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·综述·

静默性垂体腺瘤的临床病理特征

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[摘 要] 无功能型垂体腺瘤(non-functional pituitary adenomas，NFPAs)是指缺乏垂体激素的分泌及激素分泌过多引起临床症状的垂体腺瘤。其中静默性垂体腺瘤是NFPAs的一种类型，是指免疫组织化学发现垂体激素免疫阳性，通常因为免疫组织化学结果或偶然检查被发现。不同类型的静默性垂体腺瘤具有各自的临床病理特征，本文对静默性垂体腺瘤的流行病学、影像学特征、临床表现与术后复发作一综述。

[关键词] 无功能型垂体腺瘤；静默性垂体腺瘤；免疫组织化学

Clinicopathologic features of silent pituitary adenomas

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Abstract Non-functional pituitary adenoma refers to the pituitary adenoma that lacks the secretion of pituitary hormone and causes clinical symptoms by excessive secretion of hormone. Among them, silent pituitary adenoma is a type of non-functional pituitary adenoma, which means immunohistochemically found pituitary hormone immunopositively, and they are usually found because of immunohistochemical results or accidental examination. Different types of silent pituitary adenomas have their own clinicopathological features. This article reviews the epidemiology, imaging features, clinical manifestations and postoperative recurrence of silent pituitary adenomas.

Keywords non-functional pituitary adenomas; silent pituitary adenoma; immunohistochemistry

无功能型垂体腺瘤(non-functional pituitary adenomas，NFPAs)占垂体腺瘤的15%~30%[1]，通常为大腺瘤，临床表现为肿瘤占位效应，包括头痛、视力障碍、垂体功能减退等。2017年WHO[2-4]采用腺垂体细胞谱系(表1)及转录因子指导垂体腺瘤分类，分为嗜酸性谱系、促性腺激素谱系、促肾上腺皮质激素谱系。在过去十几年中已发现几种转录因子对内分泌细胞的分化和成熟至关重要，垂体转录因子(pituitary-specific POU-class homeodomain transcription factor1，PIT-1)参与生长激素、泌乳素(prolactin，PRL)、甲状腺激素细胞的分化，形成嗜酸性谱系；类固醇生长因子-1(steroidogenic factor 1，SF-1)参与促性腺激素细胞的分化，形成促性腺激素谱系；T-box成

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员TBX19(T-box family member TBX19，T-PIT)参与促肾上腺皮质激素细胞的分化，形成促肾上腺皮质激素谱系；此外雌激素受体(estrogen receptor α，ERα)、鸟嘌呤-腺嘌呤-胸腺嘌呤-腺嘌呤结合蛋白2(member of the GATA family of zinc-finger transcriptional regulatory proteins，GATA-2)也被认为参与促性腺激素、PRL、促甲状腺激素细胞的分化[4]。NFPAs根据垂体激素和垂体特异性转录因子的免疫组织化学表达可分为促性腺激素腺瘤、静默性生长激素腺瘤(silent growth hormone adenomas，SGHA)、静默性泌乳素腺瘤(silent prolactinomas，SPAs)、静默性促甲状腺激素腺瘤(silent TSH secreting adenomas，STAs)、静默性促肾上腺皮质激素腺瘤(silent corticotroph adenomas，SCAs)、零细胞激素腺瘤、多激素Pit-1阳性腺瘤、双重性或三重性腺瘤8个亚型[4-6](表2)。

表1 2017年细胞谱系分类

Table 1 Classification of adenohypophyseal cell lineage in 2017

细胞谱系	主要转录因子和其他辅助因子	腺垂体细胞
嗜酸性谱系	PIT-1；PIT-1，ERα；PIT-1，GATA-2	生长激素，PRL，促甲状腺激素
促肾上腺皮质激素细胞谱系	T-PIT	促肾上腺皮质激素
促性腺激素细胞谱系	SF-1，GATA-2，ERα	促性腺激素

表2 NFPAs的病理类型

Table 2 Histopathological types of NFPAs

肿瘤亚型	免疫组织化学激素表达
促性腺激素腺瘤	卵泡刺激素β(β-FSH)，黄体生成素β(β-LH)，α-亚基(α-SU)
促肾上腺皮质激素腺瘤	促肾上腺皮质激素(ACTH)
生长激素腺瘤	生长激素(GH)
促甲状腺激素腺瘤	TSH
泌乳素腺瘤	PRL
多激素PIT-1阳性腺瘤	GH，PRL，TSH，α-SU
零细胞激素腺瘤	无
双重性/三重性腺瘤	多变的

1 SCAs

SCAs是最常见的静默性腺瘤，属于促肾上腺皮质激素谱系，免疫组织化学显示ACTH阳性，垂体转录因子为T-PIT，临床上没有皮质醇分泌增多及库欣病的表现。根据细胞形态可以分为致密颗粒型腺瘤、稀疏颗粒型腺瘤和Crooke细胞腺瘤。

1.1 流行病学和临床表现

SCAs占无功能腺瘤的3%~19%[7-10]。在德国的垂体肿瘤登记中心[5]，SCAs约占垂体腺瘤的3%，约占无功能型垂体瘤的5.5%。一些研究[11-12]提到SCAs的发病率显著高于促肾上腺皮质激素型垂体瘤，而其他人则报告发病率较低[9-13]。SCAs发病率的变化可能取决于每个研究中所使用的标准，如使用了垂体转录因子T-PIT免疫染色，则ACTH阴性的无功能型腺瘤可重新分类为SCAs。

SCAs发病年龄与NFPAs类似[8-9,14]。有研究[8,10,15-17]表明SCAs好发于女性，而其他研究[9,18-20]则没有。SCAs常表现为头痛、视力障碍、垂体功能减退等。SCAs术前垂体功能减退发生率高达60%[21]，其中性腺功能减退最常见，与NFPAs术前垂体功能减退的发生率类似[8,19]，而视觉障碍发生率明显高于NFPAs[8,22]。SCAs与NFPAs伴有高PRL血症的发生率相似[8-9]。此外SCAs患者卒中率较高，在Cho等[8]的报道中，有25%的SCAs患者表现

为垂体卒中，而NFPAs患者卒中的发生率为8%。

1.2 影像学特征和术后复发情况

SCAs与NFPAs的放射学的一般特征基本相似，肿瘤大小无明显差异[8,13,19]，但SCAs患者中海绵窦侵袭性更普遍[7,9,21]。Jahangiri等[9]从1990年到2011年回顾性调查了75例SCAs患者，发现海绵窦侵袭率为30%，而激素阴性的垂体腺瘤海绵窦侵袭率为18%。Kim等[17]回顾性调查了55例SCAs患者，发现海绵窦侵袭率为40%，而激素阴性的垂体腺瘤仅为17.6%。一些研究[8,11]还观察到SCAs表现出更多的囊肿，MRI T2加权显示高达75%存在多发微囊。SCAs瘤内出血率明显高于NFPAs[8]。

SCAs术后报告的复发率差异很大，可能与样本数量和随访时间有关。有研究[8-9,19-20]认为SCAs与NFPAs相比复发率较高。也有研究[17]表明：当肿瘤完全切除时，SCAs与激素阴性的腺瘤相比复发率没有明显差异，当肿瘤不能完全切除时，SCAs患者肿瘤再生率明显高于激素阴性的腺瘤。SCAs患者复发时间比NFPAs患者早5年[22]。此外，与NFPAs患者相比，SCAs患者出现多次复发[8-9]。Cho等[8]发现：在SCAs患者中多次复发(>2次)显著增加，在复发的SCAs患者中有57.1%是多次复发，而在非SCAs患者中只有1例是多次复发(2.8%)，且SCAs复发患者诊断年龄与非SCAs患者年轻，复发的患者要年轻于没有复发的患者，多次复发(>2次)的患者年轻于仅复发1次或2次的患者，表明SCAs在年轻患者中更容易复发(<30岁)。部分SCAs患者可转化为功能性库欣病，特别是在接受放疗后[7,23]。

2 SGHA

SGHA属嗜酸性谱系，免疫组织化学显示GH阳性，约50%以上的SGHA合混合有PRL免疫阳性，转录因子为PIT-1，临床上没有生长激素分泌增多及肢端肥大症的表现。根据细胞角蛋白免疫染色可以分为致密颗粒型和稀疏颗粒型生长激素腺瘤。Chinezu等[24]于2016年进行了一项回顾性研究，比较了21例SGHA和59例生长激素型垂体瘤，其中85.7%的SGHA患者是稀疏颗粒型生长激素腺瘤，而生长激素型垂体瘤患者中有45.7%为稀疏颗粒型生长激素腺瘤。

2.1 流行病学和临床表现

SGHA占垂体瘤的2%~4%[5,24-26]。SGHA患者年龄为20~40岁，好发于女性，常表现为月经稀少、泌乳、头痛，并通常伴有PRL轻度升高(<100 ng/mL)，这可能由于垂体柄压迫引起[25,27]。此外，90%的SGHA患者会出现头痛[24,26]。

2.2 影像学特征及术后病程

SGHA患者的肿瘤体积及侵袭性较小，但这在其他文献中并未得到一致体现，其复发率较高，大约有30%的患者在随访期间出现复发，复发率是促性腺激素腺瘤的3倍，与SCAs患者复发率类似[26]。此外与其他NFPAs患者(SCAs除外)相比，更多SGHA患者需要进行辅助放射治疗[26-27]。年轻的SGHA患者和稀疏颗粒型SGHA患者，常表现为巨腺瘤，侵袭性及复发率高[26,28-31]，且稀疏颗粒型SGHA患者可能对生长抑素类似物治疗反应不佳[32]。Langlois等[26]提出仅表达GH的单激素类型肿瘤比表达多激素肿瘤(如混合表达PRL或TSH)更具攻击性。且仅表达GH的稀疏颗粒型腺瘤具有体积大、侵袭性大、复发率高的特点[33]，类似于肢端肥大症[34-35]。SGHA稀疏颗粒型肿瘤也可能比致密颗粒型肿瘤更具攻击性。在SGHA和生长激素型垂体瘤患者中观察到增殖标志物Ki-67标志指数和肿瘤抑制因子p53表达没有明显差异[33]。在一项大型研究[26]中，12%的SGHA患者在长期随访期间进展为IGF-1水平升高，且主要发生在女性患者中。

3 STAs

STAs属嗜酸性谱系，免疫组织化学显示TSH、α-亚单位阳性，常合并多种激素表达，最常见是FSH，其次是GH，LH，PRL和ACTH[36]。转录因子为PIT-1，GATA-2，临床上没有TSH分泌增多及甲状腺功能亢进表现。

3.1 流行病学和临床表现

促甲状腺激素型垂体瘤非常少见，占垂体瘤的0.2%~3.5%[36-39]，且大多数没有甲亢的临床表现，属于临床上无功能型腺瘤。Kirkman等[36]从2002年至2012年期间收集902例垂体腺瘤患者，通过术后病理确诊了32名TSH免疫阳性的患者，其中只有1/4的患者出现甲亢症状，其余均为STAs，患者最常见的临床症状为视力障碍、头痛、眩晕、恶心，其中视力障碍最常见(约占34%)，促甲状腺激素型垂体瘤与STAs在临床表现方面没有明显差异。

3.2 影像学特征及术后病程

促甲状腺激素型垂体瘤与STAs均以大腺瘤为主，且STAs的平均肿瘤体积明显大于促甲状腺激素型垂体瘤，STAs患者中约33%有侵袭性，而促甲状腺激素型垂体瘤患者中20%有侵袭性[39]。约1/3的患者在随访期间出现复发，促甲状腺激素型垂体瘤与STA在术后复发方面没有明显差异[36]。

4 SPAs

SPAs属嗜酸性谱系，免疫组织化学显示PRL阳性，转录因子为PIT-1，临床上没有PRL分泌增多及闭经、泌乳等临床表现。

PRL型垂体瘤是最常见的功能型垂体瘤，患病率为(45~50)人/100万[1]，常表现为闭经、泌乳、不孕、性功能减退等。但SPAs较为罕见，免疫组织化学常见于与GH混合表达[26]。德国垂体肿瘤登记中心报道[5]显示，SPAs约占垂体腺瘤1.65%，其中大部分属于稀疏颗粒状亚型。Tampourlou等[40]发现：在垂体瘤手术患者中，SPAs的患病率仅为0.6%。由于其发病率很低，其临床病理特征尚未得到深入研究。

5 结语

静默型腺瘤是一种比较常见的垂体腺瘤，术前被诊断为NFPAs，没有激素分泌增多的生化及临床表现，但免疫组织化学染色显示为垂体激素表达阳性，常常通过术后免疫组织化学结果才能确诊。不同亚型静默型腺瘤都具有独特的临床病理特征，其中一些特殊的亚型，如静默型促肾上腺皮质激素腺瘤、稀疏颗粒型生长激素腺瘤常表现出较高的复发率及侵袭性，临床上常表现为难治性垂体腺瘤，有时需要进行多次手术及辅助放射治疗等，因此对静默型垂体腺瘤正确分类有助于更好了解其临床行为，指导后续的治疗方案以及进行密切随访。

参考文献

1. Fernandez A, Karavitaki N, Wass JAH. Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK)[J]. Clin Endocrinol (Oxf), 2010, 72(3): 377-382.
2. Lopes MBS. The 2017 World Health Organization classification of tumors of the pituitary gland: a summary[J]. Acta Neuropathol, 2017, 134(4): 521-535.
3. Mete O, Lopes MB. Overview of the 2017 WHO classification of pituitary tumors[J]. Endocr Pathol, 2017, 28(3): 228-243.
4. Lloyd RV, Osamura YO, Kloeppel G, et al. World health organization classification of tumours of endocrine organs[M]. 4th ed. Lyon: IARC, 2017: 11-63.
5. Saeger W, Ludecke DK, Buchfelder M, et al. Pathohistological classification of pituitary tumors: 10 years of experience with the German Pituitary Tumor Registry[J]. Eur J Endocrinol, 2007, 156(2): 203-216.
6. Neto VL, Boguszewski CL, Araújo LA, et al. A review on the diagnosis and treatment of patients with clinically nonfunctioning pituitary adenoma by the Neuroendocrinology Department of the Brazilian Society of Endocrinology and Metabolism[J]. Arch Endocrinol Metab, 2016, 60(4): 374.
7. Baldeweg SE, Pollock JR, Powell M, et al. A spectrum of behaviour in silent corticotroph pituitary adenomas[J]. Br J Neurosurg, 2005, 19(1): 38-42.
8. Cho HY, Cho SW, Kim SW, et al. Silent corticotroph adenomas have unique recurrence characteristics compared with other nonfunctioning pituitary adenomas[J]. Clin Endocrinol (Oxf), 2010, 72(5): 648-653.
9. Jahangiri A, Wagner JR, Pekmezci M, et al. A comprehensive long-term retrospective analysis of silent corticotrophic adenomas vs hormone-negative adenomas[J]. Neurosurgery, 2013, 73(1): 8-17; discussion 17-18.
10. Yamada S, Ohyama K, Taguchi M, et al. A study of the correlation between morphological findings and biological activities in clinically nonfunctioning pituitary adenomas[J]. Neurosurgery, 2007, 61(3): 580-584; discussion 584-585.
11. Guttenberg KB, Mayson SE, Sawan C, et al. Prevalence of clinically silent corticotroph macroadenomas[J]. Clin Endocrinol (Oxf), 2016, 85(6): 874-880.
12. Pawlikowski M, Kunert-Radek J, Radek M. "Silent" corticotropinoma[J]. Neuro Endocrinol Lett, 2008, 29(3): 347.
13. Raverot G, Wierinckx A, Jouanneau E, et al. Clinical, hormonal and molecular characterization of pituitary ACTH adenomas without (silent corticotroph adenomas) and with Cushing's disease[J]. Eur J Endocrinol, 2010, 163(1): 35-43.
14. Alahmadi H, Lee D, Wilson JR, et al. Clinical features of silent corticotroph adenomas[J]. Acta Neurochir (Wien), 2012, 154(8): 1493-1498.
15. Webb KM, Laurent JJ, Okonkwo DO, et al. Clinical characteristics of silent corticotrophic adenomas and creation of an internet-accessible database to facilitate their multi-institutional study[J]. Neurosurgery, 2003, 53(5): 1076-1084.
16. Nishioka H, Inoshita N, Mete O, et al. The complementary role

of transcription factors in the accurate diagnosis of clinically nonfunctioning pituitary adenomas[J]. Endocr Pathol, 2015, 26(4): 349-355.

17. Kim J, Yoon SJ, Moon JH, et al. Clinical significance of radical surgery in the treatment of silent corticotroph adenoma[J]. J Korean Neurosurg Soc, 2019, 62(1): 114-122.
18. Langlois F, Lim DST, Yedinak CG, et al. Predictors of silent corticotroph adenoma recurrence; a large retrospective single center study and systematic literature review[J]. Pituitary, 2018, 21(1): 32-40.
19. Cooper O, Ben-Shlomo A, Bonert V, et al. Silent corticogonadotroph adenomas: clinical and cellular characteristics and long-term outcomes[J]. Horm Cancer, 2010, 1(2): 80-92.
20. Cohen-Inbar O, Xu Z, Lee CC, et al. Prognostic significance of corticotroph staining in radiosurgery for non-functioning pituitary adenomas: a multicenter study[J]. J Neurooncol, 2017, 135(1): 67-74.
21. Scheithauer BW, Jaap AJ, Horvath E, et al. Clinically silent corticotroph tumors of the pituitary gland[J]. Neurosurgery, 2000, 47(3): 723-729.
22. Ben-Shlomo A, Cooper O. Silent corticotroph adenomas[J]. Pituitary, 2018, 21(2): 183-193.
23. Melcescu E, Gannon AW, Parent AD, et al. Silent or subclinical corticotroph pituitary macroadenoma transforming into Cushing disease[J]. Neurosurgery, 2013, 72(1): E144-E146.
24. Chinezu L, Vasiljevic A, Trouillas J, et al. Silent somatotroph tumour revisited from a study of 80 patients with and without acromegaly and a review of the literature[J]. Eur J Endocrinol, 2017, 176(2): 195-201.
25. Wade AN, Baccon J, Grady MS, et al. Clinically silent somatotroph adenomas are common[J]. Eur J Endocrinol, 2011, 165(1): 39.
26. Langlois F, Lim DST, Varlamov E, et al. Clinical profile of silent growth hormone pituitary adenomas; higher recurrence rate compared to silent gonadotroph pituitary tumors, a large single center experience[J]. Endocrine, 2017, 58(3): 528-534.
27. Erickson D, Scheithauer B, Atkinson J, et al. Silent subtype 3 pituitary adenoma: a clinicopathologic analysis of the Mayo Clinic experience[J]. Clin Endocrinol (Oxf), 2009, 71(1): 92-99.
28. Chinezu L, Jouanneau E, Vasiljevic A, et al. Silent GH pituitary tumor: Diagnostic and therapeutic challenges[J]. Ann. Endocrinol (Paris), 2013, 74(5/6): 491-495.
29. Horvath E, Kovacs K, Smyth H S, et al. Silent adenoma subtype 3 of the pituitary—immunohistochemical and ultrastructural classification: a review of 29 cases[J]. Ultrastruct Pathol, 2005, 29(6): 511-524.
30. Mete O, Gomez-Hernandez K, Kucharczyk W, et al. Silent subtype 3 pituitary adenomas are not always silent and represent poorly differentiated monomorphous plurihormonal Pit-1 lineage adenomas[J]. Mod Pathol, 2016, 29(2): 131-42.
31. Villa C, Lagonigro MS, Magri F, et al. Hyperplasia-adenoma sequence in pituitary tumorigenesis related to aryl hydrocarbon receptor interacting protein gene mutation[J]. Endocr Relat Cancer, 2011, 18(3): 347-356.
32. Gomez-Hernandez K, Ezzat S, Asa SL, et al. Clinical implications of accurate subtyping of pituitary adenomas: perspectives from the treating physician[J]. Turk Patoloji Derg, 2015, 31(Suppl 1): 4-17.
33. Trouillas J, Roy P, Sturm N, et al. A new prognostic clinicopathological classification of pituitary adenomas: a multicentric case-control study of 410 patients with 8 years post-operative follow-up[J]. Acta Neuropathol, 2013, 126(1): 123-135.
34. Brzana JA, Yedinak CG, Delashaw JB, et al. Discordant growth hormone and IGF-1 levels post pituitary surgery in patients with acromegaly naive to medical therapy and radiation: what to follow, GH or IGF-1 values?[J]. Pituitary, 2012, 15(4): 562-570.
35. Katznelson L, Laws ER, Melmed S, et al. Acromegaly: an endocrine society clinical practice guideline[J]. J Clin Endocrinol Metab, 2014, 99(11): 3933-3951.
36. Kirkman MA, Jaunmuktane Z, Brandner S, et al. Active and silent thyroid-stimulating hormone-expressing pituitary adenomas: presenting symptoms, treatment, outcomes, and recurrence[J]. World Neurosurg, 2014, 82(6): 1224-1231.
37. Beck-Peccoz P, Persani L, Mannavola D, et al. Pituitary tumours: TSH-secreting adenomas[J]. Best Pract Res Clin Endocrinol Metab, 2009, 23(5): 597-606.
38. Dyer MW, Gnagey A, Jones BT, et al. Perianesthetic management of patients with thyroid-stimulating hormone-secreting pituitary adenomas[J]. J Neurosurg Anesthesiol, 2017, 29(3): 341-346.
39. Wang EL, Qian ZR, Yamada S, et al. Clinicopathological characterization of TSH-producing adenomas: special reference to TSH-immunoreactive but clinically non-functioning adenomas[J]. Endocr Pathol, 2009, 20(4): 209-220.
40. Tampourlou M, Ntali G, Ahmed S, et al. Outcome of non-functioning pituitary adenomas that regrow after primary treatment: a study from two large UK centers[J]. J Clin Endocrinol Metab, 2017, 102: 1889-1897.

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