Journal of the ASEAN Federation of Endocrine Societies

FEATURE ARTICLE

A Consensus for Pituitary Adenoma Diagnosis in Indonesia

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Abstract

Pituitary adenomas account for 10 to 15% of all intracranial masses and are the most common type of pituitary disorder. Their clinical manifestations can vary based on the tumor size and whether they secrete excess hormones. Occasionally, they are incidentally diagnosed following an imaging procedure for other indications (pituitary incidentaloma). The Pituitary Working Group of the Indonesian Society of Endocrinology has identified pituitary adenoma as a priority and has called for the development of updated evidence-based practice guidelines. These guidelines aim to provide evidence-based, comprehensive and multidisciplinary recommendations for diagnosing pituitary adenomas in Indonesia and to navigate the limitations of diagnosing pituitary adenomas in Indonesia.

Key words: pituitary adenoma, clinical practice guidelines, Indonesia

INTRODUCTION

The pituitary gland, located at the base of the brain and often referred to as the "master gland," is the most crucial endocrine gland in the body. It regulates the secretion of vital hormones.[1] A pituitary adenoma is a slow-growing benign tumor originating from pituitary gland cells.[2,3] It ranks third among the most common intracranial tumors after meningioma and glioma, comprising about 15% of all central nervous system tumors. Globally, pituitary adenomas are estimated to affect 68 to 115 individuals per 100,000. These tumors can significantly impact patients' quality of life[2-4] as clinical symptoms may vary widely based on mass effect and disrupted hormonal function.[5,6]

In Indonesia, many cases are diagnosed in advanced stages due to a delayed recognition of the symptoms and signs. A study at Cipto Mangunkusumo Hospital, the tertiary referral hospital in Jakarta, Indonesia, revealed that between 2007 and 2012, 97.8% of cases were pituitary macroadenomas, with 44.4% being functional adenomas that could have been diagnosed earlier.[7] Most cases

eISSN 2308-118x (Online)
Printed in the Philippines

Received: April 26, 2024. Accepted: July 17, 2024.
Published online first: April 29, 2025.
https://doi.org/10.15605/jafes.040.01.03

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were diagnosed in tertiary referral hospitals because of limitations in diagnostic modalities and healthcare provider awareness. Between 2017 and January 2024, 959 cases of pituitary adenoma were diagnosed and treated in Cipto Mangunkusumo Hospital, with many coming from various regions across the country. The most common complaints of patients with pituitary adenoma in Indonesia are symptoms related to mass effects, such as headaches (86.7%) and vision disturbances (77.8%).[7] Other common symptoms included hormonal disturbances, such as erectile dysfunction, menstrual irregularities, galactorrhea and facial changes.[7] These findings align with research indicating that patients with pituitary adenomas may first seek consultation with ophthalmologists, neurosurgeons, internists, neurologists, or other relevant specialists.[7]

This consensus on diagnosing pituitary adenomas was formulated as a comprehensive and multidisciplinary guide for diagnosing pituitary adenoma patients in Indonesia. This consensus aims to improve the quality of patient care, enable early diagnosis, and optimize the management of these patients through a multidisciplinary team in Indonesia.

SUMMARY OF THE METHODOLOGY FOR GUIDELINES DEVELOPMENT

The Pituitary Working Group of the Indonesian Society of Endocrinology developed this guideline by summarizing existing literature on pituitary adenoma and incorporating feedback and suggestions from multidisciplinary experts. This collaborative effort resulted in a comprehensive guideline catering to a broad spectrum of medical professionals in Indonesia, making it a versatile tool for daily practice.

SUMMARY OF RECOMMENDATIONS

Clinical manifestations of pituitary adenoma

Pituitary adenomas may present clinically in three ways: (1) with symptoms of hormone hypersecretion or deficiency, (2) with neurologic manifestations from mass effect or (3) as an incidental finding on imaging done for other indications. Pituitary adenomas are categorized based on primary cell origin and the type of hormone secreted for functioning adenomas. On the other hand, larger tumors may cause impingement of pituitary cells, leading to reduced secretion of pituitary hormones, and are termed nonfunctioning. Prolactinomas comprise 40% to 57% of all adenomas, followed by nonfunctioning adenomas (28% to 37%), growth hormone-secreting adenomas (11% to 13%), and adrenocorticotropic hormone (ACTH)-secreting adenomas (1% to 2%). Pituitary adenomas that secrete follicle-stimulating hormone (FSH), luteinizing hormone (LH), or thyroid-stimulating hormone (TSH) are rare. Tumors are also categorized based on size. If the tumor is 10 mm or larger, it is considered a macroadenoma; if it is less than 10 mm, it is considered a microadenoma.

Table 1. Clinical presentation of functioning pituitary adenomas[1,5,6]

Hormone secreted	Clinical syndrome	Presentation
Prolactin	Hyperprolactinemia	*Symptoms* Oligomenorrhea or amenorrhea, galactorrhea, decrease in libido, infertility, gynecomastia, impotence *Signs* Gynecomastia, hypogonadism (testicular atrophy, breast shrinkage, hair loss) *Morbidity* Osteoporosis
Growth hormone (GH)	Acromegaly, gigantism (if it occurs before closure of growth plate)	*Symptoms* Increase in hand and foot size, change in facial features (large and protruded mandible), enlarged tongue, carpal tunnel syndrome, hyperhidrosis, fatigue, proximal muscle weakness, decreased libido, menstrual changes, joint pain, height significantly exceeding normal or peer age (pediatric onset) *Signs* Hypertension, coarse facial features, left ventricular hypertrophy, cardiomyopathy, visceromegaly, hypercalciuria, goiter *Morbidity* Cardiovascular disease, diabetes, sleep apnea, increased risk of colon cancer, osteoporosis
Adrenocorticotropic hormone (ACTH)	Cushing disease	*Symptoms* Labile mood, proximal muscle weakness, skin changes, changes in facial features, weight gain, depression, hirsutism, decreased libido, menstrual changes *Signs* Thin skin, striae, bruising, central obesity, moon facies, plethora, hypertension, acne, glucose intolerance, neutrophilia, lymphocytopenia, eosinopenia *Morbidity* Diabetes mellitus, cardiovascular disease, osteoporosis
Thyroid-stimulating hormone (TSH)	Hyperthyroidism	Hyperthyroid symptoms, such as anxiety, palpitations, weight loss, heat intolerance, tremor
LH/ FSH	No specific syndrome	Symptoms from mass effect, hypopituitarism

Table 2. Clinical manifestations of mass effect and hypopituitarism[1,5,6]

Mass effect	Hypopituitarism
• Headache • Visual field disturbances • Blurred vision • Double vision • Strabismus • Protrusion of the eyeball (proptosis), usually accompanied by redness of the eye (conjunctival chemosis) • Deviation in eye position (esotropia, exotropia, or hypertropia) • Impaired eye movement • Ptosis • Decreased visual field (confrontation test) • Visual acuity examination may reveal decreased visual acuity • Relative afferent pupillary defect • Nystagmus (seesaw nystagmus) • Decreased color sensitivity • Decreased contrast sensitivity	• Growth hormone: growth inhibition (short stature), increased risk of osteoporosis, fatigue, weight gain • LH/ FSH: amenorrhea, decreased libido, infertility, obesity, osteoporosis, and diabetes • TSH: cold intolerance, memory impairment, constipation, excessive sleep, myxedema, coarse hair, weight gain • ACTH: orthostatic hypotension, fatigue, chronic dyspepsia, hyponatremia, hypoglycemia • Antidiuretic hormone (ADH): polyuria, hypernatremia, polydipsia (diabetes insipidus)

Table 3. Diagnostic tests in the evaluation of a suspected adenoma

Indication	Test
Prolactinoma	Serum prolactin
GH-secreting pituitary adenoma (acromegaly)	Serum insulin-like growth factor 1 (IGF-1) and GH suppression test (with oral glucose test)
ACTH-secreting pituitary adenoma*	Cortisol excess test: • 24-hour urinary free cortisol • low-dose dexamethasone suppression test • late-night salivary cortisol ACTH
TSH-secreting pituitary adenoma	TSH and FT4
Hypogonadism	LH, FSH, estradiol. Testosterone
Hypocortisolism	Morning serum cortisol Synacthen test
Hypothyroidism	TSH, FT4
ADH deficiency (diabetes insipidus)	Serum electrolytes, serum osmolarity, urine osmolarity Desmopressin suppression test

*Bilateral inferior petrosal sinus sampling (BIPSS) is indicated when clinical and biochemical evidence suggests Cushing's disease without definitive MRI findings.[8]

The clinical profile of patients with pituitary adenoma may be divided into two groups: 1) those with symptoms related to mass effect and 2) those with symptoms related to hormonal disturbances.[1,5,6] Hormonal disturbances can be further subdivided into functional pituitary adenomas producing too much hormones (Table 1), and nonfunctioning adenomas wherein hormonal hyposecretion is caused by the tumor's mass effect on the healthy pituitary gland (Table 2).

Neurologic symptoms caused by the mass effect are common in nonfunctioning adenomas or lactotroph adenomas in men because the hormonal effects may not be immediately recognizable. Hence, their diagnosis may be delayed until symptoms of mass effect become apparent. Partial or complete hypopituitarism commonly occurs due to direct compression of the pituitary gland. In the case of hyperprolactinemia, hypogonadism can occur because of its inhibitory effect on GnRH secretion and LH pulsatility.

Following thorough history taking and clinical examinations, hormonal laboratory diagnostic tests are warranted if hormone excess or deficiency is suspected (Table 3). In resource-limited healthcare centers where hormonal laboratory testing cannot be performed, general laboratory testing can be done initially to support the clinical findings, such as complete blood count, fasting blood glucose, oral glucose tolerance test and serum electrolytes.

Imaging examination

If a patient presents with neurologic symptoms due to a suspected mass effect, magnetic resonance imaging (MRI) is the best initial imaging study. The study should be done with and without gadolinium enhancement. If an MRI is contraindicated or unavailable, a computed tomography scan (CT scan) with thin sections (1.5 mm or less) and in a coronal plane will improve imaging of the pituitary region. A CT scan is limited in its ability to image the optic chiasm precisely. Adenomas are classified based on imaging using the Hardy and Wilson, and Knosp systems (Figure 1). These classifications aid in determining tumor invasion, management and postoperative prognosis.[9,10]

Classification by Hardy and modified by Wilson:[9,10]

- Microadenoma: classified as grade 0 or grade I based on the appearance of the sella or minimal changes in the sella.
- Macroadenoma: causes diffuse enlargement and can lead to focal and extensive destruction of the sella, categorized as grade II, III, and IV.

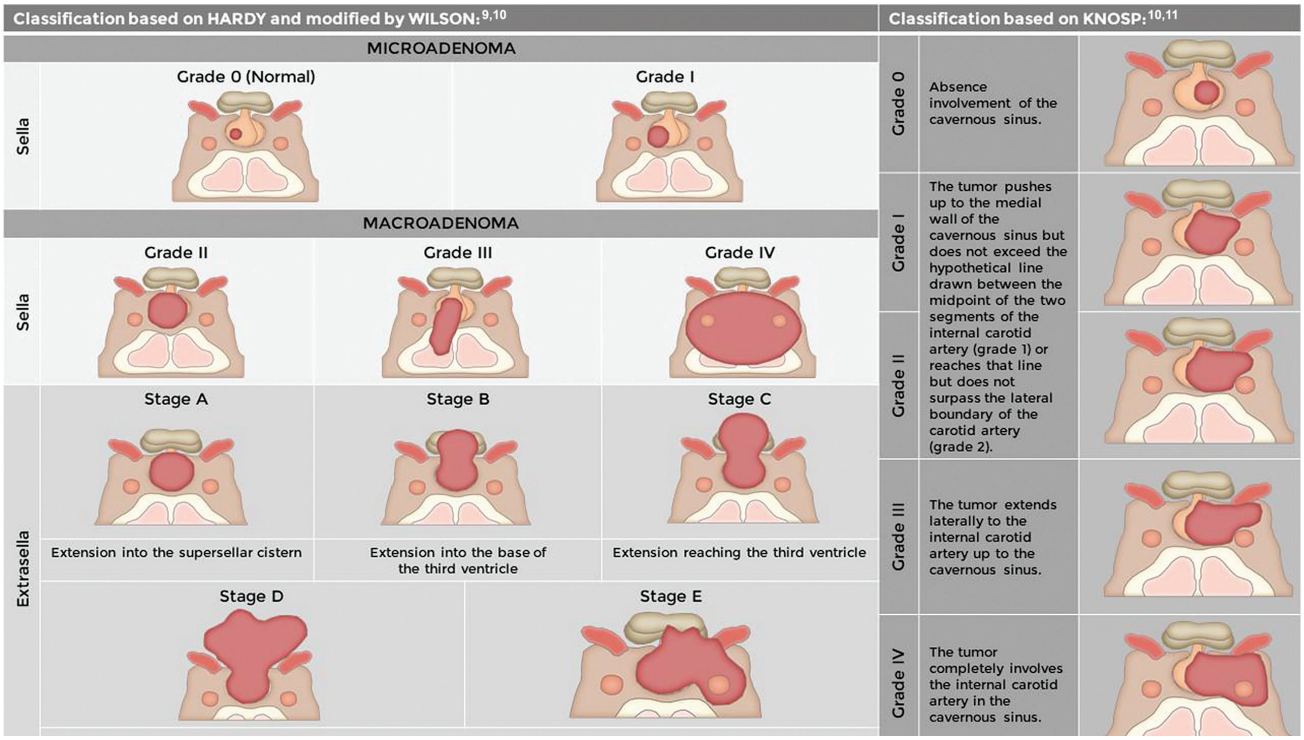

Figure 1. Classifications based on Hardy and modified by Wilson[9,10] and Knosp[10,11] *(redrawn for clarity)*.

- In this system, macroadenomas are also classified based on the degree and direction of extrasellar extension:
  - Extension into the suprasellar cistern alone is classified as stage A.
  - Extension to the base of the third ventricle is classified as stage B.
  - Extension reaching the third ventricle is referred to as stage C.
  - Tumors extending into the lateral intradural or extradural space are classified as stages D and E.

Knosp classification:[10,11]

Used to determine tumor invasion into the cavernous sinus. This classification is beneficial for describing tumor size, management and postoperative prognosis:[9,10]

- Grade 0 indicates no involvement of the cavernous sinus.
- Grade 1 and 2 tumors push up to the medial wall of the cavernous sinus but do not exceed a hypothetical line extending between the midpoints of the two segments of the internal carotid artery (grade 1) or reach that line without crossing the lateral boundary of the internal carotid artery (grade 2).
- In grade 3, the tumor extends laterally to the internal carotid artery into the cavernous sinus.
- In grade 4, the tumor completely involves the internal carotid artery in the cavernous sinus.

Ophthalmologic examination[11-13]

An ophthalmologic examination is performed to determine the extent of the mass effect of the adenoma and includes routine and more specific examinations as indicated (Table 4).

Table 4. Ophthalmologic Examinations

Routine examinations	Examination of specific indications
• Visual acuity test • Color vision and contrast sensitivity test • Perimetry test (confrontation, Goldman or Humphrey visual field test) • Ocular movement test • Funduscopy	• Optical Coherence Tomography (OCT) of the optic disc • Electrophysiological examinations, such as Pattern Visual Evoked Potential (PVEP), Multifocal VEP (mfVEP), or Pattern Electroretinography (PERG)

Anatomical pathology

Histopathological examination is warranted when surgical resection is performed. It is strongly suggested that immunohistochemical staining be done to determine the primary cell origin.[5,14] However, to date, immunohistochemical panel for pituitary adenoma is still not routinely done in Indonesia.

Incidental pituitary mass (incidentaloma)

Increased use and sensitivity of CT and MRI have identified many pituitary lesions incidentally, even when the tests were performed for other reasons.[15]

Differential diagnosis[16]

- Craniopharyngioma
- Meningioma
- Malignant tumors (germ cell tumors, chordomas, primary lymphoma, metastatic disease)
- Rathke's cysts

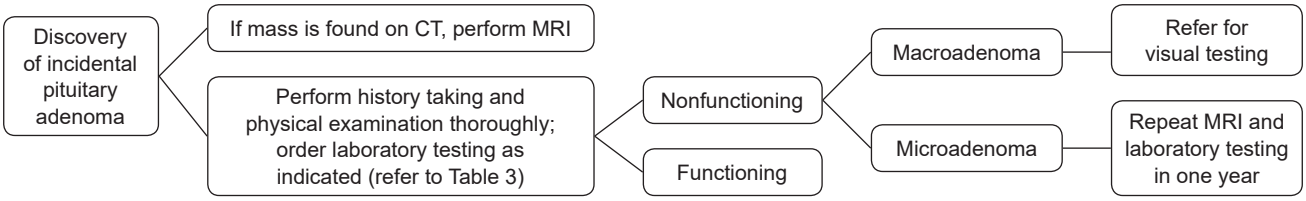

Figure 2. Approach to evaluation of pituitary incidentaloma.

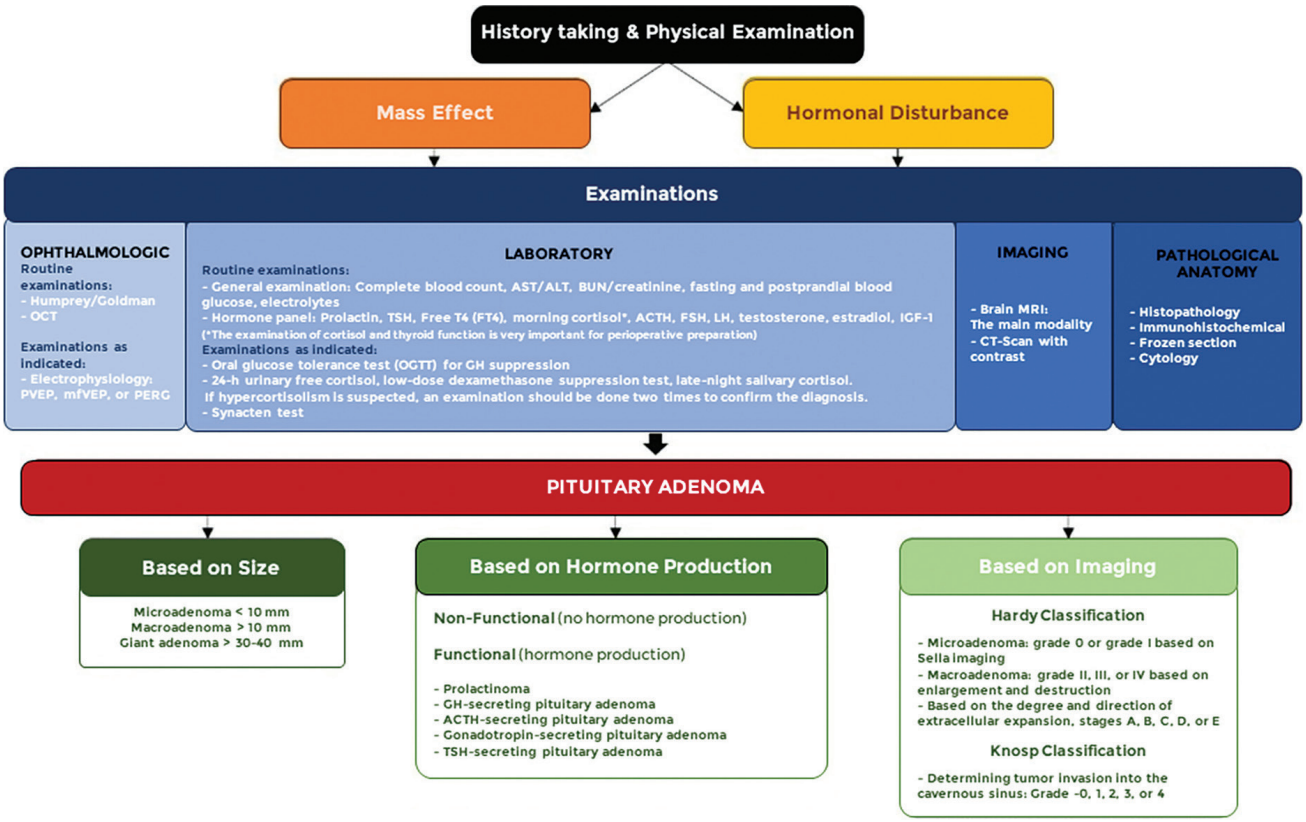

Figure 3. Guideline for the diagnostic approach to pituitary adenoma.

- Abcess
- Arteriovenous fistula of the cavernous sinus
- Hypophysitis
- Drugs that caused elevation of prolactin
- Primary adrenal Cushing syndrome
- Ectopic ACTH-secreting tumors
- Ectopic GH secretion by neuroendocrine tumors (rare)

CONCLUSION

This consensus on diagnosing pituitary adenomas was formulated as a comprehensive and multidisciplinary standard guide in Indonesia. It can be utilized to enhance the quality efficiency of the diagnostic approach to pituitary adenomas. In this regard, we propose an algorithm, that commences with a medical history and physical examination, followed by supportive examinations, including ophthalmological, laboratory, imaging and pathological examinations (Figure 3). This approach ensures a more timely and accurate diagnosis of pituitary adenomas, which will determine subsequent management. In resource-limited settings, prompt referral is strongly recommended if a pituitary adenoma (functioning or nonfunctioning) is suspected.

Acknowledgments
The authors express sincere appreciation to The Indonesian Society of Endocrinology for their invaluable facilitation and support during the development of this guideline. Furthermore, we thank Calysta Nadya Wijaya for the technical assistance in preparing this guideline.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
DLT: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration, Funding acquisition; **SO:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft preparation, Writing – review and editing, Project administration; **MK:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft preparation, Writing – review and editing, Project administration; **DAL:** Conceptualization, Methodology, Validation,

Formal analysis, Investigation, Writing – original draft preparation, Writing – review and editing, Project administration; **TTM:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft preparation, Writing – review and editing, Project administration; **REY:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft preparation, Writing – review and editing, Supervision Project administration; **HK:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft preparation, Writing – review and editing, Supervision Project administration; **APP:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft preparation, Writing – review and editing, Supervision Project administration; **MR:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision Project administration; **JP:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft preparation, Writing – review and editing, Supervision, Project administration; **LP:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft preparation, Writing – review and editing, Supervision, Project administration; **HN:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft preparation, Writing – review and editing, Supervision, Project administration; **HS:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft preparation, Writing – review and editing, Supervision, Project administration; **SN:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft preparation, Writing – review and editing, Supervision, Project administration; **TJET:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – original draft preparation, Writing – review and editing, Supervision, Project administration, Funding acquisition; **PS:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing -original draft preparation, Writing – review and editing, Supervision, Project administration, Funding acquisition; **KS:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – original draft preparation, Writing – review and editing, Supervision, Project administration, Funding acquisition

Author Disclosure
The authors declared no conflict of interest.

Data Availability Statement
No datasets were generated or analyzed for this study.

Funding Source
None.

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