

2017 版 WHO 垂体神经内分泌肿瘤分类临床指导及国际疾病分类法编码分析

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【摘要】 2017 年世界卫生组织发布第四版内分泌肿瘤分类(以下简称 2017 版分类),对垂体肿瘤分类的理论基础进行更新。垂体转录因子的发现使垂体腺瘤的分类更细化,使既往无法明确诊断、易混淆、无法判断预后的垂体腺瘤的分类得以明确。本文按照 2017 版分类对每种垂体腺瘤分类、诊断和预后进行分析,并结合国际疾病分类法-10(ICD-10)和 ICD-O 列出相应的疾病编码和形态学编码。

【关键词】 垂体肿瘤; 世界卫生组织; 国际疾病分类法; 综述

Clinical guidance and International Classification of Disease coding analysis in the 2017 WHO classification of pituitary neuroendocrine tumors

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【Abstract】 The fourth edition of the latest classification of endocrine tumors has published by World Health Organization (WHO) in 2017, in which the theoretical basis of classification has been updated. With the discovery of specific transcription factors, the classification of pituitary adenomas which could not be diagnosed definitively and confused easily, whose prognosis is impossible to determine, has been defined. In this paper, the classification, diagnosis and prognosis of each pituitary adenoma were discussed according to the latest classification, and the corresponding disease codes were summarized based on International Classification of Disease-10 (ICD-10) and ICD-O.

【Key words】 Pituitary neoplasms; World Health Organization; International classification of diseases; Review

Conflicts of interest: none declared

2017 年,世界卫生组织(WHO)发布了第四版内分泌肿瘤分类(以下简称 2017 版分类)^[1],较既往版本具有显著变化^[2]。本文重点介绍两大变化,一是 2017 版分类介绍一种根据腺垂体细胞谱系分类的新方法,部分垂体腺瘤需对垂体转录因子进行评估,方能进行准确分类,特别是无功能垂体腺瘤;二是 2017 版分类根据临床和病理诊断分析垂体腺瘤的侵袭性,既往“非典型垂体腺瘤”的概念被取消。腺垂体细胞分化相关转录因子主要包括 3 种,即垂体 T-box 限制性转录因子(T-PIT),与促肾上腺皮质激素(ACTH)细胞分化相关;垂体特异性转录因子 1

(PIT-1),与生长激素(GH)细胞、催乳素(PRL)细胞、促甲状腺激素(TSH)细胞分化相关;类固醇生成因子 1(SF-1)、GATA 结合蛋白 2(GATA-2)和雌激素受体(ER),与促性腺激素细胞分化相关。本文重点分析垂体腺瘤和垂体恶性肿瘤,并按照国际疾病分类法-10(ICD-10)和 ICD-O 分别列出相应的疾病编码和形态学编码,同时总结 2017 版分类的优点及相关 ICD 疾病编码和形态学编码变化。

一、2017 版分类及相应 ICD 编码

1. 垂体腺瘤 垂体腺瘤属神经内分泌肿瘤^[3],约占颅内肿瘤的 10% 和垂体肿瘤的 30%~50%^[4],包括非特指的垂体腺瘤、生长激素细胞腺瘤、催乳素细胞腺瘤、促甲状腺激素细胞腺瘤、促肾上腺皮质激素细胞腺瘤、促性腺激素细胞腺瘤、零细胞腺瘤(null-cell adenomas)、多激素细胞腺瘤

(plurihormonal adenomas)、双腺瘤共 9 种类型,均为垂体良性肿瘤,其在 ICD-10 第三卷(字母顺序索引)中所对应的疾病编码很易按垂体良性肿瘤检索到(D35.2 亚目)。2017 版分类根据腺垂体细胞谱系而非产生激素(hormone-producing)进行分类,部分垂体腺瘤的命名改变,例如,以催乳素细胞腺瘤(lactotroph adenoma)替代催乳素瘤(prolactinoma),在 ICD-O 中仅能以 prolactinoma 按字母顺序索引查找出 M8271/0 的形态学编码。垂体腺瘤按照肿瘤大小分为微腺瘤(直径 < 10 mm)、大腺瘤(直径 ≥ 10 ~ 40 mm)和巨腺瘤(> 40 mm)^[5],罹患大腺瘤和大微腺瘤(6 ~ 9 mm)的患者应行垂体功能评估^[6]。MRI 显示肿瘤压迫视神经或视交叉时,应行视野检测^[7]。垂体腺瘤患者很少发生尿崩症^[8]。有 2/3 的垂体腺瘤过量分泌某种激素,一项纳入 1718 例垂体腺瘤患者的研究显示,约 50% 为大腺瘤;32% ~ 66% 分泌催乳素;在 14% ~ 54% 的无功能垂体腺瘤中,8% ~ 16% 分泌生长激素、2% ~ 6% 分泌促肾上腺皮质激素、< 1% 分泌促甲状腺激素^[9-11]。(1)非特指的垂体腺瘤(ICD-10 编码:D35.200;ICD-O 编码:M8272/0)^[12]:系来源于腺垂体细胞的肿瘤,通常为良性,采取靶向药物治疗和外科手术治疗。在 ICD-10 中相当于垂体腺瘤非特指类型,即 NOS。(2)生长激素细胞腺瘤(ICD-10 编码:D35.200;ICD-O 编码:M8272/0)^[13]:既往称为生长激素腺瘤。血浆生长激素水平升高。临床表现为巨人症(青春期骨骺未闭)和肢端肥大症(成人),其所对应的内分泌编码均为 E22.000,ICD-10 国家临床版 3.0 又将这两种症状分别扩展为巨人症(E22.000 × 001)和肢端肥大症(E22.001),临床应注意区别使用。(3)催乳素细胞腺瘤(ICD-10 编码:D35.200;ICD-O 编码:M8271/0)^[14]:系催乳素分泌异常的垂体良性肿瘤,临床最为常见。男性表现为阳痿,女性出现闭经泌乳综合征,其所对应的内分泌编码为 E22.100 × 001。(4)促甲状腺激素细胞腺瘤(ICD-10 编码:D35.200;ICD-O 编码:M8272/0)^[15]:既往称为促甲状腺激素腺瘤。血浆促甲状腺激素水平升高。其所对应的内分泌编码为 E05.800 × 011,该扩展码在 ICD-10 中代表垂体促甲状腺激素瘤,不能理解为肿瘤,只能作为附加编码与促甲状腺激素腺瘤(D35.2)联合使用。(5)促肾上腺皮质激素细胞腺瘤(ICD-10 编码:D35.200、D35.200 × 004、D35.200 × 009;ICD-O 编码:M8272/0)^[16]:约 80% 的促肾上腺皮质激素细胞腺瘤表现为垂体促肾上腺

皮质激素亢进。该肿瘤分泌过量促肾上腺皮质激素,刺激肾上腺皮质分泌过量糖皮质激素。临床主要表现为库欣病,其所对应的内分泌编码为 E24.0,ICD-10 国家临床版 3.0 扩展编码为垂体促肾上腺皮质激素分泌过多,内分泌编码为 E24.000 × 001。应注意与异位促肾上腺皮质激素综合征(内分泌编码:E24.300)相区别。余 20% 的促肾上腺皮质激素细胞腺瘤表现为静寂垂体腺瘤(silent adenomas)。静寂垂体腺瘤系分泌一种或多种腺垂体激素或垂体转录因子但激素水平未能引起临床症状的肿瘤,同样显示出与相应特异性腺垂体细胞谱系一致的组织学形态和免疫组化特征,最常见的是促肾上腺皮质激素细胞腺瘤。由于缺乏库欣病的临床表现和分子生物学证据(血浆促肾上腺皮质激素或皮质醇水平升高),故称为静寂的促肾上腺皮质激素细胞腺瘤,血浆抗 T-PIT 抗体阳性、促肾上腺皮质激素水平不升高可资诊断。ICD-10 将其编码为无功能垂体腺瘤(D35.200 × 004),生长巨大时编码为巨大侵袭性垂体腺瘤(D35.200 × 009),出现瘤卒中时编码为瘤卒中特指颅内肿瘤内出血(I61.900 × 007)。(6)促性腺激素细胞腺瘤(ICD-10 编码:D35.200 × 004 或 D35.200 × 009;ICD-O 编码:M8272/0)^[17]:好发于 > 60 岁的男性,与其他分化良好的垂体腺瘤不同,大多数促性腺激素细胞腺瘤均为无功能垂体腺瘤(D35.200 × 004),通常压迫垂体和蝶鞍周围组织致头痛、垂体功能低下时才被发现。既往易因检测不到过量的性激素而被忽视,目前通过免疫组化染色和转录因子 SF-1 测定可以确诊。(7)零细胞腺瘤(ICD-10 编码:D35.200 × 004 或者 D35.200 × 009;ICD-O 编码:M8272/0)^[18]:系通过免疫组化染色无法检测到垂体激素和转录因子的腺瘤,属无功能垂体腺瘤^[19],临床与促性腺激素细胞腺瘤难以鉴别。随着特异性腺垂体细胞谱系标志物和转录因子的出现,即 SF-1 阳性可诊断为促性腺激素细胞腺瘤。组织学形态,零细胞腺瘤更倾向于大腺瘤(D35.200 × 009),肿瘤细胞呈巢状或条状排列。(8)多激素细胞腺瘤(ICD-10 编码:D35.200 × 011 或 D35.200 × 008;ICD-O 编码:M8272/0)^[20-21]:定义为由一种或两种以上细胞组成并产生两种以上激素的腺瘤,临床十分罕见。以催乳素-生长激素混合性细胞腺瘤和 β-卵泡刺激素(β-FSH)-β-黄体生成素(β-LH)混合性细胞腺瘤多见,还有 PIT-1 阳性的多激素细胞腺瘤^[22]、有临床症状的功能性腺瘤(分泌生长激素/催乳素/

促甲状腺激素,临床表现为肢端肥大症和甲状腺功能障碍组合症状)、免疫组化不能定性的多激素细胞腺瘤。其中 2017 版分类中新描述的是 PIT-1 阳性的多激素细胞腺瘤,既往称为静寂腺瘤亚型 3 (silent adenoma subtype 3),由一种低分化的细胞群构成,不分泌过量的生长激素/催乳素/ β -促甲状腺激素/糖蛋白激素 α 亚基,高泌乳素血症和肢端肥大症症状不明显。转录因子 PIT-1 阳性证明其属于嗜酸细胞谱系的腺瘤^[22-23],可见独特核包涵体,胞核呈球形。由于其较强的侵袭力、高复发率、低生存率,临床对其进行鉴别诊断很重要。根据其具有侵袭力的特征给予侵袭性垂体肿瘤的 ICD-10 编码: D35.200×008。(9) 双腺瘤 (ICD-10 编码: D35.200×011; ICD-O 编码: M8272/0): 并非多激素细胞腺瘤,而是由两种不同细胞谱系的垂体腺瘤组成^[24],因其常出现与所分泌的垂体激素相对应的明显临床症状, ICD-10 编码时应按照激素引发的症状予以对应的内分泌编码。

2. 垂体腺癌 (ICD-10 编码: C75.100; ICD-O 编码: M8272/3) 垂体腺癌 (pituitary carcinoma) 很少见,发生远处转移者亦少见,仅占 0.1%~0.2%^[1]。定义为转移至中枢神经系统或全身的腺垂体细胞肿瘤,该概念与组织学形态无关,关键词为转移而非局部浸润,在 ICD-O 中按照 Pituitary 索引易查找到 M8272/3 的形态学编码^[25-26]。

3. 垂体母细胞瘤 (ICD-10 编码: C75.100; ICD-O 编码: M8273/3) 垂体母细胞瘤 (pituitary blastoma) 系 2017 版分类新定义的肿瘤,是临床罕见的原发性垂体恶性肿瘤,好发于<2 岁的婴幼儿,女性多见,主要表现为库欣病症状与体征^[27]。垂体母细胞瘤病例均有相似的组织学形态特征,即由类似未成熟的 Rathke 上皮细胞、小而原始的胚泡样细胞和大的腺垂体细胞组成的腺样结构^[2]。此类肿瘤多表达促肾上腺皮质激素,少数表达生长激素。在 ICD-O 中, WHO 国际癌症研究机构 (IARC) 定义其形态学编码为 M8273/3^[28]。

二、2017 版分类原则

1. 垂体腺瘤的细胞谱系 2017 版分类的重大变化是以腺垂体细胞分化相关转录因子和诱导因子为标志物对腺垂体细胞谱系进行分类,这些转录因子和诱导因子对腺垂体细胞的分化和成熟至关重要,主要包括 3 种细胞谱系,即嗜酸性细胞谱系,促性腺激素细胞谱系和促肾上腺皮质激素细胞谱

表 1 2017 版分类的腺垂体细胞谱系

Table 1. Adenohypophyseal cell lineage basis in the 2017 classification of pituitary adenomas

细胞谱系	转录因子/诱导因子	腺垂体细胞
嗜酸细胞谱系	PIT-1	生长激素细胞
	PIT-1, ER	催乳素细胞
	PIT-1, GATA2	促甲状腺激素细胞
促肾上腺皮质激素 T-PIT 细胞谱系	T-PIT	嗜铬细胞 (促肾上腺皮质激素细胞)
促性腺激素细胞谱系	SF-1, GATA-2, ER	促性腺激素细胞
零细胞腺瘤	—	—
多激素细胞腺瘤	PIT-1	嗜酸细胞谱系细胞的任意组合,即促肾上腺皮质激素细胞谱系/生长激素细胞的组合、促肾上腺皮质激素细胞谱系/催乳素细胞的组合

—, none, 无。PIT-1, pituitary specific transcription factor 1, 垂体特异性转录因子 1; ER, estrogen receptor, 雌激素受体; GATA2, GATA binding protein 2, GATA 结合蛋白 2; T-PIT, T-box pituitary restricted transcription factor, 垂体 T-box 限制性转录因子; SF-1, steroidogenic factor 1, 类固醇生成因子 1

系^[29](表 1)。

2. 垂体腺瘤的分类依据 垂体腺瘤的分类主要依据垂体激素的免疫组化染色(包括生长激素、催乳素、促肾上腺皮质激素、 β -促甲状腺激素、 β -黄体生成素、 β -卵泡刺激素和糖蛋白激素 α 亚基);而垂体激素呈现微弱表达时,则需使用垂体转录因子(包括 PIT-1^[30]、SF-1^[31]和 T-PIT^[32])进行辅助分类,如 PIT-1 阳性的多激素细胞腺瘤、零细胞腺瘤、SF-1 强阳性的促性腺激素细胞腺瘤。此外,还可采用某些特异性蛋白区分同一垂体腺瘤的不同亚型,例如,低分子量细胞角蛋白(CK)可以区分稀疏颗粒型与致密颗粒型生长激素细胞腺瘤,前者较后者治愈率低^[33-34],有助于判断预后。无功能垂体腺瘤占全部垂体腺瘤的 14%~54%^[35-37],未出现特异性细胞谱系标志物前,其包含促性腺激素细胞腺瘤、静寂的促肾上腺皮质激素细胞腺瘤^[35]和生长激素细胞腺瘤、零细胞腺瘤;如今通过转录因子 SF-1 可以从无功能垂体腺瘤中区分出促性腺激素细胞腺瘤,通过转录因子 T-PIT 可以区分出静寂的促肾上腺皮质激素细胞腺瘤^[38],其余对垂体激素和转录因子均无免疫反应的腺瘤则为零细胞腺瘤。静寂的促肾上腺皮质激素细胞腺瘤通常为大腺瘤,缺血或出血(瘤卒中)的风险较高^[39]。

3. 垂体腺瘤的预后 2004 版 WHO 垂体肿瘤分类将垂体腺瘤分为典型垂体腺瘤、非典型垂体腺瘤和垂体腺癌^[40]。绝大多数垂体肿瘤为典型垂体腺

表 2 垂体内分泌肿瘤的侵袭和转移

Table 2. Invasion and metastasis of pituitary neuroendocrine tumors

按照侵袭和转移分类	垂体肿瘤
复发的可能性很低(非侵袭性)	垂体腺瘤
复发的可能性很高(侵袭性)	高增殖性垂体腺瘤 特殊亚型垂体腺瘤: 稀疏颗粒型生长激素细胞腺瘤 静寂的促肾上腺皮质激素细胞腺瘤 男性催乳素细胞腺瘤 PIT-1 阳性的多激素细胞腺瘤
恶性肿瘤(转移性)	垂体腺癌

瘤,非典型垂体腺瘤和垂体腺癌少见。Zaidi 等^[41]在大宗病例中比较侵袭性(海绵窦和斜坡)与非侵袭性非典型垂体腺瘤的攻击行为,发现肿瘤细胞侵袭能力与 Ki-67 抗原标记指数呈正相关,而非典型垂体腺瘤无关联性。2017 版分类剔除非典型垂体腺瘤,并按照侵袭和转移提出新的分类,即非侵袭性垂体腺瘤、侵袭性垂体腺瘤和垂体腺癌。侵袭性垂体腺瘤包括呈侵袭性过快增长的大腺瘤、易复发的腺瘤和对常规治疗抵抗的腺瘤^[42](表 2)。

三、结论

2017 版分类为垂体腺瘤与其他不常见的垂体和鞍区肿瘤的分类诊断与鉴别诊断提供了全面指导。垂体腺瘤是发生于垂体的最常见神经内分泌肿瘤,主要通过免疫组化染色以区分特异性细胞谱系,超微结构观察则用于诊断其他罕见肿瘤。临床早期识别有高复发风险和不良预后的侵袭性垂体腺瘤是十分必要的,主要通过组织病理学、有丝分裂指数、Ki-67 抗原标记指数和转录因子等。垂体腺瘤还应与其他鞍区肿瘤相鉴别,包括表达甲状腺转录因子-1(TTF-1)的垂体非神经内分泌肿瘤^[43]、罕见的神经元肿瘤^[44]以及间充质和间质肿瘤^[45]。

垂体激素、垂体转录因子及其他免疫学标志物(如细胞角蛋白等)的免疫组化染色是垂体腺瘤分类诊断的基础。大多数垂体腺瘤的诊断主要依靠垂体激素的免疫组化染色,无需转录因子,但在鉴别诊断垂体激素免疫组化染色呈弱阳性、可疑阳性或阴性的垂体腺瘤时,转录因子即显得至关重要,无需对肿瘤进行超微结构观察,即可鉴别出复发率高、预后差的垂体腺瘤^[46](表 2)。PIT-1 和 SF-1 是目前应用较广泛的转录因子,而 T-PIT 尚无可靠的商业抗体^[33]。

2017 版分类剔除“非典型垂体腺瘤”的概念,形

态学编码删除交界性类型(/1),仅保留/0 和/3 的分类。除垂体腺瘤和垂体母细胞瘤仍采用/3 的形态学编码外,其余垂体腺瘤无论是否具有侵袭性均为良性肿瘤,即采用/0 的形态学编码。这意味着 2017 版分类对垂体肿瘤的认定局限于“转移”的类型,这一观点与传统临床认知略有不同。垂体母细胞瘤的形态学编码 M8273/3 是 2017 版分类的新实体,目前国内教科书尚未引进。临床工作中,ICD-10 编码仍是主要的临床诊断编码,ICD-O 编码则作为附属编码和病理编码。为便于临床应用,本文给出每种垂体腺瘤的 ICD-10 编码,并针对垂体腺瘤 ICD-10 国家临床版 3.0 进行较详细的扩展,对垂体肿瘤细化分类和统计分析具有重要意义。

总之,在 2017 版分类的指导下,可靠的转录因子商业抗体的研发必将提高垂体腺瘤的分类诊断和预后判断水平。目前,我国垂体腺瘤的诊断与鉴别诊断主要依靠垂体激素测定和免疫组化染色,针对转录因子的研究尚处于空白,直接影响肿瘤的细化分类和预后判断。尽快普及 2017 版分类,使特异性细胞谱系标志物(如转录因子)国产化早日应用于临床,必将使临床医师和垂体肿瘤患者受益。

利益冲突 无

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(收稿日期:2022-01-12)

(本文编辑:彭一帆)

· 小词典 ·

中英文对照名词词汇(七)

微兴奋性突触后电流

miniature excitatory postsynaptic currents(mEPSCs)

微抑制性突触后电流

miniature inhibitory postsynaptic currents(mIPSCs)

细胞间黏附分子-1

intercellular adhesion molecule-1(ICAM-1)

细胞黏附分子 cell adhesion molecule(CAM)

B 细胞受体 B cell receptor(BCR)

T 细胞受体 T cell receptor(TCR)

细胞外基质 extracellular matrix(ECM)

细胞外结构域 extracellular domain(ECD)

下丘脑-垂体-肾上腺 hypothalamic-pituitary-adrenal(HPA)

纤维母细胞生长因子 fibroblast growth factor(FGF)

腺苷酸活化蛋白激酶

adenosine monophosphate-activated protein kinase(AMPK)

信号转导与转录激活因子 3

signal transducer and activator of transcription 3(STAT3)

兴奋性氨基酸 excitatory amino acid(EAA)

I 型单纯疱疹病毒 herpes simplex virus-1(HSV-1)

II 型单纯疱疹病毒 herpes simplex virus-2(HSV-2)

血管内皮生长因子

vascular endothelial growth factor(VEGF)

血管细胞黏附分子-1

vascular cell adhesion molecule-1(VCAM-1)

血红素加氧酶-1 heme oxygenase-1(HO-1)

血浆置换 plasma exchange(PE)

血-脑屏障 blood brain barrier(BBB)

烟酰胺腺嘌呤二核苷酸磷酸氧化酶

nicotinamide adenine dinucleotide phosphate oxidase(NOX)

眼肌型重症肌无力 ocular myasthenia gravis(OMG)

Toll 样受体 Toll-like receptor(TLR)

Toll 样受体 4 Toll-like receptor 4(TLR4)

胰岛素样生长因子-1 insulin-like growth factor-1(IGF-1)

乙酰胆碱受体 acetylcholine receptor(AChR)

乙酰胆碱酯酶抑制剂 acetylcholinesterase inhibitor(AChEI)

隐球菌性脑膜炎 cryptococcal meningitis(CM)

诱导型一氧化氮合酶 inducible nitric oxide synthase(iNOS)

原发进展型多发性硬化

primary progressive multiple sclerosis(PPMS)

脂多糖 lipopolysaccharide(LPS)

质谱流式技术 cytometry by time-of-flight(CyTOF)

中枢神经系统相关巨噬细胞

central nervous system-associated macrophages(CAMs)

肿瘤坏死因子- α tumor necrosis factor- α (TNF- α)

重症肌无力 myasthenia gravis(MG)

重症肌无力定量评分

Quantitative Myasthenia Gravis Score(QMGS)

主要组织相容性复合物 II

major histocompatibility complex II (MHC II)

转化生长因子- β transforming growth factor- β (TGF- β)

自然杀伤细胞 natural killer lymphocyte(NK)

自然杀伤 T 细胞 natural killer T lymphocyte(NKT)

自身免疫性脑炎 autoimmune encephalitis(AE)

Miller Fisher 综合征 Miller Fisher syndrome(MFS)

CC 族趋化因子受体 6 CC-chemokine receptor 6(CCR6)

阻塞性睡眠呼吸暂停 obstructive sleep apnea(OSA)