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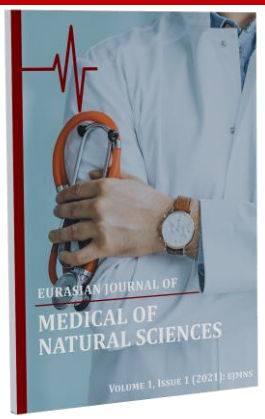

THE PRESENTATION AND MANAGEMENT OF PITUITARY TUMOURS

Mirzayeva Malika Fahriddinova
Student of Kimyo Iternational University in Tashkent
Abdurakhimova Lola Anvarovna
Scientific adviser: Professor Senior lecturer of Kimyo International University In Tashkent
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ABSTRACT

Prolactin-secreting tumors of the pituitary gland, also known as prolactinomas, are the most common secretory tumors of the pituitary gland, accounting for up to 40 percent of pituitary adenomas. Prolactinomas can lead to a wide variety of symptoms, either due to mass effect or hypersecretion of prolactin. This articl illustrates the evaluation, treatment.diagnosis.

Relevance

Hyperprolactinemia is present in a diversity of clinical settings. It can be found in 30% of women with galactorrhea or infertility in 10–25% of women with secondary amenorrhea or oligomenorrhea and in 75% of those with both amenorrhea and galactorrhea . Moreover, in a large series with 1370 participants presenting with sexual disfunction , hyperprolactinemia was present in 1.5%

The causes of hyperprolactinemia can be divided into physiologic, pharmacologic and pathologic The most common cause of hyperprolactinemia and amenorrhea is pregnancy, with 10-fold increase in PRL serum levels during the third trimester. But other physiological conditions also can elevate PRL levels, such as exercise, physical and emotional stress and nipple stimulation. Except from pregnancy, in physiologic conditions PRL levels rarely exceed 40 mcg/L The main cause of non-physiological hyperprolactinemia is pharmacological, whereas among the pathological causes prolactinomas are the most common.

Hypothalamus/Pituitary diseas

Prolactinomas are the most common cause of pathological hyperprolactinemia. In a Uzbekistan study, with 1034 patients with hyperprolactinemia, prolactinomas were responsible for 56.2% of cases Other pituitary adenomas may co-secrete prolactin and GH, TSH or ACTH, also leading to hyperprolactinemia.

Prolactin secretion is constantly inhibited by dopamine secreted by the hypothalamus, that reaches anterior pituitary gland through pituitary stalk. Therefore, any condition interrupting this influx leads to hyperprolactinemia, what is called “stalk effect”. Other pituitary adenomas, in particular clinically nonfunctioning pituitary adenomas (NFPA), with suprasellar expansion are a common cause of non-tumoral hyperprolactinemia. Pituitary stalk section, empty sella syndrome or infiltrative diseases may also lead do hyperprolactinemia

due to interruption of dopamine supply to the pituitary gland. Recently, Devuyst et al. evaluated patients with pituitary stalk thickening and central diabetes insipidus and found that the presence of elevated prolactin levels increased the likelihood of a tumoral disease. In cases of "stalk effect", prolactin levels rarely exceed 100 mcg/L

Systemic diseases

Hyperprolactinemia may be found in 8% to 43% of patients with hypothyroidism . Hekimsoy et al. described a frequency of prolactin elevation of 36% in patients with overt hypothyroidism and 22% in patients with subclinical hypothyroidism. After TSH normalization, prolactin levels decreased to normal in all patients . Glucocorticoids suppress prolactin gene expression and prolactin release, so hyperprolactinemia may be found in patients with adrenal insufficiency .

Chronic renal failure may lead to hyperprolactinemia both due to increased prolactin secretion and reduced prolactin clearance . In patients with cirrhosis, hyperprolactinemia is caused by decreased prolactin secretion inhibition and increased estrogen levels, and prolactin levels may be correlated with severity degree However, some data suggest that hyperprolactinemia may be found in a small percentage of patients In both cases, prolactin levels rarely exceed 100 mcg/L.

Neurogenic

Breast stimulation lead to reflex prolactin release, in part, by afferent neural pathways going through the spinal cord. This may explain prolactin increase associated with chest wall and spinal cord lesions Also, nipple piercing may increase prolactin levels.

Seizures

Hyperprolactinemia following seizures may occur due to propagation of epileptic activity from the temporal lobeto the hypothalamo-pituitary axis, occurring most commonly after generalized tonic-clonic seizures .

Others

Ectopic prolactin secretion is exceedingly rare and should be considered in cases with prolactin levels > 200 mcg/L, normal sella MRI and combined secondary causes excluded [22]. In 2013, Newey et al. described mutation in the prolactin receptor gene in a family with hyperprolactinemia of non-identified cause. A heterozygous A-to-G substitution at c.635 in *PRLR* was identified, which results in a His188Arg substitution, leading to a loss of function of the prolactin receptor. The patients in this family presented different clinical presentations, two sisters presenting oligo-amenorrhea with normal fertility and the other sister with infertility. The ratio of wild-type or mutated PRL-R homodimers or heterodimers in different tissues may vary between patients, what can partially explain this variability of clinical presentation.

Pharmacologic agents

The most common cause of non-physiologic hyperprolactinemia is pharmacological. Therefore, use of drugs that cause prolactin increase must be rule out before proceeding with investigation.

Drug-induced hyperprolactinemia can reach PRL levels up to 150 mcg/L. Antipsychotic drugs increase prolactin levels by blockade of D2 receptors in the hypothalamic tuberoinfundibular system and on pituitary lactotrophs. Haloperidol and risperidone cause

marked prolactin elevation, whereas other atypical antipsychotics such as quetiapine and aripiprazole may have prolactin lowering effects . Prokinetic agents also antagonize D2 receptor and may induce symptomatic hyperprolactinemia .

Antidepressants (tricyclics and serotonin reuptake inhibitors), antihypertensive, estrongens protease inhibitors and narcotics are usually associated with mild hyperprolactinemia.

When the patient is taking one of these drugs, it is suggested to withdraw it for at least 72 h, if this can be done safely, and then proceed to new serum test of prolactin to confirm or exclude hyperprolactinemia. If the drug cannot be stopped, sella turcica imaging should be performed.

If no cause is identified, the patient is considered as having idiopathic hyperprolactinemia.

Epidemiology

Prolactinomas account for up to 40% of all clinically recognized pituitary adenomas. The mean prevalence of prolactinoma is estimated to be approximately 10 per 100,000 in men and 30 per 100,000 in women, with a peak prevalence in women aged 25 to 34 years. Among patients with prolactinomas, as many as 60% of the males present with macroprolactinomas, while 90% of the females present with microprolactinomas.

Evaluation

An extensive history and physical examination are needed to exclude other causes of hyperprolactinemia and to document any visual field deficits, galactorrhea, growth changes, hypopituitarism, menstrual irregularities, impotence, infertility. Formal visual field testing by an ophthalmologist should be done, especially for macroadenomas.

The test begins with serum prolactin level. If the prolactin level is high, a comprehensive metabolic panel, TSH, and a pregnancy test (for women of childbearing age) should be obtained. Assessment of other pituitary hormones, including cortisol, ACTH, IGF-1, LH, FSH, and testosterone/estradiol, should be done based on age and gender to exclude any hypopituitarism or other co-secreting tumors.

Patients can have very high prolactin levels; however, when measured, they can be reported as falsely low due to a phenomenon called the “Hook effect.” When there is a suspicion, serial dilution of the serum sample and re-measuring the prolactin levels will be helpful.

Another condition where measured prolactin can be high, although true prolactin level is low, is when patients have higher molecular weight prolactin called macroprolactin. Macroprolactin levels should be obtained in asymptomatic hyperprolactinemia. The laboratory can pretreat the serum with polyethylene glycol to precipitate the macroprolactin before the immunoassay for prolactin.

Imaging

CT scan may demonstrate the mass, but MRI with gadolinium is the preferred imaging modality for evaluation of hyperprolactinemia as it best describes the anatomy of the hypothalamic-pituitary area. All patients with tumors adjacent to or compressing to optic chiasm should be referred for formal visual field testing.

Management

Macroprolactinomas incidentally discovered without symptoms can be observed with periodic monitoring of the labs and imaging.

Macroprolactinoma or symptomatic microadenoma should be treated with dopamine agonist therapy. The goals of treatment would be tumor shrinkage, restoration of visual fields if any defect, reversal of galactorrhea, and restoration of fertility or abnormal sexual function. Cabergoline is preferred due to a higher frequency in normalizing the prolactin level and tumor shrinkage. Amenorrhea caused by macroprolactinoma can be treated with oral contraceptives if fertility is not desired without dopamine agonists.

Unlike other pituitary tumors, the preferred treatment for prolactinomas is medical therapy. Oral contraceptives alone can be given if the only symptoms are amenorrhea and or osteoporosis. Specific treatment for prolactinomas is one of the dopamine agonists.

Cabergoline and bromocriptine are two commonly used dopamine agonists. Pergolide is withdrawn from the market due to concerns about valvular heart disease, and quinagolide. Dopamine agonists suppress the synthesis and release of prolactin and lactotroph cellular proliferation, causing shrinkage of the tumor. They can cause nausea and dizziness

A systematic review evaluated 8 randomized and 178 nonrandomized studies, including 3000 patients [76]. Compared with no treatment, DAs were able to reduce PRL levels and the risk of persistent hyperprolactinemia. Prolactin normalization was obtained in approximately 70% of patients, whereas tumor reduction was observed in approximately 60% . In aUzbekistan study, including 694 patients with prolactinoma, cabergoline normalized prolactin levels in 81.9% of patients (85.9% of micro- and 77.8% of macroprolactinomas), with a mean dose of 1.2 ± 0.7 mg/week (0.2–3.5) for micro- and 1.7 ± 0.7 mg/week (1.0–3.5) for macroprolactinomas. Resolution of galactorrhea was found in 100% of women and menstrual cycles normalization in 79%. Among men, hypogonadism symptoms improvement occurred in 60.3%. Tumor shrinkage was observed in 80% of patients, whereas complete tumor disappearance was found in 57.5%

In respect to metabolic alterations, dos Santos Silva et al. Demonstrated significant reduction of triglycerides, HDL cholesterol, fasting glucose and HOMAIR index after 6 months of treatment with cabergoline. Frequency of metabolic syndrome reduced from 23% to 14% after six months of treatment. Among 158 patients with hyperprolactinemia, treatment with DA (six to 60 months) decreased metabolic syndrome from 32% to 10%. Also, total and LDL cholesterol significantly reduced ($p < 0.001$ and $p = 0.005$, respectively) after 9 months of cabergoline treatment in 53 prolactinoma patients.

Conclusion

In conclusion, hyperprolactinemia is a very common endocrine disorder and prolactinomas are the main pathological cause of this alteration. Its diagnosis may be difficulted by some pitfalls in PRL levels evaluation and by the diversity of causes of PRL elevation. The treatment of prolactinomas is medical in the majority of cases, including patients with giant prolactinomas, with high remission rates, but with frequent relapse. DA treatment is safe and well tolerated, but potentially serious adverse effects, such as cardiac valve involvement and ICD, should be monitored. In this sense, primary surgical treatment may be considered in selected cases. Other treatment options for DA resistant prolactinomas include surgery and radiotherapy. For aggressive giant prolactinomas and carcinomas,

temozolomide can be used. Finally, pregnancy outcomes in patients with prolactinoma seem similar to general population, even if DA must be maintained during gestation, but some studies found a higher rate of miscarriage and premature birth.

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