

Management of idiopathic hyperprolactinemia: a case report and review article

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Abstract. Prolactin is a hormone derived from the anterior pituitary that plays an important role in various reproductive functions. High serum prolactin concentration (hyperprolactinemia) in women of reproductive age decreases gonadotropin secretion thus creating a condition called hypo gonadotropic hypogonadism. This condition is known to reduce ovarian cyclic function, decrease the frequency of menstrual cycles (oligomenorrhea), and even stop menstrual cycles altogether (amenorrhea). Increased levels of prolactin can cause galactorrhea, and other estrogen deficiency symptoms, such as loss of sexual desire, vaginal dryness, and even infertility. One example is a case of a 28-year-old woman with chief complaints of milky white fluid coming out from both breasts for one year. The patient is not pregnant and is not breastfeeding. Other complaints included the patient having irregular menstruation for six months, and pain during intercourse. The patient has been married four years and has never been pregnant. Prolactin levels were increased to 72 ng / dL and by examining thyroid function within normal limit with TSHs level 1,375 μ IU / mL, and Ft4 level 11.62 Pmol / L. Head MRI examination is carried out in cases of hyperprolactinemia to look for lesions in the hypothalamic-pituitary region and in this case it was of the Pons, Medulla Oblongata and Symmetrical Cerebellum with normal homogeneous signal intensity and no visible hyper-intense lesions or pathological hypointens. Hyperprolactinemia can be caused by hypothalamic-pituitary disease (prolactinoma) and Non-hypothalamic-pituitary disease. Patients diagnosed with idiopathic hyperprolactinemia by MRI examination of the head, the results were within normal limit and from other examination which can induce hyperprolactinemia could not be found. Patients are given bromocriptine therapy to reduce prolactin levels, and must be evaluated in every 3-6 months.

Keywords: *Hyperprolactinemia, Oligomenorrhea, galactorrhea, infertility*

Introduction

Prolactin (PRL) is a hormone secreted by the pituitary glands that plays an important role in reproduction such as stimulating breast milk production in post partum woman. Hyperprolactin defined as prolactin level > 35 ng/mL, where the normal level of prolactin in woman is 10 – 35 ng/mL. ⁽¹⁾

Secretion of prolactin is regulated by tonic dopamine inhibitor secretion. It is stimulated by hypothalamic peptide, thyrotropin releasing hormone (TRH), vasoactive intestine peptide (VIP), epidermal growth factor and dopamine antagonist hormone. Fenotazin or other medications that inhibit dopamine receptors or catecholamine levels which work as monoamine oxidase inhibitors cause hyperprolactinemia. Tumors, radiation or infiltrative diseases such as sarcoidosis and tuberculosis can impair pituitary

axis and affect inhibition of prolactin secretion which is mediated by dopamine. Primary hypothyroidism also causes a mild increase in prolactin serum level. High levels of estrogen that are triggered by stress and exercise also stimulate prolactin secretion. ⁽²⁾

Pathological hyperprolactinemia affected by hypothalamic – pituitary disease and also non-hypothalamic – pituitary disease. In reproductive age woman with high concentrations of prolactin serum levels can decrease gonadotropin secretion which decrease ovarian cyclic function, menstrual cycle frequency decreasing (oligomenorrhea), and even stopping the cycle (amenorrhea). ⁽³⁾ High level serum prolactin in non pregnant woman can cause galactorrhea, deficiency estrogen symptoms such as loss of sexual desire, vaginal dryness and infertility. There is a significant correlation between hyperprolactinemia and galactorrhea even though it does not fully affect

fertility, but the average time to get pregnant in this group of patients is longer than usual.⁽³⁾⁽⁴⁾

Case Report

A 28-year old woman came up at Polyclinic RSUDZA Banda Aceh, July 2nd 2019, referred from Cut Nyak Dhien Hospital, Meulaboh – West Aceh with chief complaints of milky – white discharge similar to breast milk coming from both breasts that started one year ago with pain and breast enlargement. The was pain relieved after the substance has been extracted from both breasts via the nipples. The patient did not complain about symptoms after the procedure and at the time was not breastfeeding. She has never gotten pregnant in her 4 years of marriage. Dyspareunia came and went for one month after the procedure and the patient did not complain of any bleeding during intercourse.

The Patient also complained about headache that occurred to behind the eyeball and got worse over the course of a year with no visual disorders. There was no chest discomfort or breathing problems. There were no complaints about abdominal tenderness and pain.

Micturition and defecation were smooth with no complaints. Complaint of extremities tremors and damp hands were not reported. The patient had irregular menstrual cycles for the last six months. She took bromocriptine irregularly not in accordance with her doctor's instruction. The patient had been married four years and was not pregnant.

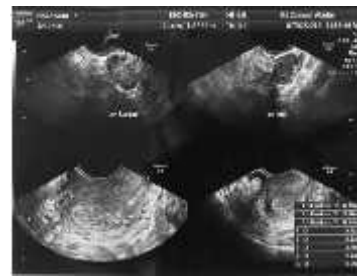
Physical examination findings, breast in normal shape and size, no palpable masses, there is milky – white discharge from both nipples.

Laboratory findings, hemoglobin level 13.1 g/dl, leucocyte level $0.3 \times 10^3/\mu\text{L}$, hematocrit 38 %. Thrombocyte $298 \times 10^3/\mu\text{L}$. Thyroid function test, TSHs 1,375 $\mu\text{IU/mL}$, Ft4 11,62 Pmol/L, and Prolactin level is 72 ng/dL.

Transvaginal ultrasound examination found uterus in normal shape and size, 5.3 cm x 3.08 cm x 3.17 cm x 2.1 cm with the largest follicles size is 7.3 mm and left ovarian size is 2.45 cm x 2.0 cm. Head Magnetic Resonance Imaging (MRI), Pons, medulla Oblongata and symmetrical cerebellum with normal homogeneous signal intensity, no hyper intense or hypo intense pathological lesions. CerebeloPontin axis within

normal limit, tentorium's intact, no sign of space occupying lesion (SOL) or signs of inflammation. Arachnoid space within normal limits and cerebrospinal fluid also within normal limits (figure 1 and 2). Patient diagnosed with idiopathic hyperprolactinemia with primary infertile.

Patient treated with bromocriptine 2x2.5 mg. Complaints of breast discharge and irregular menstruation resolves after 2 weeks of treatment. Patient plans to have FSH, LH and progesterone levels checked to evaluate the reason for infertility.



(Figure 1. Transvaginal Ultrasound)



(Figure 2. Head MRI)

Discussion

Hyperprolactinemia is defined as high concentration prolactin level in bloodstream, caused by medications that corresponds to dopaminergic pathways in hypothalamic – pituitary axis, and idiopathic. Prolactin is a polypeptide 23 kDa hormone, synthesized in lactotroph cells and secreted from alpha cells of the pituitary anterior gland. Its role in reproduction physiology is still unknown; in fact there is a correlation between a high rate of anovulation and high plasma levels of prolactin.

(2)(3)(5)

Prolactin is also produced outside the pituitary glands, such as mammae glands, placenta, uterus, T lymphocyte and endometrial stromal cells in pregnant woman. The normal level of prolactin is 10 – 35 ng/L. PRL sampling will be optimally taken in the morning.⁽¹⁾⁽⁶⁾ The main cause of hyperprolactinemia from the pituitary gland is macroedema and hyperprolactin idiopathic. Idiopathic hyperprolactinemia means finding high levels of prolactin serum in the blood with no causes to be found.⁽⁷⁾⁽⁸⁾

In this case, the cause of milky white breast discharge like breast milk from both nipples is still unknown. Galactorrhea is breast milk production in non-breastfeeding woman. It consists of fat. High levels of prolactin is found in 1/3 amenorrhea idiopathic cases. Prolactin is the most important hormone that affects pathophysiological of amenorrhea and galactorrhea. There is a list of drugs that causes galactorrhea such as dopamine receptor blocker (Butyrophenones, Metoclopramide, Phenothiazines, Risperidone), dopamine depleting agents (Methyldopa, Reserpine), dopamine releasing blockers (codein, Heroin, Morphine), histamine receptor blockers (Cimetidine), lactotroph stimulating agents (oral contraception, Verapamil). These agents can suppress hypothalamic secretion.⁽⁹⁾⁽¹⁰⁾⁽¹¹⁾ However, in this case the patient had no history of medication use that consisted of those agents.

The patient complained of headaches that spread to the back of the eyeball for one year, without any visual disorder. In prolactinoma cases, headache refers to the back of the eyeball and comes with visual disorders. In this case there was appearance of a tumor in the pituitary area upon MRI examination, but this complaint must still be evaluated.⁽¹²⁾ An MRI of the head should be performed on patients with hyperprolactinemia to look for mass lesions in the hypothalamic-pituitary region, unless the patient is using a drug that is known to cause hyperprolactinemia.⁽⁷⁾⁽¹³⁾

Patient also complains about dyspareunia, irregular menstruation for the last six months and was not pregnant after 4 years of marriage. Hyperprolactinemia causes 10 – 20 % of amenorrhea cases. The main mechanism that causes amenorrhea is due to an increase in the central dopamine reflex. This mechanism appears to involve the inhibition of luteinizing hormone

(LH), and possibly secretion of follicle stimulating hormone (FSH), through inhibiting the release of gonadotropin-releasing hormone (GHRH), thereby disrupting folliculogenesis. These mechanisms affect the decreasing secretion of LH and FSH and lost of ovarian stimulation which results in hypogonadism, infertility, and amenorrhea. Prolactin may also have a direct effect on GnRH neurons and or pituitary gonadotroph or on other afferent GnRH neurons.⁽¹⁵⁾ (Figure 3)

In pregnant woman, hypogonadism causes oligomenorrhea that can also cause infertility. Hyperprolactinemia is a cause of infertility in woman and is included in the WHO classification class 4. Current studies report hyperprolactinemia doesn't affect fertility directly, but the average time to get pregnant in this group of patients is longer than usual.⁽¹⁶⁾⁽¹⁷⁾⁽¹⁸⁾

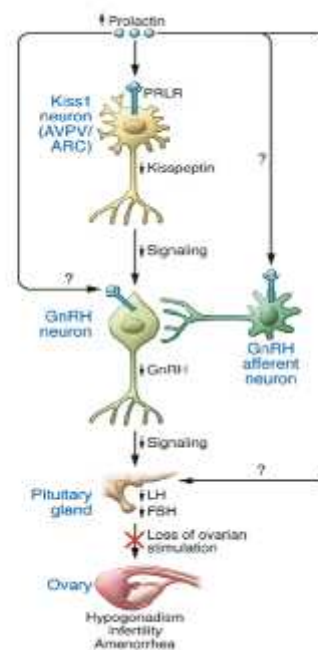


Figure 3. The diagram illustrates the process of hyperprolactinemia causing amenorrhea. (Modified from Kaiser UB. *Hyperprolactinemia and infertility : new insights*. 2012;122(10):3467–8)

The effects of estrogen deficiency can cause conditions such as loss of sexual desire, dryness in the vagina and dyspareunia.⁽¹⁹⁾

Cabergoline is the first line therapy for hyperprolactinemia whereas bromocriptine is the

second line. Cabergoline is dopamine ergot agonist that can be given for 1 or 2 times a week and has a lower nausea effect than bromocriptine. At high doses cabergoline is used for the treatment of Parkinson's disease, cabergoline is associated with an increased risk of valvular heart disease, and at low doses it is usually used for the treatment of hyperprolactinemia. At the moment cabergoline not available in the Banda Aceh regional hospital, so bromocriptine can be a replacement, which has been used for approximately three decades for the treatment of hyperprolactinemia. It is given two times a day for optimal effect.⁽²¹⁾ Prolactin levels must be evaluated every month for 3 – 6 months.⁽¹⁹⁾

There are 3 main reasons, why a patient with hyperprolactinemia needs to be treated. First, due to neurological symptoms caused by the large size of lactotroph adenoma, and second because of hypogonadism or other symptoms of hyperprolactinemia, such as galactorrhea. Finally for women with mild hyperprolactinemia with normal menstrual cycle that is trying to get pregnant but has luteal phase dysfunction.⁽¹¹⁾⁽⁸⁾

Evaluate the decrease of prolactin level, and size of adenoma, visual function will resolve eventually. Vision begins to improve within a few days after the treatment is started. Patients in macroadenoma with hyperthyroid and or hypoadrenal also can regain normal function. Recurrent rate is still high in 80% and patients will need long-term medical therapy.⁽²²⁾⁽²³⁾⁽²⁴⁾

In these patients with complaints of four-year infertility, additional laboratory evaluations and investigations must be made to look for causes of infertility, such as examining FSH levels and LH levels because an increase in prolactin levels can affect the reproductive system through inhibitory effects on the hypothalamic gonadotropin-releasing hormone neurons (GnRH) and or on the pituitary gland to reduce secretion of the hormone lutein gonadotropin (LH) and follicle stimulating hormone (FSH), which can lead to loss of ovarian stimulation.⁽¹²⁾⁽²⁵⁾

Conclusion

There are signs and symptoms of galactorrhea, irregular menstrual cycles and infertility in this patient caused by high serum prolactin levels (hyperprolactinemia). MRI examination of the head can rule out the presence of tumors in the pituitary. The patient was diagnosed with idiopathic hyperprolactinemia, because we found

high serum prolactin levels but no cause was found. Bromocriptine therapy is given to reduce prolactin levels and evaluation of serum prolactin levels needs to be conducted for 3 – 6 months.

Conflict of Interest

There is no conflict of interest.

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