other tumors of the sellar region, as well as infiltrative or infectious diseases, are the cause of hyperprolactinemia by pituitary stalk disconnection. Serum PRL is usually proportional to the tumor size in prolactinomas: in microprolactinomas, serum PRL levels up to 200 ng/ml are expected, while in macroprolactinomas, frequently values above these levels are found [16]. Karavitaki et al. [17] evaluated serum PRL levels in patients with pituitary nonfunctioning tumors with pituitary stalk disconnection, and in 98.7% of the cases, levels were lower than 95 ng/ml. Therefore, in hyperprolactinemia due to disconnection, serum PRL does not exceed 100 ng/ml, with few exceptions. The differentiation between a hyperprolactinemia due to disconnection and prolactinomas is essential, especially in the presence of mass effect, in order to indicate proper therapy.

A heterozygous mutation in prolactin receptor gene was described in three sisters, two of whom presented with oligomenorrhea and one with infertility. The amino acid substitution leads to loss of function and prolactin insensitivity [18]. When all the abovementioned causes were ruled out and sellar MRI is normal, diagnosis of idiopathic hyperprolactinemia is made, albeit the presence of microadenomas not detectable in the image cannot be excluded [6].

Current Therapies and Future Perspectives

Treatment goals include restoration of eugonadism and resolution of galactorrhea. In the presence of macroadenoma, treatment also aims to reduce its size and preserve, or even restore, pituitary function when impaired. The therapeutic modalities available for prolactinomas are medical, surgical, irradiation, and their associations.

Medical Treatment

Dopamine agonists (DA) are the gold standard for the treatment of prolactinomas being most represented by bromocriptine (BRC) and cabergoline (CAB). This class of drugs promotes PRL gene transcription inhibition, PRL secretion decrease, as well as reduction of prolactinoma dimensions [1]. CAB became the drug of choice due to its better tolerance and efficacy, explained by the high affinity and specificity to dopamine receptor subtype 2 [1]. The initial dose of CAB usually is one tablet (0.5 mg) twice per week, after dinner, and the titration is carried out according to the decrease of PRL levels and tumor dimensions [19]. CAB leads to normal serum PRL levels in over 85% of patients and tumor

reduction by more than 80% of them, while BRC promotes normal serum PRL levels in 80% and reduction of tumor dimensions in 70% of cases [20].

The most common DA side effects are nausea, vomiting, and postural hypotension and rarely nasal congestion, cramps, and psychiatric disorders [21]. CAB, in higher doses, was related to valvulopathy in patients with Parkinson's disease, usually older patients with other comorbidities that could contribute to increase the risk of heart valve disease. CAB, not BRC, has an agonist activity at serotonin receptor 5HT2B, which can promote fibroblast proliferation and valvular insufficiency, especially in tricuspid and pulmonary valves. However, valvulopathy due to CAB treatment for hyperprolactinemia is still controversial. Among 17 studies published about this issue [22–33], only one showed an association between CAB's use and the presence of moderate tricuspid insufficiency [24]. Moreover, in other four [23, 26, 29, 32] there was a higher prevalence of valvular regurgitation, especially in the tricuspid valve, without clinical repercussion. In two studies, valve structure changes were described, with a greater risk of fibrosis [31] and calcification [32] compared to the control group. Nonetheless, in our opinion individualized monitoring with echocardiography is desirable until more consistent data will be available. Recent data pointed to remission of hyperprolactinemia after withdrawal of the drug in a substantial number of patients. Passos et al. [34] pointed to normoprolactinemia after BRC withdrawal in 20.6% of patients (25.8% in microprolactinomas and 15.9% in macroprolactinomas) after drug use for a median time of 44 months. Even higher remission ratios were observed by Colao et al. [35] using CAB for a median time of 40 months (69% in microprolactinomas and 64% in macroprolactinomas). Notwithstanding, Dekkers et al. [36], in a recent meta-analysis of 19 studies about DA withdraw, showed that the mean number of patients in remission was 21% with a higher non-significant tendency toward CAB (35%) compared to BRC (20%). Two other meta-analysis published in 2015 [37] and 2018 [38], including 637 and 1106 patients on DA, showed remission rates of 35% and 36.6%. Lenght of treatment, tumor reduction, normoprolactinemia and low dose of CAB at withdrawal were factors associated with remission. Although the guideline of Endocrine Society [21] suggests that DA suspension should be performed gradually, in patients treated for at least 2 years, we suggest that the removal of DA should be individualized. In the last few years, impulse control disturbance were reported from 8 to 61% in patients harboring prolactinomas on CAB, especially hypersexuality. These symptoms should be actively investigated in the medical interview [39].

In patients with drug-related hyperprolactinemia when drug cannot be discontinued and in patients with idiopathic hyperprolactinemia or microprolactinomas without desire of fertility (particularly with resistance or intolerance to DA), hormonal replacement can be indicated [19].

Surgical Treatment

Considered secondary in the therapeutic algorithm of prolactinomas, the indications for surgery include patient's desire in non-invasive microprolactinomas, DA resistance/persistent intolerance, absence of visual impairment reversal in a short period of DA use, symptomatic apoplexy, cerebrospinal fluid leakage, and/or visual compromise due to tumor shrinkage with chiasma retraction with DA treatment. Surgery is usually performed through microscopic or endoscopic transsphenoidal route, and their results depend on neurosurgeon's experience and skillness, on serum PRL levels, and on tumor's size and the invasiveness. Gillam et al. [40] reviewing 50 surgical series showed remission in 74.7% of microprolactinomas and in 33.9% of macroprolactinomas. Of note, the recurrence rate in this same analysis was 18.2 and 22.8%, for microprolactinomas and macroprolactinomas, respectively.

Radiotherapy

Prolactinomas are among the most radioresistant pituitary adenomas, and therefore radiotherapy is limited to aggressive tumors resistant to usual treatments. Gillam et al. [40] reviewing published data show that the normalization average of PRL levels was similar with radiotherapy by conventional technique (34.1%) or by stereotactic (31.4%) approach. Side effects include optic tract damage, 50% risk of hypopituitarism in 10–20 years, neuropsychological disturbances, development of secondary tumors, and stroke.

Fertility and Pregnancy

Treatment with DA restores fertility in most cases. In the absence of response to drug treatment, and in cases of microprolactinomas or intrasellar macroprolactinomas, ovulation induction with clomiphene citrate or recombinant gonadotropins may be used [41].

The risk of tumor growth with clinical consequences during pregnancy is up to 5% in microprolactinomas, making DA withdrawn upon confirmation of pregnancy a safe procedure. Clinical follow-up should be done in each pregnancy trimester, a systematic assay of PRL not being indicated. In the presence of significant headache or visual complaints confirmed by a neurophthalmologic evaluation, sellar MRI without contrast is indicated, preferably after the first trimester. If a significant tumor growth is detected, DA should be reintroduced. In patients with macroadenomas, however, the risk of clinical significant tumor growth with is higher: 15–35%. Therefore, in patients with expansive macroprolactinomas, tumor reduction within the sellar boundaries preferable for at least 1 year of treatment with DA, before allowing pregnancy, is highly desirable. In cases of no tumor shrinkage, surgical treatment is indicated. The maintenance of DA throughout pregnancy is up to the specialist discre-

tion. Neurophthalmological evaluation should be performed periodically. Reintroduction of the drug is indicated when tumor growth occurs. If this is not effective, surgical treatment should be performed, preferably in the second trimester [42]. A multicentric Brazilian study including 233 pregnancies induced by CAB confirmed previous results of safety in materna and fetal outcomes in CAB-induced pregnancies. Although CAB maintenance after pregnancy comfirmation was associated with higher miscarriage rates [43]. In men, in addition to sexual dysfunction, hypogonadism related to hyperprolactinemia can promote changes in sperm quality, mainly asthenospermia [44]. In men with prolactinoma on DA with persistent hypogonadism, with or without normalization of serum PRL, the use of clomiphene citrate has been proven useful in the recovery of the gonadotropic axis. This approach has advantages over testosterone replacement by restoring fertility [45].

Addressing Prolactinomas Resistant and/or Aggressive

Aggressive pituitary tumors are defined by the presence of extensive expansion or invasiveness of neighboring structures, rapid tumor growth or recurrence, or the presence of giant tumor, with more than 4 cm in diameter. Diagnosis of pituitary carcinoma is performed only in the presence of metastases. They are extremely rare, being PRL secretion tumors the most prevalent. Aggressive prolactinomas are more common in young male patients. The prevalence of prolactinomas resistant to DA is approximately 10% of microprolactinomas and 18% of macroprolactinomas [1]. Reduction of dopaminergic D2 receptors is its principal mechanism [46].

The initial strategy to treat patients partially resistant to DA is the stepwise increase dose. Ono et al. [25] achieved normalization of PRL levels in 96.2% of patients with dose up to 12 mg per week of CAB, an exceeding elevated dose. For agressive/invasive prolactinomas, temozolomide can be used, with or without radiotheraphy, with tumor control in about 60% of cases. Nevertheless, lenght of treatment in responsive cases and failure in second attempt are important questions related to this chemotherapy [47]. Two cases of resistant prolactinomas were sucessfully treated with Pasireotide [48]. Lapatinibe were used in four agressive/invasive prolactinomas, with tumor control in thee [49]. Other therapies as estrogen pathway modulators and mTOR/akt inhibitors may be promissing therapies [50].

Surgical treatment, even non-curative, may be effective in obtaining normoprolactinemia in patients partially resistant to DA, who may subsequently respond to cabergoline reintroduction [51, 52].

Summary: Diagnosis and Treatment

Hyperprolactinemia is a major cause of hypogonadism and infertility, especially among young women. Proper diagnostic of its cause is essential for appropriate treatment indication. Figure 5.1 summarizes the steps for diagnosis in

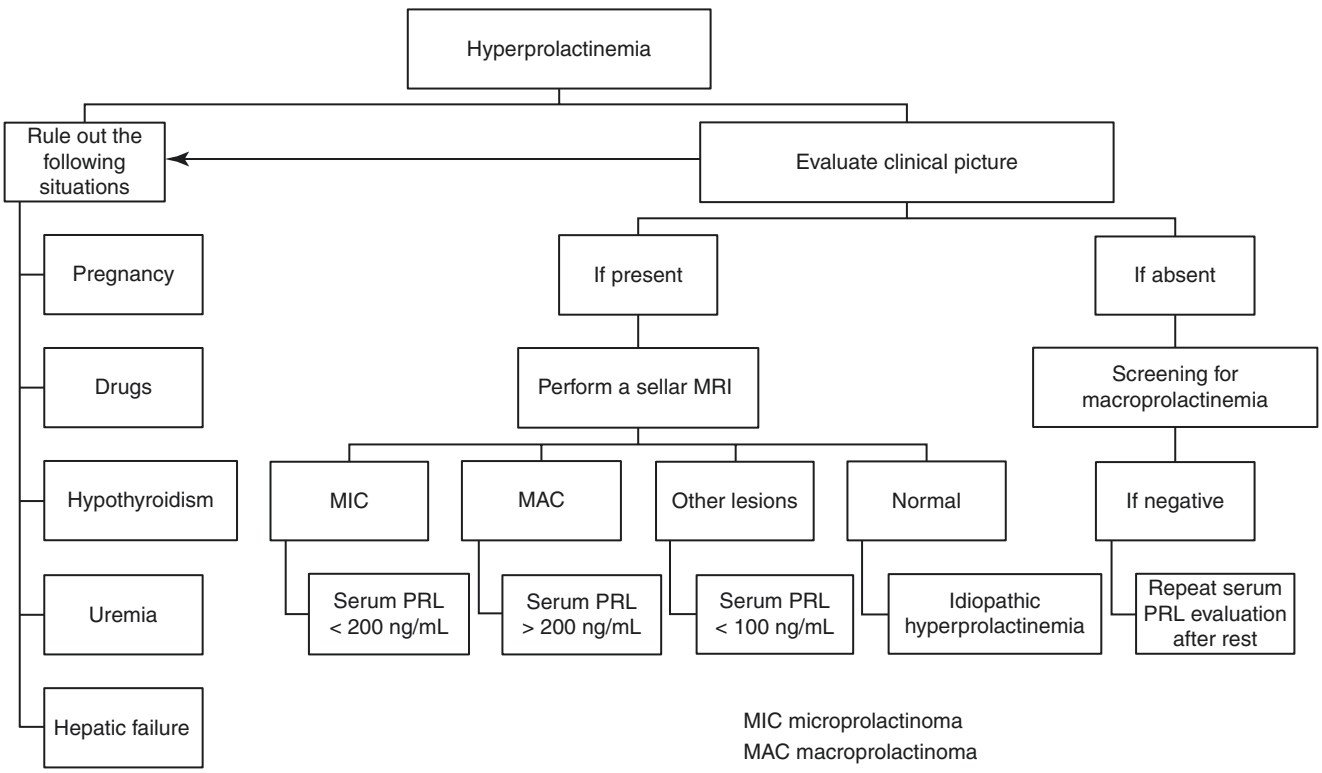

Fig. 5.1 Diagnosis of hyperprolactinemia algorithm

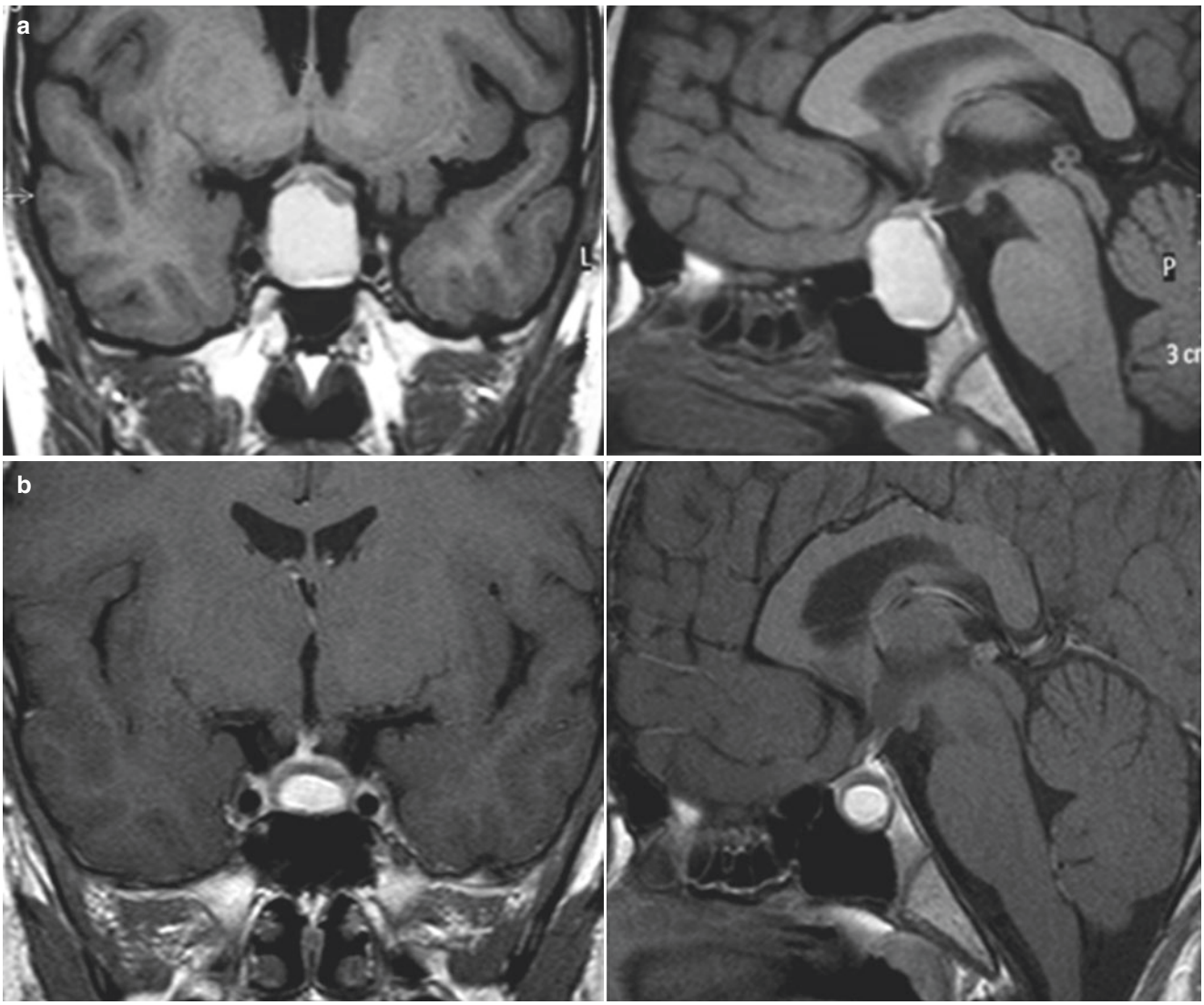

Fig. 5.2 (**a**) Before treatment. Sellar T1-weighted MRI after gadolinium enhancement, coronal (*left*) and sagittal (*right*) depicted a sellar mass impinging optic chiasma. (**b**) After 1 year of treatment with CAB. Sellar T1-weighted MRI after gadolinium enhancement, coronal (*left*) and sagittal (*right*) depicted an important reduction of tumor dimensions, with optic chiasma free of compression

an algorithm. In idiopathic hyperprolactinemia and prolactinomas, the treatment of choice is the use of DA. Surgical treatment and radiation are options for cases of resistance or intolerance to DA. Figure 5.2 depicted sellar MRI of a patient with macroprolactinoma in whom surgery was indicated. The algorithm suggested for the treatment is in Fig. 5.3.

A sellar MRI was performed in a 11-year-old male patient complaining of headache, and a sellar mass was depicted (Fig. 5.2a). Serum PRL level was 1130 ng/ml. The patient also had pubertal impairment development. Neurophthalmologic evaluation was normal. After 4 years of treatment with BRC, there was tumoral reduction without normalization of serum PRL levels. In our department, BRC was substituted for CAB, and dosage was gradually augmented until 3.5 mg a week. After 1 year of treatment with CAB, serum PRL levels were normal, and an additional tumoral reduction occurred (Fig. 5.2b).

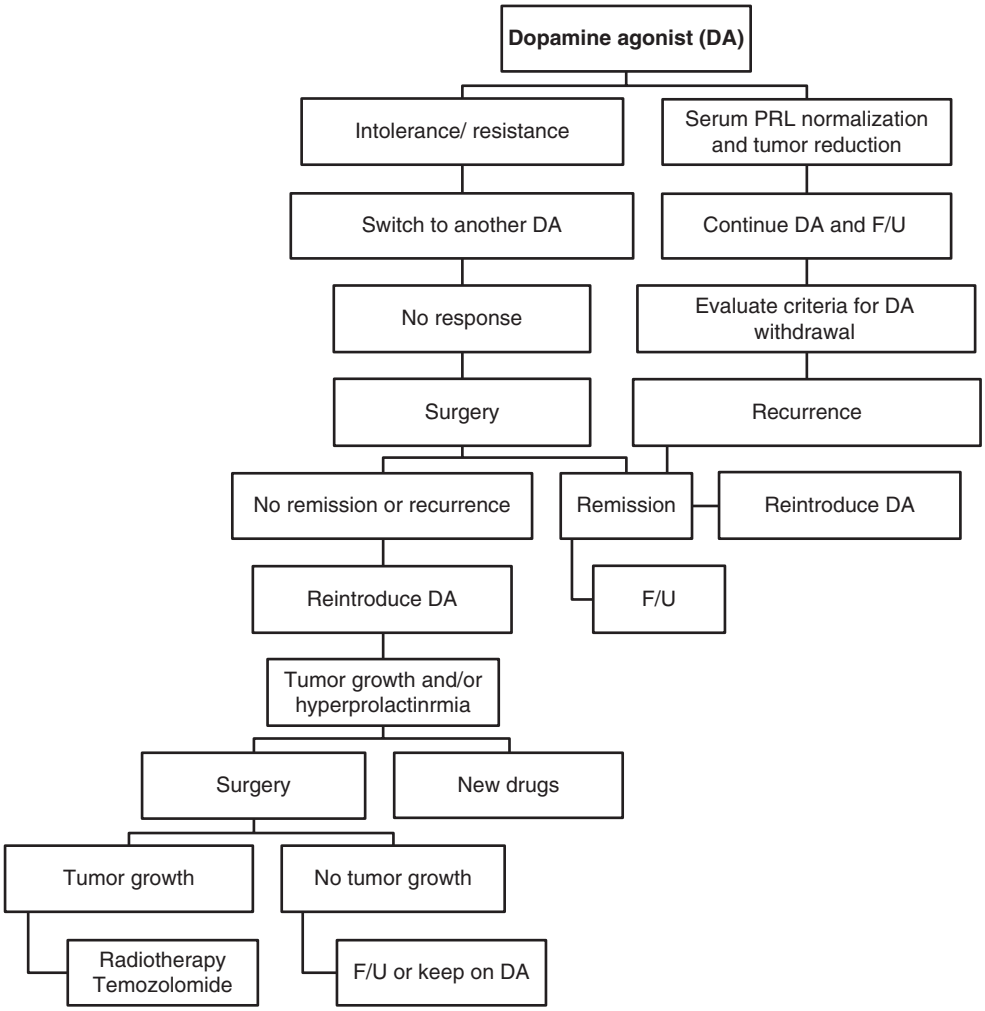

Fig. 5.3 Prolactinoma treatment algorithm

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