Idiopathic hyperprolactinemia - A challenge for primary care

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SUMMARY

Hyperprolactinemia is a condition of elevated serum prolactin, which usually occurs in women as compared to men. Most patients present to primary care clinics with a history of galactorrhoea, oligomenorrhea, amenorrhoea or infertility. Literature search reveals that there were few idiopathic causes of hyperprolactinemia, which resolved by itself without specific pharmacological or surgical treatment. This case is of a 39-year-old woman presented with amenorrhea for four months after Implanon removal and concomitantly noted to have galactorrhoea for four years without any medical attention. The condition persisted after cessation of breastfeeding. After undergoing several investigations including imaging studies, the underlying cause of hyperprolactinemia was noted to be idiopathic. Due to the unclear cause of its aetiology, this case caused various challenges to the primary care. Exhaustive physiological and pathological causes of hyperprolactinemia have been ruled out. Nevertheless, with adequate treatment, she gained her normal menstrual and resolved galactorrhoea symptoms.

INTRODUCTION

Prolactin is an anterior pituitary hormone that plays an important role in lactation during pregnancy and have many other functions such as osmoregulation, angiogenesis and immunoregulation.[1] Serum prolactin concentrations increment also known as hyperprolactinemia often manifests as amenorrhea and galactorrhoea in women and impotence in men. Most of the time, the causes can be identified. Normal serum prolactin levels vary between 5 and 25ng/ml in females. In pregnancy, the level can raise up to 200-500ng/ml.[2]

The mean prevalence of hyperprolactinemia is estimated to be around 30 per 100,000 in women and 10 per 100,000 in men; with peak prevalence in women aged 25 to 34 years.[3] The causes for hyperprolactinemia can be divided into physiological, pharmacological and pathological. Physiological causes that need to be considered are vigorous exercise, physical and psychological stress, chest wall diseases and stimulation, pregnancy, breastfeeding and sleeping. Pharmacological causes are prior intake of antidoparminegic drugs, oestrogen, calcium channel blocker, antipsychosis, and H2 receptor antagonist. Pathological causes can be due to hypothalamic and pituitary diseases compressing pituitary stalk, hypothyroidism and hepatorenal disorders. However, 29% of hyperprolactinemia cases has been classified as idiopathic as in this case report.

Patients with hyperprolactinemia can present with amenorrhea, low libido, erectile dysfunction, infertility, gynecomastia, or trivial fractures. They may have symptoms related to intracranial mass effect of a pituitary adenoma, such as headache or visual changes. Past medical history of thyroid disease, hepatorenal problems and drug history such as hormonal contraceptive, antipsychotic, antidepressant, cimetidine, verapamil is important. For example, if amenorrhea is persistent for more than two months after removal of Implanon, pregnancy must be excluded, and further workup need to be done to look for the cause of amenorrhoea. Therefore, verification on the last menstrual period is mandatory to rule out unplanned pregnancy. In terms of physical examination, it should be directed towards looking for signs of increased intracranial pressure and compressive symptoms. Visual field assessment, fundoscopy for papilloedema, cranial nerve examination and neurological examination are mandatory to be done. Respiratory examinations need to be performed to look for chest wall injury, thyroid status assessment clinically to look for hypothyroidism and genitalia examination for hypogonadism. Breast examination is also important to look for the nature of nipple discharge and exclude any breast pathology.

At the primary care level, to confirm the condition, serum prolactin levels need to be measured twice preferably in the early morning within three to four hours after waking up from sleep. Whenever the level is still high during subsequent follow up, serum thyroid stimulating hormone level needs to be measured to rule out concomitant hypothyroidism. The inadequate hormone needs to be treated. Patients usually can be followed up at primary care level for further workup together with serum prolactin monitoring. However, whenever a patient presents with red flag symptoms, or unclear diagnosis, then the referral to tertiary centre needs to be done. Among the red flags symptoms for hyperprolactinemia which occur due to mass effect of enlarged pituitary are headache, cranial nerve disturbance, and visual field defect classically bitemporal hemianopia due to compression of the optic chiasm.[4] Once patients manifest with these alarming features, further imaging studies are warranted. The imaging test is helpful in stratifying the size of pituitary gland into microadenoma (<10mm) or macroadenoma (>10mm). If the MRI findings are normal, then only the diagnosis of idiopathic hyperprolactinemia can be concluded. This can be summarised as in Figure 1 below:

The principle of management of hyperprolactinemia is based on the underlying aetiology.[5] For idiopathic hyperprolactinemia and for those due to pituitary

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Table I: Blood investigation results

Thyroid Function Test	Free T4 11.99pmmol/L TSH 2.229mIU/L
Fasting Lipid Profile	Total cholesterol 5.5mmol/L HDL 1.13mmol/L LDL 3.9mmol/L Triglyceride 1.1mmol/L
Renal Profile	Urea 3.2mmol/L Sodium 138mmol/L Potassium 4.0mmol/L Chloride 104mmol/L Creatinine 61µmol/L
Full blood count	Haemoglobin 12.9 White blood cell 5.7 Platelet 228
Fasting plasma glucose	FBS 4.3mmol/L
Liver function test	Total protein 70g/L Albumin 44g/L Globulin 26g/L Albumin globulin ratio 1.7U/L Aspartate aminotransferase 26U/L Alanine amino transferase 14U/L Alkaline phosphatase 73U/L Total bilirubin 12µmol/L Direct bilirubin 2.0µmol/L Indirect bilirubin 10µmol/L
Hormone	Oestradiol 117.4pmol/L FSH 8.83IU/L LH 4.56IU/L **Prolactin 77.21µg/L**

microadenoma, treatment is mainly by medical therapy and follow up. For hyperprolactinemia secondary to pituitary macroadenoma, both medical and surgical therapy can be initiated. Other miscellaneous causes of hyperprolactinemia such as systemic disorders, drugs, pituitary hypersecretion, and hypothalamic pituitary stalk damage must be properly identified and treated accordingly.

The pharmacological treatment that can be initiated after diagnosing idiopathic hyperprolactinemia is mainly dopamine receptor agonist, such as cabergoline. This drug is indeed very effective in in treating hyperprolactinemia.[6] Among the most common side effects of cabergoline that need to be informed include nausea, headache, dizziness or vertigo, weakness, low blood pressure, constipation, and abdominal pain.[6] Therefore, a shorter interval of appointment should be arranged to clarify the effects with patients. After initiating the medication, the patient also requires careful monitoring in terms of the symptoms progress and serum prolactin level. For patients who had idiopathic hyperprolactinemia and have had a persistent normal range of prolactin level while taking a low dose of dopamine agonist for at least two years, the medication can be gradually weaned off.

If there are no red flags and patient is well, primary care doctors can arrange for follow up to monitor serum prolactin level for six years and re-evaluate the need for imaging studies if sudden increment of serum prolactin detected.[7] Untreated hyperprolactinemia will end up with multiple complications. For example, for females in the reproductive age, they will end up with menstrual disorder especially amenorrhea and this will cause further anxiety and psychological impairment for the patient, as in our case. Other than that, amenorrhea and low oestradiol levels will lead to eventual bone loss and osteoporosis if untreated. In men, hyperprolactinemia may also be associated with erectile dysfunction and other symptoms of hypogonadism such as decreased libido, decreased energy, loss of sexual hair, loss of muscle mass, and osteoporosis.

CASE REPORT

A 39-year-old woman presented to our clinic with a complaint of persistent amenorrhoea since removal of Implanon for six months. She otherwise had no abdominal pain, headache, blurring of vision, nausea or vomiting, loss of appetite or loss of weight. On further questioning, she had underlying persistent galactorrhoea for the past four years since her last childbirth. The galactorrhoea was present upon milking, whitish in colour without any foul smell. Otherwise, there were no signs and symptoms of thyroid disorder and no history of taking supplements or over the counter drugs for milk booster. There was no significant past medical or surgical history. She never has had any gynaecological procedure, such as curettage for miscarriage. She otherwise had a family history of bone cancer, which is her late aunty.

She has been a divorcee for the past one year. She had seven children from her previous marriage. She was not sexually active. She works as a Science Officer and is not exposed to any chemical hazard. She is a non-smoker and non-alcoholic. Nevertheless, she did feel psychological and physical stress as she needed to take care of her children on her own. She benefited from good support from her family members.

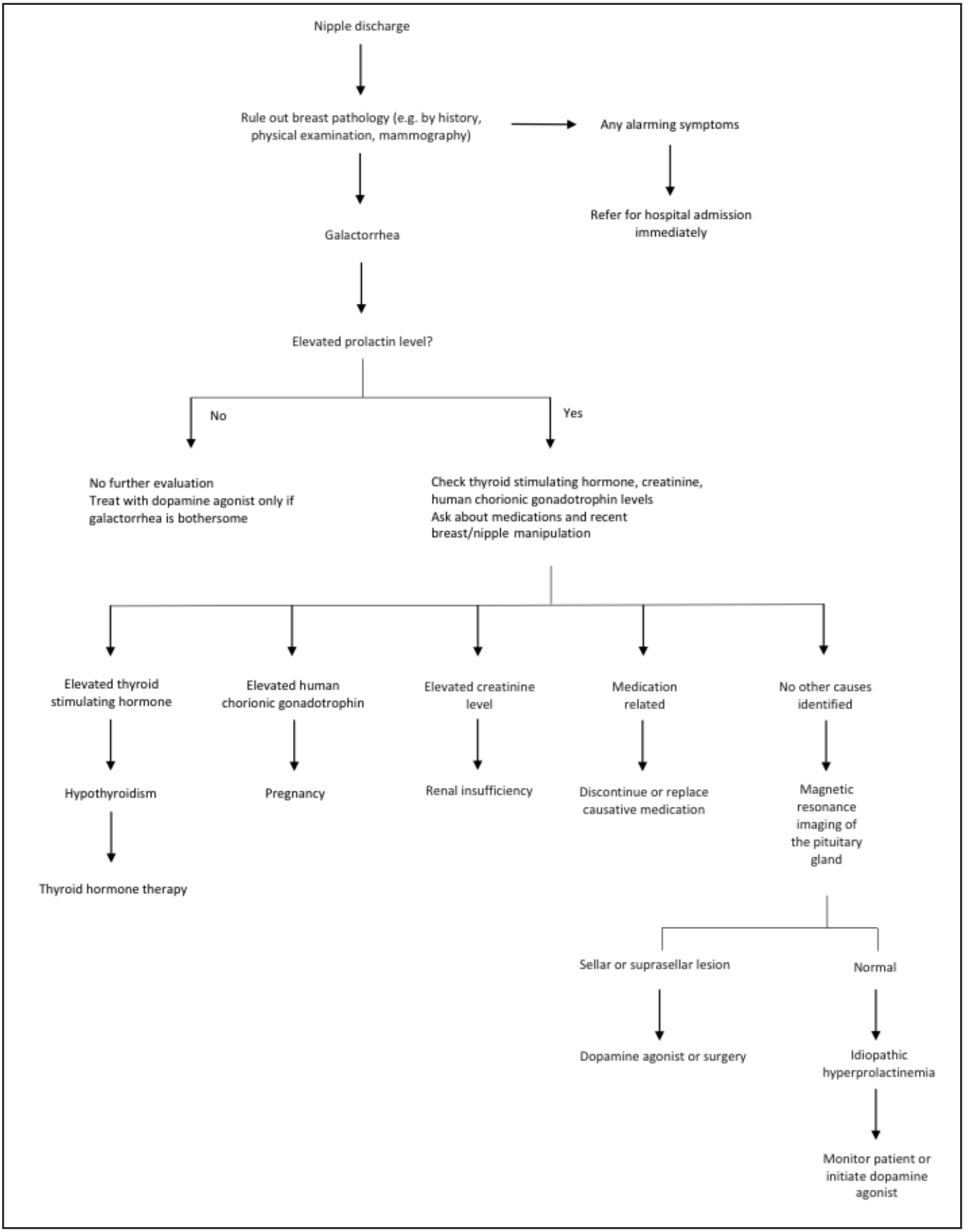

Fig. 1: Overview of hyperprolactinemia management approach (Modified from Huang 2012)[2].

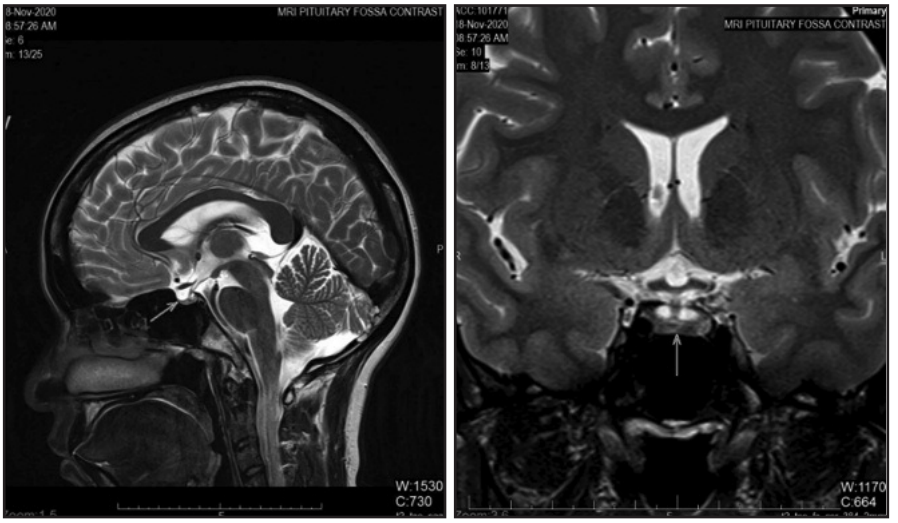

Fig. 2: MRI Pituitary Sagittal and Coronal View.

On general examination, she had a thin body build with a BMI of 22kg/m2. She had no features of hirsutism. Her blood pressure was 104/69mmHg and pulse rate was 88 beats per minute. Her thyroid was not palpable. Breast examination revealed no obvious lump, retracted nipple, or any skin lesion. However, there was an active secretion seen coming out from her both nipples upon milking, whitish in colour without any foul smelly or blood stain. Eye examination showed a normal visual field, fundoscopy, and 3rd, 4th and 6th cranial nerve. Neurology examination of the upper and lower limb was normal.

She was scheduled for blood investigation during the next visit together with opportunistic screening for cardiovascular disease. The blood investigations were listed as in Table I.

She was referred to an endocrinologist for further evaluation and expert opinion in terms of her condition. She benefited from regular follow up under primary care clinic for psychoeducation and continuous education regarding her problems. Initial abdomen and pelvic ultrasound were noted to be normal without any mass or structural abnormalities were seen to suggest ovarian pathology induced amenorhoea. She was referred to a psychiatry clinic for shared care due to her emotional stress. Repeated serum prolactin at the endocrine clinic during subsequent follow up showed increasing levels from 77.21 to 104µg/L within four months despite psychiatry intervention. She was then scheduled for MRI Pituitary to look for any mass or intracranial growth. The image is as below in Figure 2 that showed significant effacement of the anterosuperior aspect of the pituitary gland with downward displacement of the pituitary gland represent partial empty sella syndrome.

Patient was then started on tablet Cabergoline 500 mcg twice per week. She complied with the medication without any side effects. She also benefited from a counsellor follow up at a psychiatry clinic. She was then able to regain her normal menstrual cycle. Her nipple discharges were also resolved. She finally was able to experience back her usual good quality of life.

DISCUSSION

Hyperprolactinemia, despite being classically associated with gonadal dysfunction, its associations with psychological symptoms like anxiety, stress and depression has come into attention lately. For this case, she was initially diagnosed to have hyperprolactinemia with a high probability secondary to emotional stress as she was just divorced by her husband. She was referred to the psychiatry unit and was started on antidepressant, together with psychological therapy. The antidepressant that she was on is Tablet Escitalopram 20mg OD, a selective serotonin reuptake inhibitor (SSRI) with less potential to cause hyperprolactinemia. The repeated serum prolactin level after four months was noted to be increased from 77.21 to 104µg/L. Physiologically, stress from physical or psychological insult can cause an increase in the serum prolactin concentration with a magnitude of increase should not exceed 40µg/L. Women have greater increases than men, possibly due to the effect of their higher serum estradiol concentrations on the lactotroph cells with all stimuli of prolactin secretion. She decided to undergo magnetic resonance imaging of the pituitary because of the increased level despite psychological treatment.

For a patient who is found to have hyperprolactinemia, but typical symptoms and radiological abnormalities are absent, the condition of macroprolactinemia should be suspected. Macroprolactinemia is a term to describe a condition of aggregation of prolactin and prolactin antibodies in the vascular space, but not biologically active, thus, it causes no clinical symptoms abnormality. This condition can be misdiagnosed and treated as prolactin hypersecretion. However, the presence of galactorrhoea, menstrual problem, and other symptoms does not exclude the diagnosis of macroprolactinemia. The gold standard for the diagnosis of macroprolactinemia is gel-filtration chromatography, however, due to the cost and complexity of the test, polyethylene glycol (PEG) serum precipitation has been widely used as a screening method.[8]

In a condition of idiopathic hyperprolactinemia, one-third of the patients with elevated serum prolactin levels will resolve,

and in one-half of patients, the level will remain stable. But there is a study that founded a high prevalence of anti-pituitary antibodies (APA) in 25.7% of patients with idiopathic hyperprolactinemia.[9] These antibodies reduce prolactin bioactivity and delay its clearance, inducing macroprolactinemia. Antibody-bound prolactin is confined to vascular spaces and, therefore, macroprolactinemia seems to develop mostly due to the delayed prolactin clearance, rather than its increased production. It is not impossible that many cases initially diagnosed as idiopathic hyperprolactinemia were later confirmed as having macroprolactinemia.

In case of increase serum prolactin with presents of red flag symptoms, radio-imaging study is mandatory to confirm the diagnosis of prolactinoma. However, in the case of mildly elevated serum prolactin with absent of red flag symptoms, there are controversial whether to proceed with imaging or just monitor the serum prolactin level. It should be noted that microadenomas are present in about 10% of the normal population.[10] Like in this case, she might not have the symptoms of increased intracranial pressure but microadenoma cannot be excluded. Thus, radio imaging study is suggested to be done if the facility is available provided all the possible potential secondary causes of hyperprolactinaemia excluded.

As for the primary care perspective, the objectives of treatment of hyperprolactinemia are to restore and maintain the normal gonadal function, restoring normal fertility, and prevention of osteoporosis. There are benefits if primary care can monitor and manage the patient with suspected idiopathic hyperprolactinemia because the risk for macroadenoma is low, and the symptoms need to be resolved soon. Nevertheless, there is always a role for tertiary referral especially in a situation whereby the exact cause of the disease is not clear and when a patient developed alarming symptoms of increased intracranial pressure.

CONCLUSION

Diagnosis of hyperprolactinemia is challenging because of the endless list of secondary causes that can contribute to it. Primary health care may detect this condition and can manage it. However, for excluding other causes, especially for imaging studies, patients might need shared care with a tertiary setting. The prognosis of this condition is good if the cause is identified early, and patients can return to their normal life if they are properly treated. The screening for macroprolactinemia should often be considered for the correct identification of the aetiology of hyperprolactinemia.

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