How to deal with hyperprolactinaemia?

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Abstract

Hyperolactinaemia is the most common endocrine disorder of the hypothalamic – pituitary axis. Normal range of assay is 1-25 ng/ml. Physiologically production of prolactin increased during stress, breast feeding, exercise and sleep. Hyperprolactinaemia is defined as a prolactin (PRL) level exceeding 25 ng/ml.

Key words: hyperprolactinaemia, prolactine, macroprolactine, prolactinoma

Introduction

Secretion of prolactin (PRL) is pulsatile. Prolactin is a protein synthesised and secreted by lactotrophs in the anterior pituitary gland. Normal range of assay is 1-25 ng/ml. In international units it is about 500 IU/ml [3]. The production of prolactin is stimulated by thyrotropin-releasing hormone (TRH), dopamine receptor agonists, vasoactive intestinal peptide (VIP) and epidermal growth factor. Hyperprolactinaemia is also often observed in primary hypothyroidism with high TRH levels. The prolactin secretion is inhibited by dopamine via D2-type receptors located on lactotrophs. Physiologically production of prolactin increased during breast feeding, stress, exercise or sleep [2].

Prolactin stimulates breast epithelial cells proliferations and maintains milk production. Estrogen stimulates the proliferation of lactotroph cells in pituitary gland but the high level of estrogen during pregnancy inhibits lactation. After the delivery when estrogen level decreases lactation is unblocked. During the lactation menstrual periods and ovulations are usually stopped but this is not a rule. Therefore breast feeding is not considered as a fertility period.

Hyperprolactinaemia

Hyperolactinemia is the most common endocrine disorder of the hypothalamic – pituitary axis. The incidence of the condition is less than 1% of general population. However among women in reproductive age the occurrence of hyperprolactinaemia is between 5 and 14%, in subgroup of infertile women – 30 to 40% [1].

Hyperprolactinaemia is defined as a prolactin level exceeding 25 ng/ml. If the prolactin level is more than 100 ng/ml. Some investigators suggest evaluation of hyperprolactinaemia by MRI imaging only in every patient while others recommend imaging studies for all those with persistently elevated PRL levels. Prolactin level greater than 250 ng/ml and less than 500 ng/ml usually indicates microprolactinoma, but the effect of some drugs (including metoclopramide and risperidone) should be excluded. With prolactin level greater than 500 ng/ml diagnosis of macroprolactinoma should be set [4]. For diagnosis of hyperprolactinaemia dynamic tests of prolactine secretion with TRH, metoclopramide are not better than measuring a single fasting serum prolactin sample [5].

In every asymptomatic patient with elevated prolactin level the measurement of macroprolactin should be performed. Macroprolactin is less bioactive but about 40% of hyperprolactinaemia patients have macroprolactine [6]. Measurement of macroprolactin can eliminate unnecessary additional diagnostic tests and following needless pharmacological treatment [7].

Consequences of chronic hyperprolactinaemia

Hyperprolactinaemia cause hypogonadal syndromes (oligomenorrhea, infertility, galactorrhea) and general disorders. The clinical consequences of chronic hyperprolactinaemia include: sexual dysfunction (diminished libido, orgasmic dysfunction and impotence), reproductive dysfunction (anovulation, irregular menses, subfertility, decreased oestrogen and testosterone levels),

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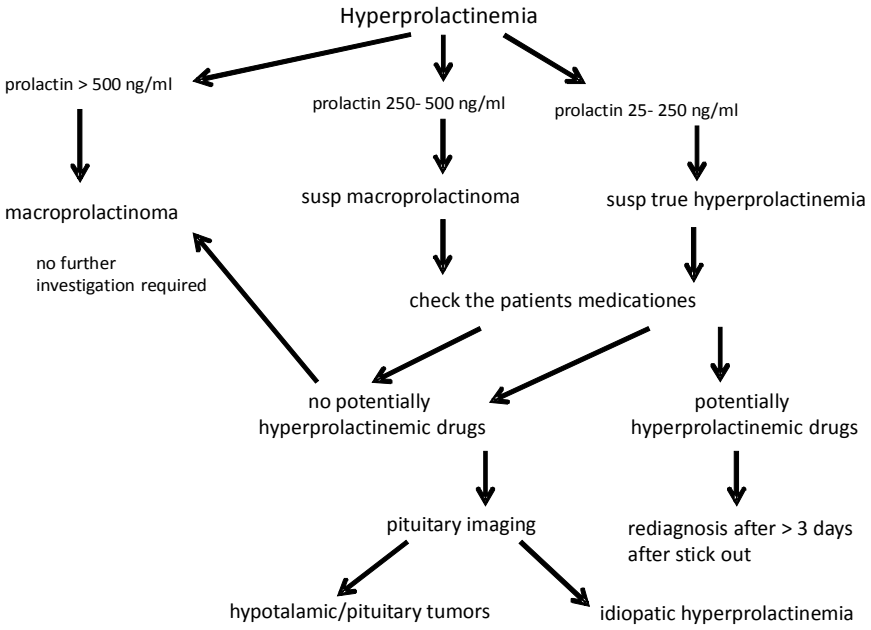

Fig. 1. The diagnostic diagram of hyperprolactinaemia

breast pathology (galactorrhea, breast enlargement, dysplasia) and other morbidities (bone demineralisation, damage ofcardiovascular endothelium, depression).

The clinical symptoms do not always correlates with the prolactin levels. Even patients with normal prolactin levels may have tumors. Highest prolactin levels are not always associated galactorrhea. Elevated PRL levels lead to inhibition of the pulsatile secretion of GnRH and finally to secondary amenorrhea but approximately 30% of women with galactorrhea have normal menses. One third of patients with secondary amenorrhea have pituitary adenoma and if galactorrhea is also present half of them have abnormal sella turcica [8]. Prolactinoma is associated with galactorrhea, sexual dysfunction and decrease bone density.

Differential diagnosis

The differential diagnosis of hyperprolactinaemia includes: hypothalamic pituitary tumors, ingestions of medicines which depleted dopamine or block its action at the receptor, neurogenic chest wall lesions, hypothyroidism, and polycystic ovary syndrome, cirrhosis and end-stage renal failure.

Management

Dopamine agonists therapy in both micro- and macroadenomas is the first line of treatment which decreases prolactine levels, tumor size and restores gonadal functions. The most frequently used medications are cabergoline, bromocriptine and quinagolide. Cabergoline is more effective than bromocriptine [6]. About 10% of patients with microadenomas and 18% of patients with macroadenomas do not respond to cabergoline therapy. In those patients the normal prolactine levels could not be achieved using cabergoline and transphenoidal surgery they should be offered [9]. The recent studies suggest the pharmacological treatment of pituitary tumors should last for 2 years. The dopamine agonists can be discontinued if the prolactin level is normal and there are no visual disturbances [10-12]. Approximately 10% of patients do not tolerate oral bromocriptine therapy. In such cases vaginal route should be considered.

Table 1. The most frequently dopamin agonists in the treatment of hiperprolactinemia

Medicine	Tablet	$t_{1/2}$	Duration of action	Dosage
Bromocriptine	2.5 mg	3.3 h	8-12 h	2.5-5 mg
Quinagolide Norprolac	25/50 μg 75/150 μg	22 h	24 h	75-150 μg
Cabergoline Dostinex	0.5 mg	65 h	7-14 dni	0.25-2 mg/weeek

The management of drug-induced hyperprolactinaemia in asyptomatic patients include discontinuation of antipsychotic drugs, of course under the supervision and with the consent of the patient's psychiatrist. The discontinuation should last for which The level of prolactine should be measured again not until 3 days after break of

treatment. The latest recommendations suggests not to treat asymptomatic drug-induced hyperprolactinemic patients. The only concern in those patient is long term hypogonadism and bone demineralisation, so those patients should be offered estogen or testosterone therapy [13-15].

Prolactinoma during pregnancy

In the pregnant women the level of prolactin increases physiologically up to 10 times of normal level. In case of microprolactinoma diagnosed and treated earlier the dopamine agonists should be discontinued during pregnancy although there is no evidence that bromocriptine and cabergoline ingestion in early pregnancy is harmful to the foetus. In some patients with macradenoma tumors the pharmacological therapy should be continued throughout the pregnancy. In the diagnosis statement the MRI can be performed during pregnancy but the use of gadolinium is prohibited [16-19].

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