Laboratory and clinical significance of macroprolactinemia in women with hyperprolactinemia

Kasum, Miro; Orešković, Slavko; Čehić, Ermin; Šunj, Martina; Lila, Albert; Ejubović, Emina

Source / Izvornik: **Taiwanese Journal of Obstetrics and Gynecology, 2017, 56, 719 - 724**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

https://doi.org/https://doi.org/10.1016/j.tjog.2017.10.002

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:686528

Taiwanese Journal of Obstetrics & Gynecology 56 (2017) 719–724

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Review Article

Laboratory and clinical significance of macroprolactinemia in women with hyperprolactinemia

Miro Kasum [a, *], Slavko Orešković [a], Ermin Čehić [b], Martina Šunj [c], Albert Lila [a], Emina Ejubović [b]

[a] Department of Obstetrics and Gynecology, University Hospital Center Zagreb, University of Zagreb School of Medicine, Zagreb, Croatia
[b] Department of Obstetrics and Gynecology, Cantonal Hospital Zenica, Zenica, Bosnia and Herzegovina
[c] Department of Obstetrics and Gynecology, Clinical Hospital Center Firule, School of Medicine, Split, Croatia

ARTICLE INFO

Article history:
Accepted 25 June 2017

Keywords:
Hyperprolactinemia
Macroprolactin
Macroprolactinemia
Prolactin

ABSTRACT

The role of macroprolactinemia in women with hyperprolactinemia is currently controversial and can lead to clinical dilemmas, depending upon the origin of macroprolactin, the presence of hyperprolactinemic symptoms and monomeric prolactin (PRL) levels. Macroprolactinemia is mostly considered an extrapituitary phenomenon of mild and asymptomatic hyperprolactinemia associated with normal concentrations of monomeric PRL and a predominance of macroprolactin confined to the vascular system, which is biologically inactive. Patients can therefore be reassured that macroprolactinemia should be considered a benign clinical condition, resistant to antiprolactinemic drugs, and that no diagnostic investigations or prolonged follow-up should be necessary. However, a significant proportion of macroprolactinemic patients appears to suffer from hyperprolactinemia-related symptoms and radiological pituitary findings commonly associated with true hyperprolactinemia. The symptoms of hyperprolactinemia are correlated to the levels of monomeric PRL excess, which may be explained as coincidental, by dissociation of macroprolactin, or by physiological, pharmacological and pathological causes. The excess of monomeric PRL levels in such cases is of primarily importance and the diagnosis of macroprolactinemia is misleading or inadequate. However, macroprolactinemia of pituitary origin associated with radiological findings of pituitary adenomas may rarely occur with similar hyperprolactinemic manifestations, exclusively due to bioactivity of macroprolactin. Therefore, in such cases with hyperprolactinemic signs and pituitary findings, macroprolactinemia should be considered a pathological biochemical condition of hyperprolactinemia. Accordingly, individualized diagnostic investigations with the introduction of dopamine agonists, or other treatment with prolonged follow-up, should be mandatory. The review analyses the laboratory and clinical significance of macroprolactinemia in hyperprolactinemic women suggesting clinically useful diagnostic and treatment strategies.

Introduction

Prolactin (PRL) is a globular protein hormone of 199 aminoacids produced by the anterior pituitary lactotrophic cells that acts with other hormones to initiate secretion of milk by the mammary glands. PRL homeostasis is under hypothalamic regulation with the primary control of its secretion being inhibitory rather than stimulatory. The hypothalamic factor that chiefly inhibits PRL secretion at the level of D2 receptors is the neurotransmitter dopamine which is believed to be the principal PRL inhibiting factor (PIF). The PRL-releasing factors include vasoactive intestinal peptide, epidermal growth factor and thyrotrophin-releasing hormone, as the only important clinical manifestation that occurs with hypothyroidism. Heterogeneity in the molecular size of PRL has been described in the majority of serum from normal and hyperprolactinemic individuals and three major variants can be classified including monomeric, dimeric and polymeric isoforms. The monomeric or little PRL (MW 23 kDa) results from a cleaved preprolactin molecule (MW 26 kDa) and it represents the major circulatory isoform (80–95%) of the total PRL in cases with normoprolactinemia and true hyperprolactinemia. The biological

* Corresponding author. Department of Obstetrics and Gynecology, University Hospital Center Zagreb, University of Zagreb School of Medicine, Petrova 13, 10000 Zagreb, Croatia. Fax: +385 1 2376267.
E-mail address: mkasum@gmail.com (M. Kasum).

https://doi.org/10.1016/j.tjog.2017.10.002

and immunological activity of PRL may be almost exclusively attributed to the monomeric form [1]. The most common symptoms of monomeric PRL excess in premenopausal women are oligomenorrhea/amenorrhea and galactorrhea, which result from the inhibitory effect on gonadotrophin-releasing hormone (GnRH) secretion and from the stimulatory effect on the proliferation and differentiation of mammary cells during lactation. The predominant physiologic consequence of hyperprolactinemia is hypogonadotrophic hypogonadism due to suppression of pulsatile GnRH. Furthermore, women with hyperprolactinemia can present with various other symptoms including; a short luteal phase, menstrual irregularities, decreased libido or orgasmic dysfunction, anovulation, infertility, chronic hyperandrogenism due to increased dehydroepiandrosterone sulfate secretion from the adrenals, prolonged hypoestrogenism, decreased bone mass and osteopenia [2].

The most common other forms of PRL with lower biological activity include the dimeric (big PRL, MW 48–56 kDa) and the polymeric isoform or macroprolactin (big–big PRL, MW > 150 kDa), that account for less than 10% and 1%, respectively, of the total PRL levels in normal sera. Macroprolactinemia represents a state of hyperprolactinemia characterized by the predominance of big–big PRL and it is mainly suspected in asymptomatic individuals or those without the typical hyperprolactinemia-related symptoms. Among the three most common causes of hyperprolactinemia, in addition to prolactinomas and neuroleptics/antipsychotic drugs, macroprolactinemia can also be included. Although the nature of macroprolactin is heterogenous it is mainly recognized as an antigen–antibody complex of high stability consisting primarily of monomeric PRL and immunoglobulin (Ig) G isotype. Furthermore, in cases with slightly elevated PRL levels, non-IgG-bound forms of macroprolactin including complexes with IgA or IgM, highly glycosylated monomeric PRL, covalent or noncovalent aggregates of monomeric PRL, have rarely been demonstrated. Macroprolactin is confined to the vascular system owing to its high molecular size and therefore its access to the PRL receptors of target organs in the periphery and centrally is prevented. Accordingly, the absence of macroprolactin in extravascular spaces and the pituitary may be proceeded by the loss of hyperprolactinemia-related symptoms [3]. It seems that asymptomatic macroprolactinemia in women with hyperprolactinemia might be a stable and long-lasting condition for up to 10-years [4]. In patients with macroprolactinemia and normal concentrations of monomeric PRL no symptomatic progression was noted during a 10-year clinical follow-up, macroprolactinemia therefore may be considered a benign variant of hyperprolactinemia. Such patients have been reassured that no pituitary imaging investigations and dopamine agonist treatments were necessary [5]. Consequently, routine diagnostic screening of all hyperprolactinemic women for macroprolactin has been recommended as financially justified due to reduced use of imaging and dopamine agonist treatment in such patients [6]. Although patients with macroprolactinemia are usually asymptomatic and have normal menstrual cycles with spontaneous conceptions, there are a number of women with macroprolactinemia presenting hyperprolactinemic clinical symptoms due to the rise in the levels of monomeric PRL, that cannot be differentiated from the patients with true hyperprolactinemia [7–11]. Since in patients with macroprolactinemia at least one of these symptoms may be found, no clinical feature can reliably distinguish macroprolactinemic from true hyperprolactinemic individuals [7]. Unfortunately, no laboratory investigations and hyperprolactinemia related symptoms are useful in differentiating patients with monomeric hyperprolactinemia from those individuals with macroprolactinemia [8]. Furthermore, a comparison of different immunoassays for the detection of macroprolactin in hyperprolactinemic patients demonstrated no difference in the incidence of hyperprolactinemia-related symptoms, including abnormal menses, galactorrhea, or abnormal pituitary imaging without regard to considering the presence of macroprolactin [9]. Since oligomenorrhea and galactorrhea occur in 57% and 29% of patients with macroprolactinemia, hyperprolactinemia was a significant cause of frequent misdiagnosis and mismanagement before the introduction of macroprolactin screening by the use of appropriate laboratory immunoassays [10]. Consequently, it is essential for clinical laboratories to introduce screening methods to analyze blood samples in hyperprolactinemic patients and to determine the presence of macroprolactin and the monomeric PRL component of all hyperprolactinemic sera [11]. Although the presence of macroprolactinemia is suspected mainly in cases of mild hyperprolactinemia without pathological pituitary findings, a few cases of macroprolactinemia with prolactinomas and typical hyperprolactinemic symptoms have been recently reported. Since the symptoms of hyperprolactinemia disappeared after treatment with dopamine agonists, biological activity of the high-molecular isoform has been suggested similar to that of elevated monomeric PRL levels. Consequently, in these rare cases of macroprolactinemia pituitary diagnostic imaging, medical treatment, and prolonged follow-up may be required [12]. The review aims to asses the laboratory and clinical significance of macroprolactinemia in women with hyperprolactinemia, and pathophysiologic mechanisms of macroprolactinemia, suggesting different approaches which may be useful in diagnostic evaluation and adequate treatment in clinical settings of such patients.

Prevalence

Although the proportion of macroprolactinemia has earlier been reported less commonly in men (0.02%) than in women (0.2%), according to more recent data it may be more common with a general prevalence of 3.7% with no difference between the sexes [13,14]. However, in hyperprolactinemic populations the mean proportion of macroprolactinemia is 25% and varies between 15 and 35% [8,12,13]. A higher incidence of macroprolactinemia of 46% reported by a study center which received samples sent from other laboratories where the possible diagnosis of macroprolactinemia was raised, may reflect selection bias [15].

Clinical features

According to earlier reports macroprolactinemia appeared in isolated cases of asymptomatic women or healthy volunteers, with normal concentration of monomeric PRL and between 85 and 90% of serum PRL big–big PRL. Limited bioactivity *in vivo* without the symptoms of hyperprolactinemia has been supported by an explanation that the big–big PRL complex is confined to the vasculature due to its high molecular mass preventing its approach to the target cells [16,17]. Consequently, the new term “macroprolactinemia” was used for the first time in 1985 for such cases of hyperprolactinemia whose PRL mainly consisted of big–big PRL, to characterize a nonprogressive state and a novel cause of hyperprolactinemia [18].

However, later investigations in patients with macroprolactinemia revealed a lower incidence of hyperprolactinemia-related clinical symptoms and abnormal imaging findings in the pituitary gland compared with patients exhibiting true hyperprolactinemia [5,10,15,19–23]. In a cohort of 51 patients with macroprolactinemia, headache was present in twelve patients (24%), oligomenorrhea in five (10%) and galactorrhea in two cases (4%), without symptomatic progression during prolonged follow-up. Therefore, such patients with macroprolactinemia and normal concentrations of monomeric prolactin can be reassured, and

extended endocrine review of such patients is not required [5]. Normal pituitary images were more common in patients with macroprolactinemia than in patients with monomeric hyperprolactinemia (78.9% vs. 25%), whereas hyperprolactinemic symptoms were more likely in individuals with true hyperprolactinemia than in patients with macroprolactinemia (90% vs. 54%) [15]. Since symptoms typical of hyperprolactinemia were not common in 55 patients with macroprolactinemia (one with galactorrhea and eight with oligomenorrhea), referral and intensive investigation of these patients was not be suggested [19]. Similarly in a study of 106 patients with macroprolactinemia, menstrual abnormalities and galactorrhea occurred less commonly than in women with true hyperprolactinemia (25% vs. 37% and 12% vs. 34%, respectively) [20]. Hyperprolactinemia occurred in 15–20% of women with menstrual disturbances and 30–40% of infertile women, and can adversely affect fertility. Since the prevalence of oligomenorrhea and galactorrhea was significantly higher in patients with true hyperprolactinemia than macroprolactinemia (46 vs. 14%, and 30 vs. 5%, respectively), measurement of PRL should be a part of routine evaluation of couples with infertility [21]. Contrary to multiple impairments of sexual functions such as sexual desire and arousal, lubrication, orgasm, sexual satisfaction, and dyspareunia. With depressive symptoms in women with elevated monomeric prolactin, it seems that macroprolactinemia only disturbs sexual desire [22]. Despite lower frequency of galactorrhea and abnormal pituitary findings in macroprolactinemic compared to monomeric hyperprolactinemia (39.2 vs. 57.1% and 65.3 vs. 81.1%, respectively), macroprolactinemia has been suggested as a pathological biochemical variant of hyperprolactinemia [23].

Moreover, according to later studies there were no differences in typical hyperprolactinemia-related symptoms between patients with macroprolactinemia and monomeric hyperprolactinemia, because the symptoms related to PRL excess were reported more frequently in subjects with macroprolactinemia [7–9,24]. Furthermore, there were no significant differences in hormonal levels such as gonadotrophins, estradiol or testosterone levels between the groups of patients. Nevertheless, the patients with macroprolactinemia had a lower infertility rate (6.7% vs. 32.7%) and a greater percentage of normal pituitary findings (73.3% vs. 34.5%) than those with true hyperprolactinemia. Despite the fact that clinical symptoms and laboratory findings cannot be used reliably to distinguish macroprolactinemia from true hyperprolactinemia, routine laboratory screening for all hyperprolactinemic sera with PEG might prevent the unnecessary use of radiological techniques and medical treatment. Consequently, physicians should encourage laboratories to make the measurement of macroprolactin in daily practice for such patients with hyperprolactinemia [24].

Diagnosis

Macroprolactinemia has often been neglected in the differential diagnosis of hyperprolactinemia, mainly due to the lack of adequate diagnostic methods and lack of awareness among specialists, and therefore patients have often undergone unnecessary diagnostic investigations, treatment and follow-up. Among laboratory techniques gel filtration chromatography (GFC) is known as the gold standard and represents an accurate and reproducible method. Since it is an expensive, time-consuming and labor-intensive technique, clinicians are often discouraged from using it in unclear situations of hyperprolactinemia [20]. Although the separation of macroprolactin by immunoadsorption with Protein A (PA) and Protein G (PG) offers acceptable precision, pretreatment of sera with PA and PG may lead to a significant overestimation of monomeric PRL concentrations [25]. Another technique - the detection of macroprolactin by precipitation and ultrafiltration represents a practical alternative to GFC for estimating the macroprolactin, although the PRL levels after ultrafiltration, may vary considerably from sample to sample, compared with those after GFC [26]. However, during recent years precipitation with polyethylene glycol (PEG) has been commonly used to separate the isoforms of PRL as a simple, cheap, accessible, rapid, reproducible and the most suitable technique for screening of macroprolactin in hyperprolactinemic patients [19,27,28]. A concentration of 25% PEG is added to the same volume of serum and after a short period of incubation it is centrifuged to precipitate out macroprolactin. Although it is not necessary to incubate the PEG-treated sample, the use of cold PEG and vortex mixing are important. Total PRL is defined as the PRL concentration in the water-treated sample and free PRL is defined as the PRL concentration in the supernatant after PEG precipitation. The amount of macroprolactin can be calculated as follows: (total PRL−free PRL)/total PRL × 100 which represents the PEG−precipitable PRL (%). It has become accepted that a PEG-precipitation ratio greater than 60%, or recovery less than 40% after PEG, is considered the reliable criteria for the diagnosis of macroprolactinemia. Since precipitation using 5-fold diluted serum with 25% PEG6000 can effectively reduce macroprolactin concentrations by increasing the PRL recovery rate, this represents a new method for the detection of genuine hyperprolactinemia [6,9,25,27–29]. Nevertheless, PEG may also induce a partial precipitation of monomeric PRL (up to 25%) and therefore this method lacks specificity, which may result in an underestimation or misinterpretation of PRL concentrations in cases of macroprolactinemia with simultaneously supraphysiological of monomeric PRL [9,25,27,30]. Since it has been demonstrated that the presence of PEG in the sample can interfere with some PRL immunoassay procedures, it has been recommended that each laboratory, undertaking macroprolactin screening, should establish method-specific reference intervals derived by use of PEG-treated sera from healthy individuals [9,27,30,31].

Although radiological evaluation of pituitary imaging by computerized axial tomography (CT) or magnetic resonance imaging (MRI) in patients with macroprolactinemia is usually negative, a few cases of radiographic abnormalities have been recently reported. The prevalence of macroprolactinemia among newly diagnosed patients with prolactinoma was similar compared with the control group of healthy subjects (3.5 vs. 3.7%). The coexistence of a pituitary adenoma and macroprolactinemia or macroprolactin production by the pituitary tumor itself has been offered as an explanation in these rare cases [12].

Pathophysiology

The pathogenesis of macroprolactinemia is mainly thought to be an extrapituitary, post-secretory phenomenon of anti-PRL autoantibodies, which are confined to the vascular system due to the high molecular weight of the macroprolactin molecules. The consequence is an asymptomatic state with a typical lack of bioactivity *in vivo* due to normal concentrations of monomeric PRL levels and the inability of macroprolactin to cross the endothelium to access PRL receptors in the extravascular compartment and centrally. Moreover, in the presence of anti-PRL antibodies, the renal clearance of PRL is slower which precludes filtration of the bound PRL filtration from the glomeruli, and therefore macroprolactinemia results due to the delayed clearance of PRL rather than increased production. Since these PRL antibodies remain stable during a long-term follow-up (>10 years), macroprolactinemia may be regarded as a state of longer duration [3–5,19,29]. Another reason for lower biological activity of macroprolactin and lack of typical hyperprolactinemic symptoms, may be the competitive binding of anti-PRL autoantibodies to their binding sites (epitopes) on PRL

molecules near the binding site 1 which are recognized by PRL receptors [32]. In addition, the biological activity of macroprolactin is dependent upon the bioassay used, because it is considerably lower toward the homologous receptor-mediated Ba/F-LLP assay, than in the commonly used heterologous rat Nb2 cell assay [33]. The pathogenesis of PRL antibodies is still controversial because some autoimmune disorders such as systemic lupus erythematodes may be accompanied with macroprolactinemia and monomeric hyperprolactinemia [34], whereas other studies found no evidence of specific correlation [20,35]. Furthermore, it may be that environmental factors and genetic susceptibility are the potential mechanisms included in the genesis of anti-PRL autoantibodies, which may alter the immune response in hosts in a similar manner like to other autoimmune disorders [36]. However, since pituitary PRL with some changes in its molecule represents an increased antigenicity to the immune system it may cause an autoimmune response resulting in the production of anti-PRL antibodies [37]. It seems that PRL antibodies represent the cause of mild hyperprolactinemia commonly found in patients with hyperprolactinemia due to a significant positive correlation between anti-PRL autoantibody titers and slower serum clearance of macroprolactin from the bloodstream. Furthermore, the complex autoantibody-bound PRL may be a cause for the absence of the hypothalamic feedback mechanism, because macroprolactin cannot access the hypothalamus due its higher size. Consequently, the hormonal concentrations of serum estradiol and luteinizing hormone (LH) are usually significantly higher in patients with macroprolactinemia than individuals with monomeric hyperprolactinemia [10,14,18,38]. Despite the fact that the majority of patients with macroprolactinemia reflect asymptomatic clinical presentation, hyperprolactinemia-related symptoms commonly occur mainly due to the rise in the levels of monomeric PRL, similar to individuals with true hyperprolactinemia [7–11]. In cases with the supraphysiological concentrations of monomeric PRL, the hypothalamic negative feedback mechanism restores by increasing of hypothalamic dopaminergic neuronal activity, to normalize elevated free PRL levels. In addition, the increased concentrations of monomeric PRL lead to suppression of kisspeptin-1 expression, secretion of GnRH and gonadotropins, resulting in oligomenorrhea or amenorrhea and reflected as an anovulatory infertility [39]. The final result of gonadotropins suppression is dependent of monomeric PRL levels and varies from a short luteal phase to amenorrhea or hypogonadism. Lower PRL concentrations in patients with mild hyperprolactinemia (20–50 ng/mL) may cause poor preovulatory follicular development with a short luteal phase, moderate hyperprolactinemia (50–100 ng/mL) usually leads to oligomenorrhea or amenorrhea, whereas higher PRL levels (>100 ng/mL) frequently result in profound hypogonadotropic hypogonadism [1]. The increased levels of monomeric PRL responsible for typical hyperprolactinemia-related symptoms frequently found in patients with macroprolactinemia may be coincidental [10], or may be explained by intermittent dissociation of the macroprolactin complex in some cases [40]. Furthermore, the simultaneous presence of macroprolactinemia and increased levels of monomeric may be found in pregnancy or due to pharmacological or pathological causes such as stress, hypothyroidism, renal and hepatic failure, intercostal nerve stimulation by trauma or surgery, and polycystic ovary disease. It is important in these symptomatic patients with macroprolactinemia to establish the exact pathologic state and to introduce dopaminergic agonists or other treatment modalities regardless of the presence of macroprolactin, because the presence of increased levels of monomeric PRL is of primarily concern. However, the use of dopamine agonists is not recommended in a macroprolactinemic patient with normal monomeric PRL levels who should be correctly evaluated for irregular menses or infertility because other causes for these symptoms could coexist with macroprolactinemia. Idiopathic hyperprolactinemia should be considered in cases if all other causes in addition to pituitary findings may be excluded [41]. However, similar hyperprolactinemia-related symptoms occurred in rare cases of macroprolactinemia associated with prolactinoma. Although macroprolactin has been generally considered as a biologically inactive molecule, decrease of macroprolactin levels after dopamine treatment suggests pituitary origin and biological activity of the high-molecular isoform comparable with that of monomeric prolactin isoform in these rare cases [12]. Since the presence of macroprolactinaemia and raised free PRL levels in women with oligo-/amenorrhoea may be associated with high risk of a micro- or a macro-pituitary adenoma (36%), therefore pituitary MRI has been suggested as mandatory in all such cases [42]. An extreme form of macroprolactinemia and an invasive pituitary macroadenoma has been reported in a female patient with hypogonadotropic hypogonadism, secondary amenorrhea, mild obesity, hirsutism, headache and blurred vision. The significant decrease in macroprolactin levels and tumor volume in response to dopamine agonist therapy, instead of transsphenoidal surgery, was suggestive for the pituitary origin of this isoform. Disappearance of clinical signs with normalization of gonadotropin levels were arguments in favor of preserved-macroprolactin bioactivity [43]. Similarly, the recovery of gigantomastia and macroprolactinemia with cabergoline treatment as an alternative to surgery may be suggestive of the possible role of macroprolactinemia in the etiology of gigantomastia. Macroprolactinemia may be attributed to pituitary adenoma itself as well as to breast tissue or may be incidental, although it could not be identified because pituitary surgery and histopathological evaluation were not made [44].

Conclusion

Since macroprolactinemia in women with hyperprolactinemia is determined by the origin of macroprolactin, the presence of hyperprolactinemia-related symptoms, and monomeric PRL levels, its role is currently controversial as it may lead to clinical dilemmas. Macroprolactinemia is mostly considered an extrapituitary phenomenon of mild and asymptomatic hyperprolactinemia with normal concentrations of monomeric PRL and the predominance of macroprolactin confined to the vascular system, which is biologically inactive. In such asymptomatic patients macroprolactinemia should be considered a benign clinical condition with resistance to antiprolactinemic drugs and no diagnostic investigations or medical treatment during prolonged follow-up are required. However, a significant proportion of macroprolactinemic patients suffer from typical hyperprolactinemia-related symptoms and radiologically diagnosed pituitary findings, which are usually associated with true hyperprolactinemia. The symptoms of hyperprolactinemia are mostly correlated to the levels of monomeric PRL excess, which may be explained as coincidental, by dissociation of macroprolactin, or by physiological, pharmacological or pathological causes. In addition, higher levels of monomeric PRL may be correlated with severity of the symptoms, which vary from a short luteal phase to amenorrhea with hypogonadotropic hypogonadism. However, macroprolactinemia of pituitary origin associated with pituitary adenomas may rarely occur with typical symptoms of hyperprolactinemia due to bioactive macroprolactin. In these cases macroprolactinemia represents a pathological biochemical variant of hyperprolactinemia. Since macroprolactinemia is a common cause of hyperprolactinemia and many clinical or laboratory features cannot be used reliably to differentiate macroprolactinemia from true hyperprolactinemia, routine screening for all hyperprolactinemic sera with PEG might prevent the unnecessary use of

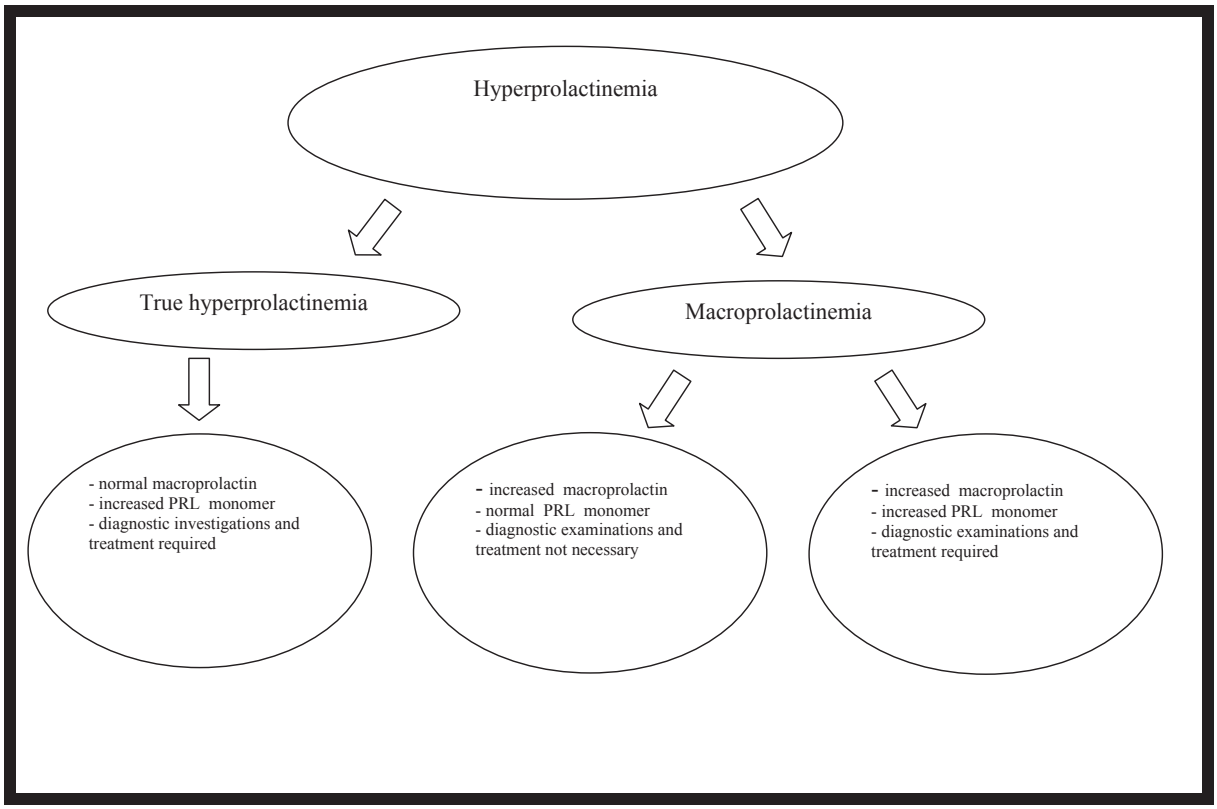

Fig. 1. Laboratory screening of hyperprolactinemic patients.

diagnostic investigations and treatment. Accordingly, physicians should encourage laboratories to make the measurement of macroprolactin in daily practice for such patients with hyperprolactinemia. The presence or absence of free PRL concentrations in patients with macroprolactinemia is crucial whether further examinations or treatments with dopamine receptor agonists are necessary or not. If free PRL concentrations are normal, further examinations and treatments are not necessary. But they are required if monomeric PRL levels are elevated. It is important in these symptomatic patients with macroprolactinemia to establish the exact pathologic state and to introduce dopaminergic agonists or other treatment modalities regardless of the presence of macroprolactin, because the presence of increased levels of monomeric PRL is of primarily concern (Fig. 1).

Conflicts of interest statement

The authors have no financial or non-financial conflicts of interest relevant to this article.

References

[1] Fritz MA, Speroff L. Hormone biosynthesis, metabolism, and mechanism of action. In: Fritz MA, Speroff L, editors. Clinical gynecologic endocrinology and infertility. 8th ed. Philadelphia: Lippincott Williams & a Wolters Kluwers Bussiness; 2011. p. 29–105.
[2] Majumdar A, Mangal NS. Hyperprolactinemia. J Hum Reprod Sci 2013;6:168–75.
[3] Molitch ME. Prolactin in human reproduction. In: Strauss III JF, Barbieri R, editors. Yen and Jaffe's reproductive endocrinology: physiology, pathophysiology, and clinical management. 7th ed. Philadelphia: Elsevier Saunders; 2014. p. 45–65.
[4] Radavelli-Bagatini S, Lhullier FL, Mallmann ES, Spritzer PM. Macroprolactinemia in women with hyperprolactinemia: a 10-year follow-up. Neuro Endocrinol Lett 2013;34:207–11.
[5] Wallace IR, Satti N, Courtney CH, Leslie H, Bell PM, Hunter SJ, et al. Ten-year clinical follow-up of a cohort of 51 patients with macroprolactinemia establishes it as a benign variant. J Clin Endocrinol Metab 2010;95:3268–71.
[6] Gibney J, Smith TP, McKenna TJ. The impact on clinical practice of routine screening for macroprolactin. JCEM 2005;90:3927–32.
[7] Can M, Guven B, Atmaca H, Acıkgoz S, Mungan G. Clinical characterization of patients with macroprolactinemia and monomeric hyperprolactinemia. Kaohsiung J Med Sci 2011;27:173–6.
[8] Vilar L, Naves LA, Freitas MC, Lima M, Canadas V, Albuquerque JL, et al. Clinical and laboratory features greatly overlap in patients with macroprolactinemia or monomeric hyperprolactinemia. Minerva Endocrinol 2007;32:79–86.
[9] McCudden CR, Sharpless JL, Grenache DG. Comparison of multiple methods for identification of hyperprolactinemia in the presence of macroprolactin. Cl Chim Acta 2010;411:155–60.
[10] Suliman AM, Smith TP, Gibney J, McKenna TJ. Frequent misdiagnosis and mismanagement of hyperprolactinemic patients before the introduction of macroprolactin screening: application of a new strict laboratory definition of macroprolactinemia. Clin Chem 2003;49:1504–9.
[11] Fahie-Wilson M, Smith TP. Determination of prolactin: the macroprolactin problem. Best Pract Res Clin Endocrinol Metab 2013;27:725–42.
[12] Elenkova A, Genov N, Abadzhieva Z, Vasilev V, Kirilov G, Zacharieva S. Macroprolactinemia in patients with prolactinomas: prevalence and clinical significance. Exp Clin Endocrinol Diabetes 2013;121:201–5.
[13] Bjoro T, Makrid L, Wergerland R, Turter A, Kvistborg A, Sand T. Frequency of hyperprolactinemia due to large molecular weight prolactin (150-170 kD PRL). Scand J Clin Lab Investig 1995;55:139–47.
[14] Hattori N, Ishihara T, Saiki Y. Macroprolactinemia prevalence and aetiologies in a large group of hospital workers. Clin Endocrinol (Oxf) 2009;71:702–8.
[15] Hauache OM, Rocha AJ, Maia AC, Maciel RM, Vieira JG. Screening for macroprolactinemia and pituitary imaging studies. Clin Endocrinol (Oxf) 2002;57:327–31.
[16] Whittaker PG, Wicox T, Lind T. Maintained fertility in a patient with hyperprolactinemia due to big-big prolactin. J Clin Endocrinol Metab 1981;53:863–6.
[17] Anderson AN, Pedersen H, Djursing H, Andersen BJ, Friesen HG. Bioactivity of prolactin in a woman with an excess of large molecular size prolactin, persistent hyperprolactinemia and spontaneous conception. Fertil Steril 1982;38:625–8.
[18] Jackson RD, Wortsman J, Malarkey WB. Macroprolactinemia presenting like a pituitary tumor. Am J Med 1985;78:346–50.
[19] Leslie H, Courtney CH, Bell PM, Hadden DR, McCance DR, Ellis PK, et al. Laboratory and clinical experience in 55 patients with macroprolactinemia

identified by a simple polyethylene glycol precipitation method. J Clin Endocrinol Metab 2001;86:2743–6.
[20] Vallette-Kasic S, Morange-Ramos I, Selim A, Gunz G, Morange S, Enjalbert A, et al. Macroprolactinemia revisited: a study on 106 patients. J Clin Endocrinol Metab 2002;87:581–8.
[21] Thirunavakkarasu K, Dutta P, Sridhar S, Dhaliwal L, Prashad GR, Gainder S, et al. Macroprolactinemia in hyperprolactinemic infertile women. Endocrine 2013;44:750–5.
[22] Krysiak R, Drosdzol-Cop A, Skrzypulec-Plinta V, Okopien B. Sexual function and depressive symptoms in young women with elevated macroprolactin content: a pilot study. Endocrine 2016;53:291–8.
[23] Isik S, Berker D, Tutuncu YA, Ozuguz U, Gokay F, Erden G, et al. Clinical and radiological findings in macroprolactinemia. Endocrine 2012;41:327–33.
[24] Lu CC, Hsieh CJ. The importance of measuring macroprolactin in the differential diagnosis of hyperprolactinemic patients. Kaohsiung J Med Sci 2012;28:94–9.
[25] Kavanagh L, McKenna TJ, Fahie-Wilson MN, Gibney J, Smith TP. Specificity and clinical utility of methods for the detection of macroprolactin. Clin Chem 2006;52:1366–72.
[26] Beda-Maluga K, Pisarek H, Komorowski J, Pawlikowski M, Świętosławski J, Winczyk K. The detection of macroprolactin by precipitation and ultrafiltration methods. Endokrynol Pol 2011;62:529–36.
[27] Espinoza JR, Trigos-Landa A, Bocanegra-Garcia V, Acosta-González RI, Bocanegra-Alonso A, Rivera-Sánchez G. Assessment of macroprolactin after polyethylene glycol precipitation in two commercial immunoassay. Bioquimia 2006;31:140–5.
[28] Hattori N, Adachi T, Ishihara T, Shimatsu A. The natural history of macroprolactinaemia. Endocrinol 2012;166:625–9.
[29] Shimatsu A, Hattori N. Macroprolactinemia: diagnostic, clinical, and pathogenic significance. Clin Dev Immunol 2012;2012:167132.
[30] Beltran L, Fahie-Wilson MN, McKenna TJ, Kavanagh L, Smith TP. Serum total prolactin and monomeric prolactin reference intervals determined by precipitation with polyethylene glycol: evaluation and validation on common immunoassay platforms. Clin Chem 2008;54:1673–81.
[31] Chen Y, Wang H, Yang W, Jin W, Yu W, Wang W, et al. A new method of using polyethylene glycol (PEG) precipitation of macroprolactin to detect genuine hyperprolactinemia. J Clin Lab Anal 2016;30:1169–74.
[32] Lippi G, Plebani M. Macroprolactin: searching for a needle in a haystack? Clin Chem Lab Med 2016;54:519–22.
[33] Glezer A, Soares CR, Vieira JG, Giannella-Neto D, Ribela MT, Goffin V, et al. Human macroprolactin displays low biological activity via its homologous receptor in a new sensitive bioassay. J Clin Endocrinol Metab 2006;91:1048–55.
[34] Toffoli Ribeiro C, Louzada Júnior P, de Sá MF. Correlation between systemic lupus erythematosus activity and plasma levels of monomeric prolactin and macroprolactin. Endocr Metab Immune Disord Drug Targets 2016;16:21–7.
[35] Kavanagh-Wright L, Smith TP, Gibney J, McKenna TJ. Characterization of macroprolactin and assessment of markers of autoimmunity in macroprolactinaemic patients. Clin Endocrinol (Oxf) 2009;70:599–605.
[36] Marrack P, Kappler J, Kotzin BL. Autoimmune disease: why and where it occurs. Nat Med 2001;7:899–905.
[37] Hattori N, Ikekubo K, Nakaya Y, Kitagawa K, Inagaki C. Immunoglobulin G subclasses and prolactin (PRL) isoforms in macroprolactinemia due to anti-PRL autoantibodies. J Clin Endocrinol Metab 2005;90:3036–44.
[38] Leaños-Miranda A, Ramírez-Valenzuela KL, Campos-Galicia I, Chang-Verdugo R, Chinolla-Arellano LZ. Frequency of macroprolactinemia in hyperprolactinemic women presenting with menstrual irregularities, galactorrhea, and/or infertility: etiology and clinical manifestations. Int J Endocrinol 2013;2013:478282.
[39] Bernard V, Young J, Chanson P, Binart N. New insights in prolactin: pathological implications. Nat Rev Endocrinol 2015;11:265–75.
[40] Olukoga AO. Macroprolactinemia is clinically important. J Clin Endocrinol Metab 2002;87:4833–4.
[41] Glezer A, Bronstein MD. Approach to the patient with persistent hyperprolactinemia and negative sellar imaging. J Clin Endocrinol Metab 2012;97:2211–6.
[42] Lewandowski KC, Gasior-Perczak D, Kowalska A, Lewinski A. Coexistence of macroprolactinaemia and hyperprolactinaemia in women with oligo-/amenorrhoea is associated with high risk of pituitary adenomas. Gynecol Endocrinol 2014;30:385–7.
[43] Elenkova A, Abadzhieva Z, Genov N, Vasilev V, Kirilov G, Zacharieva S. Macroprolactinemia in a patient with invasive macroprolactinoma: a case report and minireview. Case Rep Endocrinol 2013;2013:634349.
[44] Dellal FD, Ozdemir D, Aydin C, Kaya G, Ersoy R, Cakir B. Gigantomastia and macroprolactinemia responding to cabergoline treatment: a case report and minireview of the literature. Case Rep Endocrinol 2016;2016:3576024.