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Pituitary Neuroendocrine Tumors (PitNETs) – a literature review

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Abstract

Introduction and Purpose: Pituitary neuroendocrine tumors (PitNETs), commonly known as pituitary adenomas, are tumors originating from the adenohypophysis. The purpose of this review was to provide a comprehensive overview of the latest classification, clinical presentation, diagnosis and treatment options for different types of PitNETs.

Description of state of knowledge: The World Health Organization (WHO) 2022 guidelines introduced a new classification system for PitNETs, emphasizing the importance of immunohistochemistry in diagnosing these tumors and identifying key transcription factors like PIT1, TPIT, and SF1. Clinical presentation of PitNETs vary widely, with symptoms ranging from mass effect related issues like headaches and visual disturbances to hormone excess syndromes such as hyperprolactinemia, acromegaly, and Cushing's disease. Magnetic resonance imaging (MRI) is the gold standard for diagnosing adenomas. Treatment approaches depend on tumor type, with dopamine agonists being the first-line treatment for prolactinomas, while endoscopic transsphenoidal surgery (EETS) is the preferred treatment for other PitNETs. EETS achieves high rates of gross total resection and low recurrence. For patients with persistent or recurrent disease, reoperation, medical therapy, or radiotherapy may be required.

Conclusions: Pituitary neuroendocrine tumors represent a diverse group of tumors that require an individualized, multidisciplinary approach for accurate diagnosis and effective treatment, aimed at optimizing patient outcomes.

Keywords: PitNET, TSHoma, prolactinoma, acromegaly, Cushing's Disease, pituitary adenoma

1. Introduction and purpose

Pituitary neuroendocrine tumors (PitNETs), commonly known as pituitary adenomas, are benign tumors that arise from the adenohypophysis. Although they are generally non-cancerous, their clinical significance lies in their potential to cause a range of endocrine and

neurological symptoms. The diagnosis of PitNETs occurs in approximately 78 to 116 cases per 100,000 individuals [1]. However, their prevalence is likely much higher, as studies using imaging techniques and autopsy data estimate that these tumors may be present in up to 16.7% of the general population [2].

Pituitary adenomas are classified based on size and secreted hormone. Tumors with a diameter of less than 10 mm are called microadenomas, those with more than 10mm macroadenomas and those with more than 40 mm giant adenomas [3]. Larger tumors can cause symptoms related to mass effect, such as headaches, visual disturbances or hormonal deficiency. Approximately 60% of PitNETs are hormone-secreting, leading to various endocrine symptoms. The most common type of hormone-secreting adenoma is a prolactinoma (53%) followed by those that secrete growth hormone (12%), adrenocorticotropic hormone (ACTH) (4%), and thyroid-stimulating hormone (TSH) (less than 1%) [4, 5].

Diagnosing and treating pituitary adenomas requires a multidisciplinary approach that integrates endocrinology, ophthalmology, neurosurgery, and radiology. The aim of this review is to provide a comprehensive overview of the new classification, symptoms, diagnosis and current treatment options for different PitNETs, including conservative medical management, surgical interventions, and radiotherapy.

2. State of knowledge

2.1 New classification

The term "Pituitary Neuroendocrine Tumor" (PitNET) has been proposed as a more precise term than "pituitary adenoma" as it better reflects the tumor's potential for invasion into surrounding structures and its rare ability to metastasize. While "PitNET" emphasizes the neuroendocrine nature and biological aggressiveness of certain tumors, both terms are still used interchangeably in current medical nomenclature [6]. The 2022 WHO guidelines introduced an updated classification, highlighting the critical role of immunohistochemistry in diagnosing PitNETs [7]. This diagnostic approach involves the identification of specific transcription factors such as PIT1, TPIT, SF1, GATA3, and ERα, which are essential for determining the tumor's lineage and subtype [8, 9]. The PIT1 lineage is associated with somatotroph, lactotroph, and thyrotroph tumors, while TPIT and SF1 are connected to corticotroph and gonadotroph tumors, respectively. In addition classification introduced new tumor types; the immature PIT1-lineage tumor and the mature plurihormonal PIT1-lineage

tumor, which are rare tumors capable of secreting multiple hormones such as prolactin, growth hormone, and TSH [7].

2.2 Symptoms

The clinical presentation of PitNETs varies significantly and is influenced by tumor size, growth characteristics and excessive hormonal secretion. Macroadenomas frequently manifest with nonspecific symptoms of mass effect, such as headache, visual defects and hypopituitarism, with growth hormone (GH) being the most commonly affected axis, followed by gonadotropins (LH/FSH), adrenocorticotropic hormone (ACTH), and thyroid-stimulating hormone (TSH) [10]. When these tumors extend suprasellarly, they compress the optic chiasm and pituitary stalk, leading to visual disturbances and hyperprolactinemia [11]. The most characteristic visual impairment associated with pituitary adenomas is bitemporal hemianopsia, occurring in about 40% of patients who experience vision problems. Other visual defects can include homonymous visual field defects and reduced visual acuity [12]. In cases where pituitary adenomas are hormonally active, prolactin is the most commonly secreted hormone. Among women, these tumors typically present with symptoms such as oligo- or amenorrhea (85-90%), galactorrhea (84%), osteoporosis and infertility [13]. In men, prolactinomas tend to be more aggressive due to gender-related differences, leading to hypogonadism, loss of libido, erectile dysfunction, gynecomastia, and infertility [14]. The second most common PitNET is the somatotroph type, which produces excess growth hormone and results in acromegaly. Patients typically present with acral enlargement (77%), coarse facial features (54%), excessive sweating (52%), carpal tunnel syndrome (51%), and osteoarthritis [15]. ACTH secreting adenoma leads to Cushing's disease, which is responsible for approximately 70% of all Cushing's syndrome cases. Symptoms of hypercortisolism include weight gain with central obesity, fatigue accompanied by proximal muscle weakness, thinning of the skin with the appearance of purplish striae, and a tendency for easy bruising [16]. TSH PitNETs are the primary cause of central hyperthyroidism, which manifests with different degrees of thyrotoxicosis. Symptoms include heat intolerance, hyperhidrosis, arrythmias, weight loss, irritability, and sleep disturbances [17]. Additionally, 10-15% of all PitNETs have the ability to secrete more than one hormone, with the combination of growth hormone and prolactin secretion being the most common [18].

2.3 Diagnosis

2.3.1 Non-functioning PitNET

Magnetic resonance imaging is the current gold standard for detecting all types of PitNETs [19]. On T1-weighted MRI scans, pituitary microadenomas typically appear as either hypointense or isointense when compared to the normal pituitary tissue. On T2-weighted MRI sequences, the appearance of a pituitary microadenoma varies based on its endocrine activity. In cases where the diagnosis is equivocal, the use of gadolinium enhancement is required. In contrast-enhanced images the hypointense signal of the microadenoma differs significantly from the intense signal of the unaffected pituitary gland [20]. In the case of pituitary macroadenomas, the adenomatous tissue can extend into extrasellar regions such as the suprasellar cistern, the third ventricle, the sphenoid sinus, or the cavernous sinus. MRI is used to evaluate the extension of the macroadenoma and its invasion into surrounding anatomical structures [21]. On both T1- and T2-weighted MRI scans, macroadenomas typically show an isointense signal similar to that of gray matter. However, it may vary due to the occurrence of necrosis or hemorrhage [22]. In 6 to 10% of cases the pituitary macroadenoma extend into the cavernous sinus. The Knosp classification is used to describe the growth of this extension and assess the chance of gross total resection [23].

2.3.2 Prolactinoma

A serum prolactin level exceeding 25 µg/L confirms the diagnosis of hyperprolactinemia, with levels being higher in women than in men. Hyperprolactinemia can be caused by physiological conditions such as pregnancy, breastfeeding, stress, exercise, and sleep, as well as by medical conditions like renal insufficiency, hepatic failure, primary hypothyroidism and certain drugs [20]. A non-prolactin-secreting mass can also lead to hyperprolactinemia by compressing the pituitary stalk or hypothalamus, which disrupts dopamine transport to the pituitary gland. These causes, along with idiopathic hyperprolactinemia, should be ruled out during the diagnostic process. There is a correlation between PRL serum levels and the size of a prolactinoma. PRL values over 250 µg/L are typically indicative of a macroadenoma rather than stalk compression. In the majority of prolactinoma cases, PRL levels exceed 150 µg/L. [24, 25].

2.3.3 Acromegaly

The initial step in diagnosing patients with clinical symptoms is the measurement of serum Insulin-like Growth Factor 1 (IGF-1) levels. This assessment should also be performed for patients who, despite not exhibiting typical clinical symptoms, present with comorbidities such as sleep apnea syndrome, type 2 diabetes mellitus, debilitating arthritis, carpal tunnel syndrome, hyperhidrosis, or hypertension. Additionally, this evaluation is recommended for patients with a pituitary mass. In cases where serum IGF-1 levels are elevated or inconclusive, an oral glucose tolerance test is recommended to confirm that hyperglycemia cannot suppress growth hormone (GH) levels below 1 μg/L [26].

2.3.4 Cushing's Disease

To confirm the presence of hypercortisolism, one or two of the following screening tests should be conducted: late-night salivary cortisol test (≥ 2 tests), 24-hour urinary free cortisol test (≥ 2 tests), the overnight 1 mg dexamethasone suppression test (DST), or the low-dose 2-day dexamethasone test (LDDT) [27]. The next step is to establish the underlying cause of the elevated cortisol levels by measuring ACTH levels. Normal or elevated ACTH levels suggest the presence of either Cushing's disease or ectopic ACTH-dependant Cushing's syndrome. Inferior petrosal sinus sampling can be performed to differentiate between the two diagnoses. The procedure involves measuring ACTH levels in the veins that drain the pituitary gland [28].

2.3.5 TSH PitNET (TSHoma)

TSH PitNETs are characterized by biochemical findings of secondary hyperthyroidism, with elevated free T4 (FT4) and free T3 (FT3) levels, along with elevated or inappropriately normal TSH levels [17].

2.4 Treatment

2.4.1 Non-functioning PitNET

Transphenoidal surgery is the first-line treatment for PitNETs and is recommended for patients with visual field defects, compression of the optic chiasm or nerves, pituitary dysfunction, headaches or evidence of tumor growth on follow-up MRI [29]. Although headache and hypopituitarism are not strong indications for surgery, the procedure can improve pituitary function in up to 30% of patients with pre-existing hypopituitarism [30]. However, there is a 2–15% risk of developing new hormone deficiencies and about 18% for diabetes insipidus (DI) as a result of the surgery [31, 32]. Asymptomatic cases should be

assessed individually, as tumor growth is rare (10%) [33]. Surgery may be recommended for younger patients, as they face a higher lifetime risk of tumor progression. In contrast, for older patients, surgery is generally not advised due to the heightened risk of complications associated with the procedure [34].

Pituitary tumor resection is most commonly performed via the transnasal transsphenoidal route. Neurosurgeons typically utilize one of two techniques: the endoscopic or microscopic approach. Recent meta-analyses have demonstrated the superiority of Endoscopic Endonasal Transsphenoidal Surgery (EETS). EETS is associated with a higher rate of gross total resection (GTR) and offers significant clinical advantages, including reduced complication rates, lower risk of tumor recurrence, and decreased morbidity [35]. Radiotherapy is considered a treatment for PitNETs in cases of subtotal resection (STR), tumor recurrence or remnant growth [36]. Combined therapy in patients without GTR leads to lower recurrence rates and progression [37, 38]. Several radiation techniques are available, including 3D conformal radiotherapy (3D-CRT), intensity modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT), stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (FSRT). Modern techniques allow for precise dose delivery, minimizing dose to surrounding tissues and reducing long-term toxicity [39]. Patients with non-functioning pituitary adenomas have a lower remission rate when compared to those with secreting adenomas [40]. As a result, long-term follow-up is crucial, with at least 10 years of postoperative imaging recommended, along with regular biochemical monitoring, to detect potential tumor recurrence or regrowth [41]. The extent of tumor resection remains the most significant factor influencing remission rates in these patients [42]. Despite significant advancements in both surgical and radiation therapies for pituitary adenomas, complications remain a concern and can reduce quality of life. Most common side effects of treatment include hypopituitarism, transient or permanent diabetes insipidus and postoperative CSF leakage [42, 43]. Patients with non-functioning pituitary adenomas exhibit an overall increase in mortality, with the risk being particularly pronounced in women and younger individuals. Elevated mortality is largely attributed to a higher incidence of cerebrovascular events and infectious diseases [44, 45].

2.4.2 Prolactinoma

The first-line treatment for prolactinomas is pharmacotherapy, making it the only type of pituitary tumor that can be fully managed with medical treatment alone. The primary goals of

treatment are suppression of excess prolactin secretion, reversal of endocrine and mass effect symptoms, reduction of tumor size, preservation of normal pituitary function and prevention of progression and recurrence. Dopamine agonists (DA) are the primary drugs used for therapy of prolactinomas [46, 47]. These agents bind to D2 receptors on normal and tumorous lactotroph cells leading to decreased prolactin secretion and inducing apoptosis [48]. The most commonly used dopamine agonists are bromocriptine and cabergoline, with cabergoline demonstrating superior efficacy in achieving normoprolactinemia and tumor shrinkage in clinical studies. Cabergoline is also associated with fewer side effects and has shown greater effectiveness in treating aggressive prolactinomas in men, as well as in cases resistant to bromocriptine or quinagolide [49, 50]. Dopamine agonist therapy is commonly associated with adverse effects such as nausea, vomiting, fatigue, headaches, and dizziness. Additionally, rare but serious complications, including cabergoline associated cardiac valvular or pleural fibrosis, impulse control disorders, and psychosis, have been reported in the literature [47, 51]. Special consideration is required for pregnant women with prolactinomas due to the potential for tumor enlargement during pregnancy. The risk of tumor growth is approximately 2.1% for microprolactinomas and 21% for macroprolactinomas [52]. Although dopamine agonist treatment is considered safe during pregnancy (FDA class B), it is generally recommended to discontinue the medication, with close monitoring for any signs of tumor enlargement. If significant tumor growth occurs, dopamine agonist should be resumed immediately [53, 54]. Transsphenoidal surgery is the next line of treatment for prolactinomas. Indications for surgery include resistance or intolerance to DAs, failure to achieve a significant reduction in prolactin levels or tumor size, as well as rare but serious adverse effects of DAs. Surgery is also recommended for patients with symptomatic macroadenomas planning pregnancy, during pregnancy and for younger patients who prefer to avoid prolonged medical therapy [55, 56]. The remission rates after EETS varies between 50% and 93% for microprolactinomas and 30% to 80% for macroprolactinomas. Recurrence rate range from 30% to 80%, largely depending on the length of follow-up and indications for surgery [57].

2.4.3 Acromegaly

Transsphenoidal surgery is the first-line treatment for GH PitNETs, with the primary goals of reducing growth hormone levels to less than 1 μg/L, normalizing insulin-like growth factor 1 levels to the age-adjusted range, reducing tumor size and alleviating acromegaly symptoms [26]. Remission is achieved in approximately 78% of patients with microadenomas and 53%

of those with macroadenomas [58]. For patients who do not achieve remission, options include repeat surgery, pharmacological therapy, or radiotherapy [26, 59]. In cases of mild symptoms and slightly elevated IGF-1 and GH levels, dopamine agonists are used as medical treatment. For patients with significant symptoms, somatostatin receptor ligands (SRLs), such as octreotide and lanreotide, are preferred [26]. However, studies have shown a wide variability in response and efficacy with SRL therapy [60]. The most common adverse effects of somatostatin analogs include gastrointestinal symptoms such as abdominal cramps, diarrhea, and gallbladder stones [26].

2.4.4 Cushing's Disease

Endoscopic Transsphenoidal Surgery is preferred treatment for Cushing's disease with remission rate of approximately 78% and recurrence rate of 11.5% [61]. Treatment response is assessed by a rapid decrease in cortisol levels below 2 μg/dL. For patients who do not achieve remission or experience recurrence, second-line treatment options include repeat transsphenoidal surgery, radiotherapy/radiosurgery, medical therapy, or uni/bilateral adrenalectomy [62]. Medical therapy can be categorized into three groups: inhibitors of steroidogenesis (ketoconazole, metyrapone), tumor-directed drugs (cabergoline, pasireotide), and glucocorticoid receptor antagonists (mifepristone, relacorilant). Ketoconazole reduces adrenal cortisol production in approximately 50-70% of patients, but its use is limited by significant side effects, including liver toxicity and prolongation of the QT interval. Cabergoline and pasireotide normalize cortisol level by decreasing ACTH secretion and reducing tumor size [63].

Bilateral adrenalectomy leads to an immediate decrease in cortisol levels with a 100% success rate in controlling hypercortisolism. However, this procedure comes with significant drawbacks, including the need for lifelong steroid replacement therapy and risk of developing Nelson's syndrome [64].

2.4.5 TSH PitNET (TSHoma)

The main treatment for TSH PitNETs is transsphenoidal surgery, which achieves biochemical remission in 70% of patients and gross total resection in about 54% of cases [65]. Before surgery, it is essential to achieve an euthyroid state with antithyroid medications such as methimazole or propylthiouracil. In patients who do not achieve remission or for whom

surgery is contraindicated, the next line of treatment includes radiotherapy or medical therapy with somatostatin analogs or dopamine agonists [66].

3. Summary

Pituitary neuroendocrine tumors are relatively common, with imaging studies showing a prevalence of up to 17% in the general population. Prolactinomas are the most frequent subtype. The symptoms of PitNETs result from mass effects and hormone secretion. Magnetic resonance imaging remains the gold standard for diagnosing these tumors. Treatment varies based on the tumor subtype, with dopamine agonists being the first-line treatment for prolactinomas and endoscopic transsphenoidal surgery for other types.

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Author's contribution

Conceptualization - Jakub Skiba and Zuzanna Skiba; methodology - Kinga Tylczyńska; software ,- Natalia Tylczyńska and Ignacy Maciejewski; check - Szymon Szypulski, Maria Michalska and Sebastian Iwaniuk; formal analysis - Ignacy Maciejewski and Kinga Kowalik; investigation - Aleksandra Zielińska; resources - Zuzanna Skiba; data curation - Kinga Tylczyńska and Maria Michalska; writing - rough preparation - Kinga Kowalik and Szymon Szypulski; writing - review and editing, Kinga Kowalik and Aleksnadra Zielińska; visualization, Natalia Tylczyńska; supervision - Jakub Skiba; project administration – Jakub Skiba; receiving funding not applicable, All authors have read and agreed with the published version of the manuscript.

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