Epidemiology of Functioning Pituitary Adenomas

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Pituitary adenomas (PAs) are defined as benign monoclonal tumors in the pituitary gland that cause symptoms due to either hormonal hypersecretion or a space-occupying effect [1]. These generally slowly-growing tumors are known to be the most common cause of hormonal hypersecretion or hyposecretion in adults. Following gliomas and meningiomas, PAs are the third most common type of brain tumor, accounting for 10% to 15% of all brain tumors [2], and they are the most common type of neuroendocrine tumor found in the central nervous system [3]. Pituitary carcinomas—defined as pituitary tumors with distant metastasis—are very rare, accounting for fewer than 0.2% of all cases of pituitary tumors [4].

PAs are divided into macroadenomas (>10 mm in diameter) or microadenomas (≤10 mm in diameter), and those with a diameter >40 mm are also called giant adenomas [4,5]. In addition, PAs are classified as either functioning or non-functioning depending on whether they have a hormonal hypersecretory capacity [6]. Depending on the type of hormone secreted, functioning PAs are sub-classified as prolactin-, growth hormone (GH)-, adrenocorticotropic hormone (ACTH)-, or thyrotropin-producing adenomas. A third of PAs are non-functioning, mostly including macroadenomas that frequently secrete gonadotropin or prolactin but have no symptoms resulting from hormonal hypersecretion [3,7-9]. Also, the pathologic classifications based on the immunohistochemical analyses, electron microscopy findings, and the demonstration of various transcription factors have been also introduced (Table 1) [10].

PAs were previously considered to be very rare, but recent data have revealed that their prevalence is higher than previously reported, potentially due to developments in imaging techniques and the increased detection of incidentalomas found during radiological work-ups for other diseases [11]. Traditionally,
epidemiologic data on PAs were collected from anatomical studies using data obtained from the autopsy studies or the magnetic resonance imaging. However, these methods often have the limitations of representing a relatively old population or not reflecting the actual epidemiology of clinically relevant PAs [1]. Epidemiologic data on PAs based on a national-level cancer registry have been reported, but it has also limitation of underestimating the actual prevalence of PAs due to the lack of mandatory reporting [12]. Recently, population studies on the basis of big data analysis using national insurance claims data in Korea have been published [13,14]. Despite the issue on the accuracy of their operational definitions, used in these studies, they have the advantage of enabling investigators to obtain epidemiologic data from the general population, and this method has therefore been applied in various studies for other diseases [15-17]. This review summarizes the previously reported epidemiologic data on functioning PAs in Korea and other countries.

**GH-PRODUCING PITUITARY ADENOMAS (ACROMEGALY)**

Acromegaly is a chronic disease caused by the hypersecretion of GH, and GH-producing PAs are found in 95% of acromegaly patients [18]. Although acromegaly has also been reported to be caused by ectopic hypersecretion of GH [19,20] or excess production of GH-releasing hormone [21], these etiologies are very rare. Since GH-producing PAs account for most cases of acromegaly, it is reasonable to assume that the prevalence and incidence of acromegaly are identical to those of GH-producing PAs. According to large population-based studies published as of 2000, the prevalence of GH-producing PAs was 3.3 to 13.7 cases per 100,000, and the annual incidence was 0.2 to 1.1 cases per 100,100 [22-33]. These figures are relatively higher than those reported before 2000 (prevalence: 3.8 to 6.9/100,000; annual incidence: 0.28 to 0.4/100,000) [34-37]. As described above, this difference may be due to the disparities in the study population (general population vs. limited cases from tertiary centers or smaller numbers of included cases), developments in imaging techniques, and the increased frequency of performing imaging work-ups.

Not many studies have investigated the epidemiology of acromegaly in Korea. The first case of acromegaly in Korea was reported in 1965 [38], and the Survey Committee for Endocrine Diseases in the Korean Endocrine Society performed a nationwide survey regarding PAs in Korea in 1994. Based on the clinical information of 279 cases of acromegaly collected from 26 university hospitals in Korea, the annual incidence rate was estimated to be 1.4 cases per million [39]. This was lower than the rates previously reported in other countries, and the discrepancy was speculated to be due to limitations in the survey methodology. In the early 2000s, the Rare Disease Study Group in the Science and Research Committee of the Korean Endocrine Society performed a nationwide study regarding the epidemiology of acromegaly in Korea. According to their report, the prevalence of GH-producing PAs was 4.3 to 10.3 cases per 100,000, and the annual incidence was 0.2 to 0.5 cases per 100,000 [40]. These figures are relatively lower than those reported in other countries, and the discrepancy may be due to differences in the study population (general population vs. limited cases from tertiary centers or smaller numbers of included cases), developments in imaging techniques, and the increased frequency of performing imaging work-ups.

### Table 1. Classification of Pituitary Adenomas

| Size                  | Function | Hormone        | Pathology (WHO) | Morphotfunctional subclassification |
|-----------------------|----------|----------------|-----------------|------------------------------------|
| Microadenoma          | Functioning | Prolactin     | Lactotroph adenoma (LA) | Sparsely granulated LA              |
| Macroadenoma          | Non-functioning | Densely granulated LA | Acidophilic stem cell adenoma |
| Giant adenoma         |          | Growth hormone | Somatotroph adenoma (SA) | Densely granulated SA                |
|                       |          |                | Sparsely granulated SA | Mammosomatotroph adenoma            |
|                       |          |                | Mixed somatotroph and lactotroph adenoma | Acidophilic stem cell adenoma |
| Adrenocorticotropic hormone | Corticotroph adenoma (CA) | Sparsely granulated CA | Acidophilic stem cell adenoma |
| Thyroid-stimulating hormone | Thyrotroph adenoma | Densely granulated GA | Acidophilic stem cell adenoma |
| Luteinizing hormone/follicular-stimulating hormone | Gonadotroph adenoma (GA) | Sparsely granulated GA | Acidophilic stem cell adenoma |
| Plurihormonal         | Plurihormonal adenoma | Plurihormonal PIT1-positive adenoma | Adenomas with unusual IHC combinations |
| Double adenoma        | Distinct adenomas | | |

WHO, World Health Organization; PIT1, pituitary-specific positive transcription factor 1; IHC, immunohistochemical.

Adapted from Laws et al. [10], with permission from Springer Nature.
Epidemiology of Pituitary Adenomas

With mostly benign, prolactin-producing PAs (prolactinomas) are known to be one of the most common causes of hyperprolactinemia. Although hyperprolactinemia can be caused by various etiologies, including pregnancy, breastfeeding, exercise, stress, renal or thyroid insufficiency, drugs, and pituitary stalk compression by a non-prolactin-producing tumor or other parasellar masses [41], prolactin-producing PAs are considered to be the most clinically important etiological factor underlying hyperprolactinemia [42].

Ezzat et al. [43] performed a meta-analysis demonstrating that prolactinomas were the most common PAs, accounting for 25% to 41% according to radiologic or autopsy studies. According to the community-based cohort studies conducted in Liège, Belgium and Banbury, the United Kingdom (UK), prolactinomas were found to be the most common PAs (66.2% in Liège, Belgium and 57% in Banbury, UK), with a prevalence of 6 to 44.4 cases per 100,000 [22,23]. Both studies demonstrated a female predominance of prolactinomas with being most common in those under the age of 60. Consistent results were reported in a retrospective analysis of patients who received surgical therapy for PAs; prolactinomas were 10-fold more common in female patients aged between 18 to 50 years, but the male-to-female ratio equaled in older patients [44].

As with acromegaly, there are not many studies which have investigated the epidemiology of prolactinomas in Korea. Clinical information of 1,350 patients with acromegaly diagnosed and treated between 2003 and 2007 at 74 hospitals in Korea was collected and analyzed. The annual incidence was calculated as 3.9 cases per million and the prevalence was 27.9 cases per million [40]. A limitation of survey methods is their high likelihood of representing patients treated at tertiary hospitals. In order to compensate for this limitation, Park et al. [13] analyzed the Korean Health Insurance Review and Assessment (HIRA) claims database between 2010 and 2014 and reported an annual incidence rate of 3.57 per million.

**PROLACTIN-PRODUCING PITUITARY ADENOMAS (PROLACTINOMAS)**

According to the analysis by Park et al. [14] of the HIRA claims database between 2009 and 2013, the prevalence of prolactinomas in Korea increased from 38.5 to 68.6 cases per million, while the annual incidence showed a sex disparity, at 1.0 to 1.6 cases per million in males and 27 to 29 cases per million in females [14].

**ACTH-PRODUCING PITUITARY ADENOMAS (CUSHING DISEASE)**

Cushing syndrome (CS) was first reported by Dr. Harvey Cushing in 1912 [45]. It is divided into exogenous CS, which is caused by glucocorticoid use, and endogenous CS, which is classified as (1) ACTH-producing PAs (Cushing disease [CD]); (2) cortisol overproduction by adrenal adenomas or carcinomas via ACTH-independent mechanisms; and (3) ectopic production of ACTH or corticotropin-releasing hormone by neuroendocrine tumors [46]. ACTH-producing PAs are the most common cause of endogenous CS, accounting for approximately 60% of cases [46].

CD is a very uncommon disease. Most publications presenting epidemiologic data on CD focused on the entire spectrum of endogenous CS, while few studies have investigated the epidemiology of CD only. A population-based study from Vizcaya in a region of Basque Country (Spain) between 1975 and 1992 reported that there were 49 patients diagnosed with CD, corresponding to an annual incidence of 2.4 cases per million and a prevalence of 39.1 cases per million [47]. A similar study conducted using the National Patient Register of the Danish National Board of Health between 1985 and 1995 found that approximately 60% of patients with endogenous CS were diagnosed with CD, with 73 (1985 to 1990) and 99 cases (1991 to 1995) of CD among a total of 166 cases of endogenous CS [48]. The annual incidence was 1.2 (1985 to 1990) and 1.7 cases (1991 to 1995) per million [48].

In Korea, the Survey Committee for Endocrine Diseases in the Korean Endocrine Society performed a nationwide survey to collect clinical data from patients diagnosed with endogenous CS between 1992 and 1998. In total, 180 cases of endogenous CS from 51 university hospitals in Korea were collected and analyzed, yielding an annual incidence of 0.84 cases per million [49]. The proportion of CD was 48.3%, similar to that of adrenal CS (48.9%) [49]. Since then, no additional studies have investigated the epidemiology of CD in Korea. A report by Park et al. [14] only demonstrated the prevalence of endogenous CS because of the small number of CD cases collected during the analysis. The annual incidence of endogenous CS was 4.5 cases (male) and 17.2 cases (female) per million, and the prevalence was 51.7 cases per million in 2013 [14].
THYROTROPIN–PRODUCING PITUITARY ADENOMAS

Thyrotropin-producing PAs are extremely rare, accounting for the smallest proportion of functional PAs. This disorder may be suspected when thyroid-stimulating hormone (TSH) is inappropriately normal or elevated in patients with hyperthyroidism. Defined as central hyperthyroidism, this condition requires a careful differential diagnosis between thyrotropin-producing PAs and thyroid hormone resistance syndrome. Thyrotropin-producing PAs were first reported by Jailer and Holub [50] in 1960, and more than 450 cases have been reported worldwide [50,51].

In the United States, a single-center study that investigated a total of 1,628 patients who underwent surgical treatment for PAs between 1993 and 2013 demonstrated that 1.2% of the cases (n=20) were found to be thyrotropin-producing PAs, and their proportion increased in recent years [52]. In Japan, a single-center study reported that 2.7% of patients (n=90 of 3,276) who underwent surgical treatment for PAs had a diagnosis of a thyrotropin-producing PA [53]. Yoon et al. [54] reported the first patient with a thyrotropin-producing PA in Korea, and since that time 11 cases have been reported in Korea [55]. According to the result of a single-center study in Korea that analyzed the clinical information of 484 patients who received surgical treatment for PAs, 1.65% (n=8) of the patients had a diagnosis of a TSH-producing PA [55].

A study in Sweden using the Swedish Pituitary Registry reported that the annual incidence of thyrotropin-producing PAs recently increased from 0.05 (1990 to 1994) to 0.26 cases per million (2005 to 2009) [56]. The annual incidence was reported to be 0.32 per million in Finland [27]. This trend is likely due to physicians’ increased awareness regarding the concept of inappropriately secreted TSH, the introduction ofultrasensitive immunometric TSH assays that reliably differentiate between suppressed and normal TSH levels, and advances in pituitary imaging techniques that detect pituitary microadenomas more accurately [57].

CONCLUSIONS

Because of their rarity and slow-growing, symptomless nature in most cases, it is very difficult to collect clinically reliable information on patients with PAs, which presents a solid barrier to investigations of the epidemiology of this disorder. As population studies based on big-data analyses have become more common and provided easier access to more dependable data; however, the prevalence and incidence of PAs have been found to increase over the past years. Considering their impacts upon public health and their associations with increased morbidity and mortality, as well as the economic burden that they place on the health care system, it is essential to understand the epidemiology of PAs. As mentioned repeatedly, not many studies have investigated the epidemiology of PAs in Korea, and updated and larger studies regarding the epidemiology of PAs are necessary.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Aflorei ED, Korbonits M. Epidemiology and etiopathogenesis of pituitary adenomas. J Neurooncol 2014;117:379-94.
2. Sivakumar W, Chamoun R, Nguyen V, Couldwell WT. Incidental pituitary adenomas. Neurosurg Focus 2011;31:E18.
3. Cho HJ, Kim H, Kwak YJ, Seo JW, Paek SH, Sohn CH, et al. Clinicopathologic analysis of pituitary adenoma: a single institute experience. J Korean Med Sci 2014;29:405-10.
4. Raverot G, Jouanneau E, Trouillas J. Management of endocrine disease: clinicopathological classification and molecular markers of pituitary tumours for personalized therapeutic strategies. Eur J Endocrinol 2014;170:R121-32.
5. Buchfelder M, Schlaffer S. Imaging of pituitary pathology. Handb Clin Neurol 2014;124:151-66.
6. Arafah BM, Nasrallah MP. Pituitary tumors: pathophysiology, clinical manifestations and management. Endocr Relat Cancer 2001;8:287-305.
7. Krysiak R, Okopien B, Korzekwa M. Atypical pituitary tumors. Pol Merkur Lekarski 2012;32:323-8.
17. Seong SC, Kim YY, Kang YH, Heon Park J, Kang HJ, Lee H, et al. Data resource profile: the national health information database of the national health insurance service in South Korea. Int J Epidemiol 2017;46:799-800.

18. Melmed S. Acromegaly pathogenesis and treatment. J Clin Invest 2009;119:3189-202.

19. Melmed S, Ezrin C, Kovacs K, Goodman RS, Frohman LA. Acromegaly due to secretion of growth hormone by an ectopic pancreatic islet-cell tumor. N Engl J Med 1985;312:9-17.

20. Beuschlein F, Strasburger CJ, Siegerstetter V, Moradpour D, Lichter P, Bidlingmaier M, et al. Acromegaly caused by secretion of growth hormone by a non-Hodgkin’s lymphoma. N Engl J Med 2000;342:1871-6.

21. Thorner MO, Perryman RL, Cronin MJ, Rogol AD, Draznin M, Johanson A, et al. Somatotroph hyperplasia. Successful treatment of acromegaly by removal of a pancreatic islet tumor secreting a growth hormone-releasing factor. J Clin Invest 1982;70:965-77.

22. Fernandez A, Karavitaki N, Wass JA. Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). Clin Endocrinol (Oxf) 2010;72:377-82.

23. Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirowa MA, Beckers A. High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. J Clin Endocrinol Metab 2006;91:4769-75.

24. Tjormstrand A, Gunnarsson K, Evert M, Holmberg E, Ragnarsson O, Rosen T, et al. The incidence rate of pituitary adenomas in western Sweden for the period 2001-2011. Eur J Endocrinol 2014;171:519-26.

25. Agustsson TT, Baldvinsdottir T, Jonasson JG, Olafsdottir E, Steinthorsdottir V, Sigurdsson G, et al. The epidemiology of pituitary adenomas in Iceland, 1955-2012: a nationwide population-based study. Eur J Endocrinol 2015;173:655-64.

26. Hoskuldsdottir GT, Fjalldal SB, Sigurjonsdottir HA. The incidence and prevalence of acromegaly, a nationwide study from 1955 through 2013. Pituitary 2015;18:803-7.

27. Raappana A, Koivukangas J, Ebeling T, Pirila T. Incidence of pituitary adenomas in Northern Finland in 1992-2007. J Clin Endocrinol Metab 2010;95:4268-75.

28. Dal J, Feldt-Rasmussen U, Andersen M, Kristensen LO, Laurberg P, Pedersen L, et al. Acromegaly incidence, prevalence, complications and long-term prognosis: a nationwide cohort study. Eur J Endocrinol 2016;175:181-90.

29. Bex M, Abs R, T’Sjoen G, Mockel J, Velkeniers B, Muehmann K, et al. AcroBel—the Belgian registry on acromegaly: a survey of the ‘real-life’ outcome in 418 acromegalic subjects. J Endocrinol 2001;153:152-8.

30. Park KH, Lee EJ, Seo GH, Ku CR. Risk for acromegaly-related comorbidities by sex in Korean acromegaly. J Clin Endocrinol Metab 2020;105:dgz317.

31. Park KH, Choi JG, Tae ES, Song SO, Nam JY, Song YD. Rare intractable pituitary diseases: analysis on their epidemiology and use of benefit extension policy (No. 2015-20-025). Goyang: National Health Insurance Service Ilsan Hospital; 2015.

32. Yun JM, Shin DW, Hwang SS, Cho J, Nam YS, Kim JH, et al. Effect of public disclosure on antibiotic prescription rate for upper respiratory tract infections. JAMA Intern Med 2015;175:445-7.

33. Seo GH, Choe EK, Park KJ, Chai YJ. Incidence of adhesive bowel obstruction after colon cancer surgery and its risk factors: a nationwide claim study. Ann Surg 2018;268:114-9.  

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Cena T, et al. Use of administrative health databases to estimate incidence and prevalence of acromegaly in Piedmont Region, Italy. J Endocrinol Invest 2019;42:397-402.

34. Sader MA, McGrath KC, Hill MD, Bradstock KF, Jimenez M, Handelsman DJ, et al. Androgen receptor gene expression in leucocytes is hormonally regulated: implications for gender differences in disease pathogenesis. Clin Endocrinol (Oxf) 2005;62:56-63.

35. Bengtsson BA, Eden S, Ernest I, Oden A, Sjogren B. Epidemiology and long-term survival in acromegaly. A study of 166 cases diagnosed between 1955 and 1984. Acta Med Scand 1988;223:327-35.

36. Ritchie CM, Atkinson AB, Kennedy AL, Lyons AR, Gordon DS, Fannin T, et al. Ascertainment and natural history of treated acromegaly in Northern Ireland. Ulster Med J 1990;59:55-62.

37. Etxabe J, Gaztambide S, Latorre P, Vazquez JA. Acromegaly: an epidemiological study. J Endocrinol Invest 1993;16:181-7.

38. Lee SJ, Chai ES, Chough CB, Kim CH, Choi HJ. Case report: two cases of active acromegaly. Korean J Med 1965;8:241-7.

39. Yang IM. Clinical characteristics of acromegalic patients in Korea. J Korean Soc Endocrinol 1994;9:290-306.

40. Kwon O, Song YD, Kim SY, Lee EJ; Rare Disease Study Group; Science and Research Committee, et al. Nationwide survey of acromegaly in South Korea. Clin Endocrinol (Oxf) 2013;78:577-85.

41. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:273-88.

42. Vroonen L, Daly AF, Beckers A. Epidemiology and management challenges in prolactinomas. Neuroendocrinology 2019;109:20-7.

43. Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, et al. The prevalence of pituitary adenomas: a systematic review. Cancer 2004;101:613-9.

44. Colao A, Sarno AD, Cappabianca P, Briganti F, Pivonello R, Somma CD, et al. Gender differences in the prevalence, clinical features and response to cabergoline in hyperprolactinemia. Eur J Endocrinol 2003;148:325-31.

45. Cushing H. The pituitary body and its disorders: clinical states produced by disorders of the hypophysis cerebri. Philadelphia: JB Lippincott; 1912.

46. Pivonello R, Isidori AM, De Martino MC, Newell-Price J, Biller BM, Colao A. Complications of Cushing’s syndrome: state of the art. Lancet Diabetes Endocrinol 2016;4:611-29.

47. Etxabe J, Vazquez JA. Morbidity and mortality in Cushing’s disease: an epidemiological approach. Clin Endocrinol (Oxf) 1994;40:479-84.

48. Lindholm J, Juul S, Jorgensen JO, Astrup J, Bjerre P, Feldt-Rasmussen U, et al. Incidence and late prognosis of cushing’s syndrome: a population-based study. J Clin Endocrinol Metab 2001;86:117-23.

49. The Korean Society of Endocrinology; The Survey Committee for Endocrine Disease in Korea. The incidence and clinical characteristics of Cushing’s syndrome in Korea. J Korean Soc Endocrinol 2000;15:31-45.

50. Jailer JW, Holub DA. Remission of Graves’ disease following radiotherapy of a pituitary neoplasm. Am J Med 1960;28:497-500.

51. Amlashi FG, Tritos NA. Thyrotropin-secreting pituitary adenomas: epidemiology, diagnosis, and management. Endocrine 2016;52:427-40.

52. Azzalin A, Appin CL, Schniederjan MJ, Constantine T, Ritchie JC, Veledar E, et al. Comprehensive evaluation of thyrotropinomas: single-center 20-year experience. Pituitary 2016;19:183-93.

53. Yamada S, Fukushima H, Horiguchi K, Yamaguchi-Okada M, Nishioka H, Takeshita A, et al. Clinicopathological characteristics and therapeutic outcomes in thyrotropin-secreting pituitary adenomas: a single-center study of 90 cases. J Neurosurg 2014;121:1462-73.

54. Yoon HJ, Hong DS, Hong KS, Cha BY, Kim YW, Son HY. A case of TSH secreting pituitary tumor. J Korean Soc Endocrinol 1986;1:55-62.

55. Lee WK, Hwang S, Lim JS, Kim HM, Lee EY, Lee SK, et al. Clinical and biochemical characteristics and treatment of patients with thyrotropin-secreting pituitary adenomas. Korean J Med 2011;80:47-55.

56. Onnestam L, Berinder K, Burman P, Dahlqvist P, Engstrom BE, Wahlberg J, et al. National incidence and prevalence of TSH-secreting pituitary adenomas in Sweden. J Clin Endocrinol Metab 2013;98:626-35.

57. Beck-Peccoz P, Lania A, Beckers A, Chatterjee K, Wemeau JL. 2013 European Thyroid Association guidelines for the diagnosis and treatment of thyrotropin-secreting pituitary tumors. Eur Thyroid J 2013;2:76-82.