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CLINICAL PRACTICE GUIDELINE

Croatian guidelines for the management of hyperprolactinemia: a viewpoint from a developing country

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Abstract

Objectives: Hyperprolactinemia is a common endocrine problem seen in everyday practice. Therefore, the Croatian society for endocrine oncology decided to write Croatian guidelines for the management of hyperprolactinemia that implements current scientific evidence with acknowledgement of economic and cultural specificities in Croatia.
Methods: These guidelines were written by a Working group in the Croatian society for endocrine oncology, which included experts from different medical specialities that manage hyperprolactinemia, and were based on relevant scientific data.
Results: These guidelines provide a comprehensive review of prolactin pathophysiology, the aetiology of hyperprolactinemia, as well as recommendations for the diagnostic and therapeutic approach to patients with hyperprolactinemia.
Conclusion: These practical guidelines are in agreement with current scientific knowledge and will ensure better management of hyperprolactinemia in Croatia.

Key words: Croatia; developing; country; hyperprolactinemia; prolactinoma; management; guidelines

1. Introduction

Hyperprolactinemia is an important health issue because of its effect on infertility [1]. It is important to identify the correct aetiology of hyperprolactinemia because specific aetiologies require different clinical and pharmacological approaches. There are a number of conditions that can cause hyperprolactinemia. The most common cause of hyperprolactinemia is a prolactinoma, a pituitary adenoma that secretes excess prolactin [2]. The biochemical characteristics of prolactin (PRL), as well as the pathophysiology, aetiology and management of hyperprolactinemia will be reviewed. In order for this important medical condition to be optimally managed, health care practitioners must be educated and current scientific achievements must be acknowledged. Therefore, the Croatian society for endocrine oncology decided to write Croatian guidelines for the management of hyperprolactinemia in accordance with current globally used guidelines and as well as local health regulations [3-4].

2. Materials and Methods

Various medical specialties that are involved in the management of hyperprolactinemia contributed to these guidelines. The members of the Working group are doctors experienced in management of these patients. These guidelines were developed based on currently used Endocrine Society guidelines and Pituitary Society guidelines, as well as from current scientific medical literature and databases (PubMed, Medline) [4].

3. Biochemical and pathophysiological functions of prolactin

PRL is a polypeptide hormone composed of 199 amino acids with a molecular mass of 23 kDa. PRL is synthetized by lactotrophs in the anterior pituitary gland, immune, mammary, uterine, fat and epithelial cells. Its secretion is pulsatile (4 to 14 secretory pulses each lasting 67 to 76 minutes over 24 hours) and increases with stress, sleep, pregnancy, chest wall stimulation, and trauma [5-6]. Several factors exert a stimulatory effect on PRL secretion like thyrotropin releasing hormone (TRH), vasoactive intestinal peptide (VIP), epidermal growth factor, oxytocin, serotonin and opioid peptides. The role of main prolactin-inhibiting factor (PIF) has dopamine, although others must be mentioned as well: somatostatin (SST), and γ-aminobutyric acid (GABA). PRL release is controlled on several different levels. Hypothalamic control is through dopaminergic neurosecretory cells which inhibit prolactin release, while TRH has stimulatory effect. Oestrogen stimulates PRL secretion on the level of pituitary gland and also through the hypothalamus. PRL secretion is also regulated by PRL itself through a short loop feedback, where PRL stimulates the secretion of inhibitory factor (dopamine) [7].
PRL is crucial for the development of the mammary gland and milk production. It has a two-sided effect on reproduction. In states of excess PRL, it prevents ovulation in women, and spermatogenesis in men. On the other hand, in physiological levels PRL enhances synthesis of enzymes responsible for sex hormone production [8]. PRL has several different actions on metabolism and energy balance. PRL is involved in adipogenesis and adipocyte differentiation [9], as well as in increased insulin expression and glucose-stimulated insulin secretion [10]. Studies investigating the influence of PRL as a risk factor for metabolic syndrome, type 2 diabetes mellitus (T2DM) and obesity are controversial. Balbach et al. reported an inverse association between PRL and prevalence of T2DM in both genders, and absent causal role of PRL as a risk factor of incident metabolic syndrome or T2DM [11]. Ernst et al. didn't detect any significant association between basal PRL levels and the degree of obesity or other metabolic disturbances, nor any systematic changes in basal concentrations of the hormone after massive weight loss [12]. On the other hand, some evidence exists that patients with prolactinomas have higher BMI and LDL levels than patients with nonfunctional pituitary adenomas [13]. It was shown that PRL mobilises lipid stores and contributes to development of altered lipid profile [14]. It is important to mention the osmoregulatory effects of PRL, like reduction of renal Na^+ and K^+ excretion, decreased Na^+ and Cl^- in sweat, increased water and salt absorption in all regions of the intestine and also reduction in fluid volume in the amnion [15]. PRL has immunomodulatory effects that are concentration dependent. At moderate levels it acts immunostimulatory and at higher levels as immunoinhibitory, in pregnancy for example. Some studies showed that PRL may have a role in neurogenesis as well as in the pathogenesis of hypertension, peripartal cardiomyopathy, arrhythmias and arteriosclerosis [16].

4. Clinical features of hyperprolactinemia

Clinical manifestations of hyperprolactinemia vary depending on age and sex, as well as on the level of PRL. Hyperprolactinemia causes hypogonadotropic hypogonadism which is manifested in women as irregular menstrual cycles (oligo/amenorrhea), galactorrhoea, infertility and decreased libido. Symptoms in men are less obvious. Male patients mainly present with loss of libido and erectile dysfunction. Hyperprolactinemia inhibits ovary and testes funcion by decreasing their sensitivity to gonadotropins. Also, hyperprolactinemia decreases pulsatile

excretion of gonadotropin-releasing hormone (GnRH) from hypothalamus, where consequently supressed luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion inhibits ovulation. In women, there are low levels of oestrogen and inhibited secretion of progesterone, while in men levels of testosterone are normal or decreased [5]. Chronic hyperprolactinemia can result in decreased bone mass in both sexes [17]. Hyperprolactinemia caused by a pituitary tumour can present with symptoms related to mass effects such as hypopituitarism (as a result of compression of other pituitary cells), visual impairment (as a result of compression on optic chiasm), or headache [18].

5. Causes of hyperprolactinemia

There are several etiologies of hyperprolactinemia: physiological, pathological, pharmacological and macroprolactinemia. Idiopathic hyperprolactinemia describes the condition were hyperprolactinemia exists and all other known etiological factors are excluded. Physiological hyperprolactinemia is most often caused by pregnancy and breast-feeding, when serum prolactin levels are between 200 to 500 ng/mL (4 000 to 10 000 mIU/L). Higher levels of oestrogen from the placenta stimulate secretion of PRL from the pituitary gland due to lactotroph cell hyperplasia. Six weeks after delivery, PRL levels normalize due to a decrease in oestrogen level [19]. Other conditions can also cause physiological hyperprolactinemia, such as: stress, sleep, meals, exercise, sexual intercourse and chest wall stimulation [20]. It is important to note that physiological causes of hyperprolactinemia can coexist with pathological forms.

The most common cause of pathological hyperprolactinemia is a prolactinoma, which make up 40% of all functional pituitary adenomas. PRL elevation of more than 200 ng/ml is typically associated with prolactinomas [21]. Prolactinomas mostly occur sporadically in the form of microadenomas (<10 mm), 10% are macroadenomas (>10 mm), and in rare cases they appear as a part of multiple endocrine neoplasia type 1 (MEN 1) [22]. There are also rare cases of mixed adenomas, made of lactotroph and somatotroph cells, secreting both PRL and growth hormone (GH). In this case, clinical features of hyperprolactinemia and acromegaly coexist [23]. Other diseases of the hypothalamic and pituitary region can cause hyperprolactinemia by either disrupting synthesis or transmission of PIF. This includes primary or secondary hypothalamic and pituitary tumours (craniopharyngiomas, meningiomas), granulomatous or infiltrative diseases (sarcoidosis, histiocytosis), hypophysitis, aneurysms, empty sella, trauma, or radiotherapy [20].

There are several systemic diseases that can cause hyperprolactinemia. High levels of TRH, that can be found in primary hypothyroidism, causes stimulation of lactotroph cells in the pituitary gland [24]. In rare cases hyperprolactinemia can be found in patients with adrenal insufficiency. After glucocorticoid replacement therapy, prolactin levels normalizes because of the suppressive effect of glucocorticoids on prolactin [25-26]. The polycystic ovary syndrome (PCOS) is also associated with hyperprolactinemia, although some evidence suggests that they are two distinct entities with no causal relationships [27]. Chronic renal and hepatic failure can result in hyperprolactinemia because of decreased metabolic clearance of PRL and impaired dopamine regulation by lactotroph cells [28-29]. Very rare causes of hyperprolactinemia occur due to ectopic PRL secretion usually by an ectopic pituitary gland [30]. There are a few case reports of hyperprolactinemia caused by teratomas, dermoid cysts, acute lymphoblastic leukaemia, acute myeloid leukaemia, non-Hodgkin lymphoma, renal cell carcinoma, gonadoblastoma, cervical and colon adenocarcinomas, perivascular epithelioid cell tumours, and low grade malignant mesenchymal tumours [31].

A long list of drugs can lead to hyperprolactinemia, as seen in table 1 [32]. Hyperprolactinemia can also occur during conditioning and after autologous blood stem-cell transplantation, as well as during chemotherapy [33].

Macroprolactinemia is defined as the chronic presence of aggregate forms (50-150 kDa) of PRL in the circulation. In most cases it consists of a complex of PRL and an anti-PRL IgG autoantibody. These forms have reduced bioactivity [34]. It is estimated that macroprolactin is found in 26% of patients screened for hyperprolactinemia [35]. The prevalence of macroprolactinemia among newly diagnosed prolactinomas do not statistically differ from the prevalence in healthy control groups (3.5 vs. 3.7%) [36]. This means that macroprolactinemia doesn't exclude the presence of prolactinoma. If macroprolactinemia was used to explain clinical manifestations of patients in which it coexists with abnormal MRI finding, it can result in the delay of diagnosis and redefinition of treatment to more conservative approach [37].

Idiopathic hyperprolactinemia occurs when elevated PRL levels are found in the absence of other recognizable causes of hyperprolactinemia [38]. In some cases this is due to very small microprolactinomas which cannot be seen on currently available imaging techniques [39]. Some research suggests that autoimmune pituitary involvement is responsible for idiopathic hyperprolactinemia, where high levels of antipituitary antibodies (25.7%) are found in these patients [40]. PRL levels are usually lower than 100 ng/mL [41].

Table 1. Drugs associated with hyperprolactinemia*

Antipsychotics	Typical	Haloperidol Chlorpromazine, Thioridazine, Thiothixene
	Atypical	Risperidone, Amisulpride Molindone, Zotepine
	Tricyclics	Amitriptyline, Desipramine Clomipramine, Amoxapine
Antidepressants	SSRI	Sertraline, Fluoxetine, Paroxetine
	MAO-I	Pargyline, Clorgyline
Other Psychotropics		Buspirone, Alprazolam
Prokinetics		Metoclopramide, Domperidone
Antihypertensive		Alpha-methyldopa, Reserpine, Verapamil
Opiates		Morphine
H2 Antagonists		Cimetidine, Ranitidine
Others		Fenfluramine, Physostigmine Chemotherapics, Estrogen

* Adapted from Torre 2007.

6. Diagnosis

6.1. Laboratory studies

The diagnostic evaluation of hyperprolactinemia starts with laboratory analyses. PRL levels are determined by a single measurement, making sure to avoid venepuncture stress. PRL levels are determined 1 h after awakening or eating. If PRL levels are not diagnostic, sampling should be repeated on another day, taking two to three samples separated by 15-20 minutes to avoid PRL pulsatile secretion. PRL values between the upper limits of normal and 100 ng/mL (~ 2000 mIU/l) are mostly drug-induced, idiopathic or caused by microprolactinomas or non-functioning macroadenomas that compresse the pituitary stalk. Macroprolactinomas are associated with levels over 1000 ng/mL (~ 20 000 mIU/l). [4]

The definition of macroprolactin is as said before, a complex of PRL and an anti-PRL IgG autoantibody [34]. Gel filtration chromatography is considered to be golden standard for separation of different PRL molecules based on molecular weight and three-dimensional shape. With this method we can differentiate little (monomeric) PRL (molecular size: 23 kDa), big PRL (45–50 kDa), and big-big PRL (more than 100 kDa) [42]. Macroprolactin can also be measured with assays using polyethylene glycol (PEG) where low recovery of PRL (<40%) demonstrates presence of macroprolactin [43-44]. This percentage of recovery is not specific, because PEG induces a partial precipitation of monomeric PRL (up to 25%). This is important when an excessive macroprolactin occurs simultaneously with high concentrations of monomeric PRL. Therefore, it was recommended that laboratory establish method-specific reference intervals derived from PEG-treated sera from healthy individuals [42].

In cases of hyperprolactinemia without an identified cause, we recommend measurement of macroprolactin. It should also be measured in asymptomatic patients or those with atypical symptoms [3]. If aetiology of hyperprolactinemia is clear, we do not recommend measuring macroprolactin.

The high-dose hook effect explains falsely low PRL values usually associated with giant prolactinomas that cause very high levels of PRL. The high-dose hook effect is a laboratory pitfall that occurs when high antigen levels are present which impair antigen-antibody binding. This results in a low antigen determinant. In this case, very high levels of PRL causes antibody saturation which results in falsely low PRL levels. This is a rare effect, which can be avoided by preforming serum dilution [45-46]. We recommend excluding the high-dose hook effect when these is a discordance between PRL levels and tumour size.

Dynamic tests (TRH test, administration of L-dopa, nomifensine, domperidon and insulin-induced hypoglycaemia) are not golden standard tests for hyperprolactinemia because their sensitivity is not sufficient to determine whether MRI is necessary [47-48].

After initial evaluation of prolactin levels, it is essential to exclude other causes of hyperprolactinemia. We recommend basal determination of pituitary and peripheral hormones. This includes *free* thyroxine (fT4), thyroid-stimulating hormone (TSH), FSH, LH, testosterone, oestrogen, progesterone, cortisol, adrenocorticotropic hormone (ACTH), Insulin-like growth factor 1 (IGF-1) as well as a pregnancy test and biochemical analysis to evaluate kidney and liver function. In addition, a review of medications used by the patient must be made. Medication considered to contribute to the development of hyperprolactinemia should be discontinued for 48-72 hours and serum levels of PRL should be repeated.

6.2. Clinical assessment

Physical evaluation is still an important part of the diagnostic algorithm. The physician should evaluate the presence of galactorrhoea, signs of acromegaly, hypopituitarism, and neurological status. The presence of amenorrhea-galactorrhoea is highly suggestive of prolactinoma [49]. If a macroprolactinoma is diagnosed, visual field assessment is necessary. It is also important to evaluate bone mineral density in patients with long-term hyperprolactinemia because secondary hypogonadism impacts bone metabolism. Untreated prolactinomas are associated with an increased fracture risk [17].

6.3. Imaging studies

MRI is the most useful modality for imaging the sellar and parasellar region. It has several advantages: absence of ionizing radiation, direct multiplanar imaging capabilities without patient mobilization, better contrast resolution than CT, and better tissue characterization. The standard pituitary protocol includes sagittal and coronal T1-weighted spin-echo sequences performed before and following intravenous gadolinium administration and T2-weighted sequence in the sagittal plane. In most centres a 1.5 Tesla (T) MR imaging device is used, while the role of 3T MRI needs further research. In specific cases a variety of MR techniques can be used: a 3D volume analysis of pituitary volume, 3 T high-resolution MR imaging, diffusion-weighted imaging, MR spectroscopy, magnetization transfer ratio and intraoperative MRI. Evaluation of the intracranial vasculature can be achieved using MR angiography (MRA) and MR venography (MRV) [50].

Computed tomography (CT) has a role in preoperative planning. It is also a modality used for the evaluation of osseous structures [51]. CT can be used as the modality of choice if MRI is contraindicated (pacemaker, ferromagnetic vascular clips, intraocular metallic foreign bodies) or unavailable.

7. Management of hyperprolactinemia

7.1. Pharmacological treatment

Several drugs are used for the medical treatment of hyperprolactinemia. Dopamine agonists (DA) are well tolerated, available, and for the most important efficient drugs for hyperprolactinemia. They act as agonists of dopamine receptors, whose stimulation leads to inhibition of PRL secretion, as well as reduction in tumour size. By supressing PRL secretion, DA restorate gonadal function [52]. Therefore, it is necessary to warn patients about the possibility of pregnancy. Pregnancy should be planned after PRL normalization and MRI should be done before conception to document tumour size and to serve as comparison for later MRI studies. Besides their use in the treatment of hyperprolactinemia, they are also indicated in GH- secreting tumours, preventing and stopping lactation, and in Parkinsons disease. The two most frequently used DA are bromocriptine and cabergoline. Cabergoline is considered as a first line medication due to its effectiveness and better tolerance [53].

Bromocriptine was the first DA used. In comparison to cabergoline, it is short acting and less specific for dopamine receptors. Therefore, it has more side effects and is less efficient. It is administered orally. The starting dose is 1.25 mg a day, building up to 2.5 mg three times a day. Cabergoline is a newer long-acting DA with a higher affinity for dopamine D2 receptors (D2 receptors); therefore, it is better tolerated and more efficient than bromocriptine [54]. Disadvantages include a higher price, and this is an important drawback in low-income countries [55]. It is given at starting dose od 250 μg twice a week, increasing to up to 3 mg a week.

Common side effects of DA are: nausea, vomiting, mild orthostatic hypotension, and headaches. Less common side effects are: fatigue, nasal stuffiness, constipation, abdominal cramps, and a Raynaud-like phenomenon. Hallucinations and psychosis are exceedingly rare, but have been reported [56]. Side-effects can be avoided and minimized by slowly escalating drug dose, taking the medication before going to bed and taking the medication with food. Although better tolerated than bromocriptine, some studies suggest that cabergoline can be associated with fibrotic adverse reactions (cardiac valvular fibrosis, pleuropulmonary and retroperitoneal fibrosis). This side-effect was observed in patients with Parkinson disease in whom the dose of cabergoline is higher than the one used in the treatment of prolactinoma [57]. However, in a meta-analysis by Bogazzi et al. patients with hyperprolactinemia treated with cabergoline were at an increased risk of tricuspid valve regurgitation [58]. Therefore, it is important to consider the

duration of the therapy. DA can also cause tumour tissue fibrosis. Prolactinomas treated with bromocriptine before surgery had a greater probability of developing fibrosis compared to ones treated with cabergoline [59]. This effect can be considered positive in a sense of reducing tumour mass and improve surgical outcome [60]. On the other hand, some evidence exists that previous treatment with DA may increase complication rates and lower remission rates. Therefore early surgery is preferred for patients in whom this modality of treatment is indicated [61].

After initiating medical treatment it is important to control PRL levels after one month [3]. If PRL returns to normal levels, the next control should be after 6-9 months, then once a year. In cases of inadequate response to treatment, DA dose should be increased and PRL controls made according to the clinical response. Having in mind the potential negative effect of prolonged therapy of DA, it is advisable to consider therapy cessation in certain cases that will be mentioned in the next sections.

The systematic review and meta-analysis by Dekkers et al. showed that withdrawal of DA treatment resulted in persistent normoprolactinemia in 21% of patients. Better results were achieved with cabergoline treatment (35%) in comparison to bromocriptine treatment (20%). Also, success rates were higher in patients with idiopathic hyperprolactinemia (32%) than in those with microprolactinomas (21%) or macroprolactinomas (16%). It is important to note higher success rates if treatment duration was more than 2 years. [62].

7.2. Surgical treatment of prolactinomas

The first line treatment for patients with prolactinomas is medicamentous therapy. Surgery is indicated in patients who are resistant or intolerant to pharmacological therapy, in patients with invasive prolactinomas, and in patients with acute complications (e.g. apoplexy). Remission rates for prolactinomas treated by trans-sphenoidal surgery vary depending on the experience of surgical team (50-100% for microprolactinomas, 30-80% for macroprolactinoma) [63-64]. Recurrence rates are also highly variability depending on the length of follow up and indications for surgery (5-58%) [63]. Like any surgical procedure, there are complications: anaesthetic related, venous thrombosis and pulmonary embolism, haemorrhage, hypothalamic damage, meningitis, visual deterioration or loss, cranial nerve damage, hypopituitarism, diabetes insipidus, syndrome of inappropriate antidiuretic hormone (ADH) secretion (SIADH), CSF rhinorrhoea, and cerebral salt wasting [65]. The preferred technique for most prolactinomas is trans-sphenoidal surgery. In comparison to craniotomy, the trans-sphenoidal approach is less invasive, associated with less complications, and reduced duration of hospital stay. Transcranial surgery is required for large tumours with suprasellar extension, dumbbell configuration, indurated adenoma, "ectatic" kissing carotids, sphenoid sinusitis, and dural tail of supraselar/tubercular meningioma [66]. Studies have shown a beneficial effect of surgery in terms of improvements in hormonal control in previously drug-resistant patients [63]. Therefore, previously drug-resistant patients need lower doses of medications and are at lower risk of developing dose-related side effects.

7.3. Pituitary radiotherapy

Radiotherapy leads to a slow reduction of PRL, reduction of tumour size and regrowth. Its effect is seen years after application. Normalization of PRL is seen in 10-80% of patients with a mean time to normalization of 2-8 years. Reduction of PRL is seen in up to 80%, and reduction in tumour size in 20-50% of patients treated with gamma knife [67]. A better response is seen in microadenomas (remission rate of 70%) than in macroadenomas (remission rate of 30%) [68]. Also, better biochemical responses are seen in tumours irradiated while off of medical therapy, and in smaller tumours that have a decreased risk of developing hypopituitarism [69].

There are two radiotherapy techniques used: conventional radiotherapy and stereotactic radiosurgery (gamma knife "radiosurgery"). Its application is limited by proximity of tumour tissue to the optic chiasm. Radiotherapy is rarely used as first line treatment in prolactinomas. It is indicated after the surgical treatment of macroprolactinomas, or before, if surgery is contraindicated. While waiting for radiotherapy to be effective, it is recommended to continue DA therapy. Side effects that occur short term are nausea, headache and temporary hair loss. Hypopituitarism can occur gradually for up to 4 years after radiotherapy; therefore, it is important to continue hormone evaluation at least once a year. The incidence of hypopituitarism varies from 0-40% depending on published data [70]. Based on existing evidence, radiosurgery should not be used as first line treatment for prolactinomas. It can be considered in patients with residual aggressive and/or DA resistant prolactinomas. It can also be considered in elderly patients with pre-existing hypopituitarism.

7.4. Management of microprolactinomas

Microprolactinomas are usually indolent tumours that rarely progress to macroprolactinomas. Microprolactinomas should always be treated in men and women of reproductive age. Previous guidelines suggested that microprolactinomas

may not be treated in postmenopausal women and elderly patients. However, increasing evidence links hyperprolactinemia with osteoporosis and the metabolic syndrome. Although data from large prospective studies are lacking, we recommend that all patients with microprolactinomas be treated with DA. Cabergoline was found to be more effective (83%) in normalization of PRL than bromocriptine (59%) [71]. Nevertheless, we recommend bromocriptine as a first-line therapy and cabergoline in patients with pronounced side effects and bromocriptine-resistant prolactinomas. DA induce tumour shrinkage of [72]. When starting DA therapy, one should measure serum prolactin levels in 3-month intervals until normoprolactinemia develops. MRI should be performed annually. Shorter intervals should be considered in patients with increasing prolactin levels, and in patients with new symptoms. Once normal PRL are achieved, it is necessary to evaluate PRL once a year.

DA therapy could be discontinued in patients who have been treated for at least 2 years, have normal PRL levels, and no visible tumour on MRI. The PRL levels should be assessed in regular periods (every 3 months for the first year, then annually). MRI should be performed in patients with an increase in serum prolactin, and DA should be reintroduced. Although there is a risk of recurrence, the withdrawal of therapy is not associated with tumour growth [62].

Pituitary surgery should be performed only by well-trained neurosurgeons who perform at least 50 procedures per year. Pituitary surgery should be used for symptomatic patients intolerant or resistant to DA [73]. On the other hand, pituitary surgery is safe and very effective for patients with microprolactinomas, with low rates of hypopituitarism and recurrence [64]. Hence, the choice of surgery as the initial treatment modality may be left to the patient. The main advantages of surgery are the possibility of inducing a definitive remission of hyperprolactinemia and avoiding chronic medical therapy, which is associated with an impaired quality of life [74].

7.5. Management of macroprolactinomas

The treatment of macroprolactinomas should address: reduction in tumour size, restoration of gonadal function and preservation of anterior pituitary function. Although DA may be useful in the management of macroprolactinomas, they can rarely provide long-term remission. Patients with macroprolactinomas usually need greater doses of DA, which is associated with more side effects and poor compliance [55]. Therefore, pituitary surgery can be considered as a first-line treatment for patients with macroprolactinomas in centres with well-trained neurosurgeons, since DA can cause tumour fibrosis and higher rates of post-operative complications [61]. Biochemical revaluation is recommended 3, 6 then 9 months after surgery, and MRI should be repeated 3-6 months after surgery. If remission is achieved, biochemical assessment is recommended once a year because recurrence can occur 3 years or more after surgery [63]. In cases of residual tumour, re-operation, radiotherapy, or DA can be considered. Radiotherapy is recommended in cases of inadequate biochemical control after DA therapy and/or operation [75].

7.6. Management of resistant and malignant prolactinomas

In 10-20% of cases prolactinomas can be resistant to DA therapy as a result of reduced numbers of D2 receptors [76]. Resistance to DA treatment is defined as a failure to normalize PRL despite the administration of more than 15 mg of bromocriptine daily, or weekly treatment with up to 3.5 mg of cabergoline for at least 3 months, and failure to decrease tumour size in <50% [77]. The majority of these patients have macroadenomas (>80%) and/or invasive tumour (>50%) [78]. Resistance to DA occurs in 25% of patients treated with bromocriptine, and in 10-15% patients treated with cabergoline [79]. The first step in the management of patients with resistant prolactinoma, should be reinitiating different DA and then increasing the dose of DA. Surgery, radiotherapy, chemotherapy (temozolomid) or oestrogen therapy should be considered if this strategy fails. If fertility is desired in patients with resistant prolactinomas, then clomiphene, gonadotropins and GnRH can be added to DA [78].

Malignant prolactinomas are extremely rare and have a poor prognosis. They usually have an atypical presentation and sometimes can manifest with metastases. The most common presentation is hyperprolactinemia and local compression. Survival after the onset of initial symptoms of prolactinoma is approximately 8 years [80]. They can be distinguished by resistance to DA therapy and recurrence after surgery. It has been shown that certain histological and immunohistochemical parameters can predict aggressive behaviour of pituitary adenoma like proliferative index of Ki-67 more than 3%, positive p53 immunoreactivity, cellular atypia, invasion, nuclear pleomorphism and more than two mitotic figures per ten high-powered fields [81]. In such cases cytotoxic chemotherapy may be considered, while surgery and radiotherapy are palliative. Studies showed promising results with temozolomide, although there is not enough experience with this modality of treatment [82].

7.7. Management of prolactinomas in pregnancy

Th pituitary gland doubles in volume during pregnancy, due to an increase in oestrogen levels. This should be always considered, when assessing the risk of local compression symptoms [83]. Only 1-2% of microprolactinoma, and 15-35% of prolactinomas increases during pregnancy. Interestingly, tumour growth occurs in only 4-7% of macroprolactinomas treated with surgery and/or radiotherapy before pregnancy [71]. Therefore, it is advisable to continue treatment with DA in patients with macroprolactinomas, along with regular visual field testing. In cases of inadequate therapy response, the tumour can be operated in the second trimester. MRI should be performed in the postpartum period in women with macroprolactinomas to reassess tumour size. In patients with microprolactinomas, DA therapy can be discontinued [83]. MRI is indicated in patients with microprolactinomas who become symptomatic. Bromocriptine therapy during pregnancy is not associated with a higher incidence of complications or teratogenicity [84]. Post-natal development is also not affected, as shown in a study that followed children born from mothers taking bromocriptine [85]. There is less data regarding cabergoline's safety profile in in pregnancy; although, current evidence suggests no significant increase in miscarriages or fetal malformation [86]. Monitoring of prolactinomas during pregnancy is mostly based on detailed clinical examination and medical history, since prolactin levels cannot be used to assess treatment response. Women with microprolactinomas should be followed every 2-3 months. PRL should be checked after cessation of breastfeeding. DA treatment should be started in patients after cessation of breastfeeding if PRL is in the range of pre-treatment values, while studies have shown that breastfeeding is not associated with an increased risk in these patients [87]. It is also important to note that studies have shown that pregnancy induces remission of hyperprolactinemia in two-thirds of women after discontinuation of DA (76-100% with non-tumoral hyperprolactinemia, 66-70% with microprolactinomas, 64-70% with macroprolactinomas). Although the exact mechanism is still unclear, it was hypothesized that autoinfarction of the tumour might be the reason for remission [88-89].

7.8. Management of macroprolactinemia

Although the presence of macroprolactin is asymptomatic in most cases, it may lead to typical (ovulatory dysfunction, galactorrhoea, decreased libido) or atypical features of hyperprolactinemia [90]. As shown by Vallete-Kasic et al., macroprolactinemia can present as pseudoresistance to DA therapy [91]. In symptomatic patients with macroprolactinemia, further investigations are mandatory in order to elucidate the aetiology of hyperprolactinemia, as it was shown that macroprolactinemia can coexist with other causes of hyperprolactinemia [91]. We do not recommend treatment of asymptomatic patients with confirmed macroprolactinemia. The possible negative effect of macroprolactin is still controversial. Anaforoglu et al. showed that a group of patients with monomeric hyperprolactinemia and macroprolactinemia compared to a group with normoprolactinemia demonstrated greater platelet activation and atherosclerotic disorders [92]. Further research is necessary to elucidate the potential biological effect of macroprolactin and its treatment requirement.

7.9. Management of idiopathic hyperprolactinemia

If all previously mentioned causes of hyperprolactinemia are ruled out, than we define hyperprolactinemia as idiopathic. We recommend follow up in these patients, since serum prolactin levels may increase in 10-15% [71]. In this case, MRI should be performed. Normalization of PRL was noted in 30% of patients, and in 50% of patients PRL levels remain stable [93]. We do not recommend DA therapy for prevention of tumour growth, as microprolactinomas occur in only 10% of cases [93]. Treatment with DA is advisable in patients with symptomatic idiopathic hyperprolactinemia. Treatment with DA can induce ovulation in 80-90% of patients and in the remaining patients gonadotropin stimulation can be added [5].

7.10. Management of other causes of hyperprolactinemia

Hyperprolactinemia caused by a primary hypothyroidism or adrenal insufficiency is resolved after thyroid and glucocorticoid replacement therapy [94-95]. PCOS and hyperprolactinemia are two distinct entities that can coexist together [27]. Treatment with DA (bromocriptine) alone compared to a placebo-treated group of patients with PCOS didn't show clinical results (restoration of ovulatory cycles) [96]. Therefore, it is important to asses other causes of hyperprolactinemia in patients with PCOS and treat it according to the recommendations already mentioned. Hyperprolactinemia in chronic renal failure remains unchanged after dialysis, or slightly increased, whereas after renal transplantation, PRL levels return to normal and previous DA resistance is eliminated[29]. There are several studie that support a positive effect of DA treatment in patients with chronic renal failure. Mejía-Rodríguez et al. found that bromocriptine treatment in patients with left-ventricular hypertrophy and end-stage renal disease on peritoneal dialysis decreased left-ventricular mass [97]. Symptomatic

hyperprolactinemia in patients with chronic kidney disease can be treated with DA [98]. In currently available literature no clear recommendations regarding treatment of hyperprolactinemia in liver diseases exists. Hyperprolactinemia caused by hypothalamic or pituitary disorders that lead to disruption or compression of pituitary stalk (tumours, granulomatous diseases, infiltration, trauma), is usually resolved after treatment of these conditions. Although DA treatment lowers the levels of PRL in non-functioning pituitary adenoma, the effect on tumour size is heterogeneous. This may be due to the different pattern of dopamine receptor expression in the tumour cells [99]. Therefore, the definitive treatment for all non-functional pituitary adenomas is surgery.

7.11. Management of drug-induced hyperprolactinemia

Numerous drugs can cause hyperprolactinemia. If a medication is necessary for the patient and cannot be discontinued then hormonal therapy can be initiated in order to prevent the long term effects of hyperprolactinemia such as osteoporosis. DA should be initiated if the ovulation is desired. Based on the medical history and clinical examination, MRI can be performed in certain cases in order to rule out a sellar mass. DA should be avoided in patients using psychotropic agents, since they may compromise the effectiveness of psychotropic agents and antagonise their effect. If drug-induced hyperprolactinemia is confirmed, it is recommended to switch to alternative drug when possible [100].

12. Discussion

Hyperprolactinemia is a state of abnormally high levels of PRL. Its relevance lies in the fact that it is the most common disorder of the hypothalamic-pituitary axis [101]. It deserves even more attention considering its effect on fertility as well as on bone metabolism and the metabolic syndrome [102]. Although similar guidelines in the global scientific community already exist, there should also be guidelines with respect to local health care systems and capabilities, especially in cases of developing countries such as Croatia. In October 2015, members of the Croatian society for endocrine oncology met and formed a Working group that consisted of experienced endocrinologists, neurosurgeons, and radiologists that were involved in the management of hyperprolactinemia. These guidelines were written based on the analysis of current recommendations and scientific data. It provides comprehensive review of pathophysiology of PRL, aetiology of hyperprolactinemia, as well as the diagnostic and therapeutic approach to patients with hyperprolactinemia. Recommendations mentioned in these guideline are summarized in the next section.

13. Summary of recommendations

Diagnosis

The diagnosis of hyperprolactinemia requires a single measurement of serum PRL.

Macroprolactin should be determined in cases of hyperprolactinemia without an identified cause, in asymptomatic patients, and in those with atypical symptoms.

The high-dose hook effect should be excluded in cases of discordance between PRL levels, tumour size, and clinical presentation.

We recommend basal determination of pituitary and peripheral hormones (fT4, TSH, FSH, LH, testosterone, oestrogen, progesterone, cortisol, ACTH, IGF-1), a pregnancy test, and biochemical analysis to evaluate kidney and liver function.

Drug-related hyperprolactinemia should be excluded after discontinuing medications that can cause hyperprolactinemia for 48-72 hours, and repeating PRL measurement.

Dynamic tests are not recommended for the diagnosis of hyperprolactinemia.

MRI should be performed in all patients with symptomatic hyperprolactinemia.

In all patients with macroprolactinomas, visual field assessment and pituitary function testing is necessary.

Bone densitometry and lipid profiles should be performed in all patients with hyperprolactinemia.

Management of hyperprolactinemia

All patients with symptomatic hyperprolactinemia or concomitant osteoporosis and/or metabolic syndrome should be treated.

DA (bromocriptine, cabergoline) should be considered as first-line treatment for patients with microprolactinomas and secondary hyperprolactinemia, but second-line treatment for patients with macroprolactinomas.

Side-effects of DA can be avoided and minimized by slow initiation of therapy, taking medication before going to bed, and taking medication with food.

After initiating DA, measurement of prolactin levels should be performed in 3-month intervals and DA dose increased, until reaching normoprolactinemia.

In cases of inadequate response to treatment, bromocriptine should be replaced with cabergoline and vice versa.

Surgery is indicated for all patients with prolactinomas who are resistant or intolerant to pharmacological therapy, in patients with invasive prolactinomas and in patients with acute complications (e.g. apoplexy).

The endoscopic technique is the preferable method of pituitary surgery and should be performed by experienced neurosurgeons with at least 50 procedures per year.

Surgery as a first-line treatment for microprolactinomas should be left to the discretion of the patient.

Surgery can be considered as a first-line treatment for patients with macroprolactinomas in centres with well-trained neurosurgeons.

Radiosurgery should be considered in patients with residual aggressive and/or DA resistant prolactinomas. It can also be considered in elderly patients with pre-existing hypopituitarism.

In cases of malignant prolactinomas, cytotoxic chemotherapy may be considered

If fertility is desired in patients with resistant prolactinomas, then clomiphene, gonadotropins and GnRH can be added to DAs.

Continue treatment with DA in pregnant patients with macroprolactinomas, along with regular visual field testing is necessary. In cases of inadequate therapy response, the tumour can be operated in second trimester.

In pregnant patients with microprolactinomas, DA therapy can be discontinued.

Author contributions

JMR wrote the article and gave the final approval. MS, LK, IK and BP performed literature review, participated in drafting the article and gave the final approval. GM, DS, AB, VČ, HIP, TG, ŽBM, MR, ŽCO, SKM, BM, MJB, AT, MB, DR, MK and VKF critically revised the manuscript, gave suggestions regarding data presentation and gave the final approval MV gave the idea for the article critically revised the manuscript, gave suggestions regarding data presentation and gave the final approval.

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