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Treatment of Prolactinoma

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Abstract

Pituitary Neuroendocrine Tumors (PitNET) are most frequently prolactinomas, which account for around half of all such tumors. The bulk of prolactinomas has typically been treated with Dopamine Agonists (DAs), with surgery being the last resort. The goal is to examine the historical and contemporary management of prolactinomas, with a focus on the effectiveness, safety, and potential future directions of current therapeutic modalities. This includes medical therapy with DAs, trans-sphenoidal surgery, and multimodality therapy for the treatment of aggressive prolactinomas and metastatic PitNETs. Since the 1970s, DAs have been the cornerstone of prolactinoma therapy, first with bromocriptine and more recently with cabergoline. In up to 85% of patients, cabergoline normalizes prolactin, and in up to 80% of cases, it shrinks tumors. Similar to cabergoline, the primary surgical excision of microprolactinomas and contained macroprolactinomas is undertaken by skilled pituitary neurosurgeons. Aggressive prolactinomas and metastatic PitNETS should be treated with a multimodal approach that includes surgery, radiation therapy, stereotactic radiosurgery when appropriate, and temozolomide. The majority of prolactinomas can still be successfully treated with DAs, but during the past decade or so, outcomes from transsphenoidal surgery under skilled surgeons have significantly improved. Surgery has a crucial role in the management of DA-resistant and aggressive prolactinomas, and it should be firmly considered as the first line of treatment, especially in the case of microprolactinomas, non-invasive macroprolactinomas, or prior to attempting pregnancy.

Keywords: Prolactinoma • Dopamine agonist

Introduction

Pituitary lactotropic cells, which are descended from the Pit1 lineage, release prolactin, a 199 amino acid, 23kDa protein. Prolactin was not discovered in humans until Kleinberg and Frantz created a bioassay in the early 1970s that could measure prolactin levels in nursing mothers and galactorrhea patients. The primary regulator of prolactin secretion is hypothalamic dopamine. Dopamine is inhibitory while other anterior pituitary hormones are mostly under positive hypothalamic control. Although experimental data suggest that some hormones, including Thyrotrophin Releasing Hormone (TRH), Vasoactive Intestinal Polypeptide (VIP), and oxytocin, may increase prolactin, none of these or other putative candidate hormones have, to date, met the requirements for being a true hypothalamic prolactin-releasing factor. However, the influence of dopamine alone does not seem to be sufficient to explain prolactin dynamics, and the existence of a prolactin-releasing component is yet unknown.

The most frequent physiological reasons for hyperprolactinemia are pregnancy and lactation. However, there are other causes as well. Spinal cord damage and stimulation of the nipple and thorax may cause an increase in prolactin. After seizures, including those treated with electro-convulsive treatment, prolactin levels may rise. Both sexes experience a stimulation of prolactin during orgasm. The most typical Pituitary Neuroendocrine Tumor (PitNET) is a prolactinoma, which accounts for 53% of PitNETs according to a recent epidemiological assessment.

Diagnosis of prolactinoma

Prolactinoma can be diagnosed by hormonal testing of reproductive dysfunction symptoms such monthly irregularities and galactorrhea in females and erectile dysfunction, loss of libido, and infrequently galactorrhea in males. Alternately, it could occur by the accidental discovery of a PitNET during neuroimaging, either to explore pituitary mass effect symptoms like a bitemporal visual field deficit or as an incidental finding for an unrelated rationale. Prolactin can be easily detected using an immunoassay, and many labs use reference ranges based on sex, with a lower upper limit of normal for men. The exact maximum limit varies depending on the assay, although it is often in the range of 400 mIU/L to 500 mIU/L (18.8 g/L to 23.5 g/L). Once the concentration reaches more than twice the upper limit of normal, or roughly 1000 mIU/L (47 g/L), the risk of a pathogenic cause increases. By taking a sample using an intravenous cannula, one can avoid an immediate surge in prolactin that could be caused by the stress of venepuncture. 61% of women with hyperprolactinemia on 2 prior independent samples collected by venepuncture in 1 trial, which was sampled at 30-minute intervals for 2 hours, had normal serum prolactin levels. A blood prolactin level of 4000 mIU/L to 5000 mIU/L (188 g/L to 235 g/L), the upper limit of the reference range, is typically linked with a macroprolactinoma. The so-called "stalk effect" is characterized by hyperprolactinemia caused by any sellar or parasellar lesion that prevents dopamine from moving from the hypothalamus to the anterior pituitary. This includes non-functioning sellar tumors. The serum prolactin level in non-functioning masses is typically 2000 mIU/L (94 g/L), while there are some exceptions to this rule. Due to saturation of both antibodies in extremely high prolactin concentrations, known as the "hook effect," two-site immuno- or chemiluminometric tests may give deceptively low values. If unsure, proceed with a series of dilutions to 1:100 to determine the true prolactin content. Rarely, PitNETs of the Pit-1 lineage that expresses prolactin (frequently plurihormonal) may not be secretory or operate "poorly," even though serum prolactin levels are within the range predicted for the stalk effect, which is 2000 mIU/L (94 g/L). Without histological proof, including transcription factor immunohistochemistry, it might be impossible to tell these lesions apart from non-functioning PitNETs of a different origin. The presence of macroprolactin, a biologically inactive immune complex between prolactin and IgG, which is responsible for about 10% of cases of hyperprolactinemia, and drug-induced hyperprolactinemia (particularly with antipsychotics and antiemetics) is also important for clinicians to be aware of. As with all PitNETs, a tumor's diameter determines its classification as a macro adenoma or microadenoma. A "giant" macro adenoma has a maximum diameter of more than 40 mm. Young women are more likely to develop microprolactinomas than older women, and the most prevalent pituitary cause of secondary amenorrhea is hyperprolactinemia. Studies on the natural history of microprolactinomas in patients have shown that, even in the absence of treatment, they hardly ever enlarge. Overall, prolactinomas are less frequent in men, but macro adenomas—particularly large, invasive tumors—are more prevalent. Only a small portion of the causes of the sex-based size disparity can be attributed to the predominance of galactorrhea and amenorrhea in women as a clear indicator of reproductive failure. Although microprolactinomas hardly ever become larger, there is evidence that prolactinomas in men are inherently more aggressive, more likely to grow, and more likely to be resistant to dopamine agonists.

Succinate Dehydrogenase (SDH) mutations, Arylhydrocarbon Receptor-Interacting Protein (AIP)-associated familial pituitary adenoma syndrome, Multiple Endocrine Neoplasia type 1 (MEN1) or type 4 (MEN4), and prolactinomas are all examples of hereditary syndromes in which prolactinomas can manifest. Although a thorough investigation of this subject is outside the purview of this study, a prolactinoma diagnosis should always be accompanied by thorough family history and genetic testing that is started in accordance with current standards.

Management

Dopamine agonists: Bromocriptine was discovered to decrease prolactin secretion shortly after prolactin was isolated in the early 1970s and it was used to treat galactorrhea and the resulting hypogonadism. The Dopamine Agonist (DA) bromocriptine was shown by various researchers to cause the regression of macroprolactinomas in addition to lowering blood prolactin concentrations by the end of the 1970s with the advent of computed tomography. The use of medicinal therapy in the form of DAs has been the main strategy after prolactinoma diagnosis. Before the development of cabergoline in the late 1980s and early 1990s, bromocriptine was the drug of choice. Published in 1994 was a comparison study of the two medications for the treatment of hyperprolactinemic amenorrhea. Cabergoline was more effective in this trial at reestablishing normoprolactinemia and ovulatory menstrual periods, required less frequent treatment, and had fewer negative gastrointestinal symptoms. Quinagolide, a different DA, was also created in the 1990s. It has the benefit of not being an ergotamine derivative and, in certain patients, is more tolerable than bromocriptine. Overall, cabergoline has demonstrated superior efficacy; there is evidence that prolactinomas resistant to quinagolide or bromocriptine may react to cabergoline treatment, leading to both enhanced biochemical control and greater tumor shrinkage. DA-naive patients experienced greater tumor shrinkage on lower cabergoline doses than those who had previously received treatment, including those who were DA responsive, intolerant, or resistant, according to a large comparative study comparing patients who had previously received treatment with other DAs (bromocriptine or quinagolide) to those who had not. Cabergoline outperformed the other dopamine agonists in the treatment of macroprolactinomas in terms of both prolactin normalization and tumor reduction. According to a review from Brazil, cabergoline caused prolactin to normalize in 86% of treatment-naive prolactinoma patients overall (91% in those with microadenoma, 83% in those with macroadenoma), and it reduced the size of the tumor in 80% of those with macroprolactinomas. Men are more likely than women to have larger, more resistant prolactinomas, and studies specifically looking at the effectiveness of cabergoline in male patients have shown that it is effective in terms of restoring sexual function and semen analysis.

Dose and administration: To reduce gastrointestinal side effects, cabergoline is typically started at low doses of 0.25 mg twice weekly, given in the evening after food (predominantly nausea). A typical dose for microadenomas would be 0.5 mg to1 mg per week, with up-titration suggested if this dose did not cause the serum prolactin to normalise within 6 weeks to 8 weeks. Similar starting doses for macroprolactinomas are possible, with the possibility of increasing the dose to 1 mg twice weekly by week 3. Where a suprasellar extension has caused visual field abnormalities, the dose can be increased more quickly to 1mg twice weekly by the beginning of week 2. A resistant prolactinoma has been identified when prolactin fails to normalize after 2 mg/week of cabergoline; dose escalation to 12 mg/week has been seen. In cabergoline-sensitive people, a second visual field evaluation after 2 weeks of medication may already show normalization.

Cabergoline can be administered vaginally to women to lessen any potential gastrointestinal side effects. Starting with a dose of 37.5 mg to 75 mg per day, quinagolide is increased as needed based on the prolactin response. Although doses as high as 600 g per day have been utilized, the typical dose range is 75 g to 450 g daily. In general, bromocriptine is started at a dose of 1.25 mg to 2.5 mg per day and increased to twice daily dosing as needed. It is possible to use amounts upto 30 mg/day divided into 2 doses. Since bromocriptine has been around for a longer time and has more cases to support its safety during pregnancy, some physicians still recommend using it in women who are trying to get pregnant. Treatment-limiting adverse effects of dopamine agonists include nausea, vomiting, exhaustion, headaches, and dizziness. According to the study, 31% of women taking cabergoline experienced nausea, compared to 50% of women on bromocriptine. 5% of women using bromocriptine experienced severe vomiting, compared to 0% of women taking cabergoline. For both drugs, the rates of headache and dizziness were comparable, at about 30% and 25%, respectively. 12% of patients receiving bromocriptine experienced treatment withdrawal overall, compared to 3% of individuals receiving cabergoline.

Impulse control disorders: In patients receiving dopamine agonist therapy for prolactinoma, Impulse Control Disorders (ICDs) were previously believed to be uncommon, but numerous studies conducted over the past 10 years have shown that they are common (8% to 25%) and can have serious negative effects. Failure to withstand urges to partake in pleasurable but dangerous activity is a hallmark of ICDs. Hypersexuality, pathological gambling, compulsive shopping, punding (an obsession with pointless motor activities like cleaning or rearranging objects), preoccupation with hobbies, and aimless wandering—whether on foot or in a car—are ICDs connected to DA use. Male sex, eugonadal states in both sexes, a lower Hardy's tumor score (less invasive tumor), the existence of psychiatric comorbidities such as anxiety and depression for hypersexuality, and age for compulsive buying have all been identified as risk factors for ICD. There is research linking ICD to bromocriptine, quinagolide, and cabergoline, but there isn't enough of it to say that switching your DA will make your symptoms go away. An unselected sample of patients with DA-treated hyperprolactinemia completed a battery of cognitive questionnaires, and 61% of them tested positive for any ICD. 8% of DA-treated patients scored positively on a specific questionnaire testing hypersexuality, compared to 0% of the controls. ICD development is not predicted by the dosage or duration of DA medication. Even though some patients respond better to dose reduction, this is not always the case and the ICD is frequently resolved by stopping the DA.

Conclusion

Prolactinomas are biologically varied tumors that can range in size and aggressiveness from small, slow-growing micro adenomas to big, invasive macroadenomas. They are the most responsive PitNET to medical therapy, and cabergoline therapy is still a very suitable and effective technique for the majority of patients. With the proviso that the procedure is carried out by a specialized high-volume pituitary neurosurgeon, pituitary surgery is now a viable first-line therapeutic option for individuals with microadenomas, non-invasive macroadenomas, and women seeking conception. Surgery is still recommended for those who are DA-resistant or DA intolerant. Pituitary tumors should be addressed by a multidisciplinary team, which is why patients with aggressive prolactinomas and metastatic PitNETs need multimodality treatment.

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