· 脑肿瘤专题 ·

癫痫相关低级别发育性脑肿瘤研究进展

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【摘要】 癫痫相关低级别发育性脑肿瘤（LEAT）是青少年局灶性癫痫的第二常见病因，这类肿瘤以癫痫发作为主要症状，预后较好，常见类型包括节细胞胶质瘤（GG）、胚胎发育不良神经上皮肿瘤（DNT）等。2021 年的《WHO 中枢神经系统肿瘤分类》第五版（CNS WHO 5th）引入了分子学分型，这有助于 LEAT 的诊断和分类。LEAT 的分子分型包括 *BRAF V600E* 突变为主、成纤维细胞生长因子受体 1（*FGFR1*）突变为主和 *MYB* 改变为主的肿瘤。手术治疗是本病的主要治疗方式，多数患者术后癫痫症状缓解，但对于持续癫痫发作的患者，建议长期使用抗癫痫药物。目前，关于 LEAT 的分子分型对治疗和预后的影响尚需进一步研究。本文基于 CNS WHO 5th 对 LEAT 进行综述，以期为 LEAT 的诊疗提供参考。

【关键词】 难治性癫痫； 长期癫痫相关肿瘤； 癫痫相关低级别发育性脑肿瘤； 低级别胶质瘤； 综述

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【**Abstract**】 low-grade developmental and epilepsy-associated brain tumors (LEAT) are the second most common cause of focal epilepsy in adolescents. These tumors present primarily with epileptic seizures and carry a favorable prognosis. Common types include ganglioglioma (GG) and dysembryoplastic neuroepithelial tumor (DNT). The 2021 fifth edition of the WHO Classification of Tumors of the Central Nervous System (CNS WHO 5th) has introduced molecular typing, which aids in the diagnosis and classification of LEAT. LEAT molecular types include tumors predominantly driven by *BRAF V600E* mutation, fibroblast growth factor receptor 1 (*FGFR1*) mutation, and *MYB* alterations. Surgical treatment is the primary method for this condition. Most patients experience relief from epileptic symptoms after surgery. However, for patients with persistent seizures, long-term use of antiepileptic drugs is recommended. At present, the impact of LEAT molecular typing on treatment and prognosis requires further investigation. This paper provides a review of LEAT based on CNS WHO 5th, aiming to provide reference for the diagnosis and treatment of LEAT.

【**Key words**】 Drug resistant epilepsy; Long-term epilepsy-associated tumors; low-grade developmental and epilepsy-associated brain tumors; Lower-grade gliomas; Review

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脑肿瘤是 18 岁前发生局灶性癫痫发作并接受手术治疗的患者的第 2 位常见病因[1]。2003 年，Luyken 等[2]最先提出长期癫痫相关肿瘤（long-term epilepsy-associated tumors）的概念，将其定义为存在超过 2 年耐药性癫痫发作症状的脑肿瘤。研究发现，多数长期癫痫相关肿瘤患者早期接受手术治疗，“长期”癫痫这一术语被认为不再合理。因此，2020 年 Slegers 和 Blumcke[3]将这类肿瘤重新命名为癫痫相关低级别发育性脑肿瘤（low-grade developmental and epilepsy-associated brain tumors，LEAT）。与其他脑肿瘤不同，癫痫发作是 LEAT 患者主要或唯一的临床症状。LEAT 具有广泛的组织形态学谱系，通常为 CNS WHO 1 级的混合性胶质神经元肿瘤[3]和低级别胶质瘤。早期接受手术治疗的 LEAT 患者预后较好。常见的 LEAT 包括节细胞胶质瘤（ganglioglioma，GG）、胚胎发育不良神经上皮肿瘤（dysembryoplastic neuroepithelial tumor，DNT）等。随着 CNS 肿瘤分类的不断更新，LEAT 谱中增加了一些罕见和（或）新的

肿瘤类型。

2021年发布的《WHO CNS肿瘤分类》第五版(CNS WHO 5th)引入了分子学分型。LEAT形态学的非特异性常导致诊断和分类困难,而分子遗传学的发展为诊疗带来新的机遇,因此基因驱动的LEAT分类方案被提出。然而,关于LEAT肿瘤谱和LEAT实体的诊断及分子亚型仍未达成共识。在此背景下,本文基于CNS WHO 5th对LEAT肿瘤实体进行分类总结,见表1。旨在为LEAT的组织学和分子学异质性研究提供参考。

一、混合性胶质神经元肿瘤

GG是目前最常见的LEAT,约占LEAT的37.3%[4],多发生于儿童或青年人颞叶[1]。发生于颞叶的GG患者均表现为复杂性部分癫痫发作,绝大多数会进展为全身性癫痫发作,仅依靠抗癫痫药物(antiseizure medications, ASM)无法控制癫痫[5]。显微镜下,肿瘤由神经元和胶质细胞成分组成。胶质成分通常以纤维型星形细胞瘤为主,也可见少突胶质细胞瘤或毛细胞型星形细胞瘤(pilocytic astrocytoma, PA)形态[6],同时可见嗜酸性颗粒性小体、Rosenthal纤维[5]。肿瘤表达神经元标志物微管结合蛋白2(microtubule-binding protein 2, MAP2)、神经丝蛋白(neurofilament, NF)、嗜铬素(chromogranin, CgA)及突触素(synaptophysin, Syn),80%的肿瘤及瘤周可见CD34阳性,Ki67多小于5%。GG具有独特的甲基化谱系,绝大多数肿瘤存在*BRAF p.V600E*突变或其他MAPK信号通路激活[例如成纤维细胞生长因子受体(fibroblast growth factor receptor, *FGFR1*)*1*、*FGFR2*、*RAF1*、*KRAS*、*NF1*等变异][7]。62.5%的患者经手术切除后无明显癫痫发作(Engel的Ⅰ级)[8]。与其他LEAT相比,手术对GG患者癫痫发作的缓解率更高[9]。大多数GG被认为是CNS WHO 1级肿瘤,预后良好[10];存在*CDKN2A*纯合性缺失,或发生于中线并伴*H3 p.K28M*的GG预后不良[11-12]。部分WHO 3级的间变性GG预后较差[13]。

DNT是第二常见的LEAT肿瘤,约占LEAT总数的19.6%[4]。多数DNT患者临床表现为复杂性部分癫痫发作,超过半数患者至少出现过一次全身性癫痫发作,少部分患者仅表现为单纯部分性癫痫发作[14]。约2/3的DNT发生于颞叶,该位置

表1 LEAT临床病理学特征

肿瘤分类	发病年龄	主要发生部位	组织形态学	CNS WHO分级	主要分子学特征	治疗方式
混合性胶质神经元肿瘤						
节细胞胶质瘤	儿童或青年人	颞叶	神经元和胶质细胞成分	1、3级	*BRAF p.V600E*突变或其他MAPK信号通路激活	手术切除
胚胎发育不良性神经上皮肿瘤	儿童或青年人	颞叶	多结节样,少突样胶质细胞呈柱状排列,间质黏液变,黏液池内间神经元	1级	*FGFR1*改变,*BRAF p.V600E*突变	手术切除
多结节和空泡状神经元肿瘤	成人	颞叶、额叶或顶叶	皮质深层或灰白质交界由神经元组成多个离散或融合的淡染结节	1级	MAPK通路激活异常	无症状长期随访,症状明显患者手术切除
乳头状胶质神经元肿瘤	青少年	颞叶、额叶或顶叶	双相分化,假乳头状结构及乳头间的神经细胞	1级	*SLC44A1-PRKCA*融合	手术切除
局限性胶质瘤						
多形性黄色星形细胞瘤	儿童	颞叶	多形性细胞、梭形细胞和脂化细胞	2、3级	*BRAF p.V600E*阳性,MAPK信号通路相关基因改变	手术切除
毛细胞型星形细胞瘤	儿童	小脑	双相模式,毛样及少突样细胞,生长不活跃	1级	MAPK通路改变,*KIAA1549*: :*BRAF*融合	手术切除
儿童型弥漫性低级别胶质瘤						
MYB/MYBL1改变的弥漫性星形细胞瘤	儿童	颞叶	温和的肿瘤细胞低密度、低增殖和弥漫性生长	1级	*MYB/MYBL*基因改变	手术切除
血管中心性胶质瘤	儿童	额颞叶	肿瘤细胞围绕血管呈放射状排列	1级	*MYB*融合	手术切除
青少年多形性低级别神经上皮肿瘤	儿童或青年人	颞叶	少突样肿瘤细胞浸润性生长,常见钙化	未定级	MAPK信号通路激活异常	手术切除

注:LEAT癫痫相关低级别发育性脑肿瘤;CNS中枢神经系统;WHO世界卫生组织;*FGFR1*成纤维细胞生长因子受体1

与更好的癫痫发作结局相关[15-16]。该肿瘤影像学表现为典型的“肥皂泡”外观，无明显的占位效应或瘤周水肿[17]。显微镜下，DNT 呈多结节样形态，少突胶质细胞样肿瘤细胞在黏液基质中呈柱状排列，其间可见漂浮的神经元[18]。少突样肿瘤细胞表达胶质细胞标志物 S100、少突胶质细胞转录因子 2(oligodendrocyte transcription factor 2，Olig-2)、PDGFRA，不表达胶质纤维酸性蛋白(glial fibrillary acidic protein，GFAP)；其间的神经元表达神经元标志物，但不表达 CgA。DNT 具有独特的甲基化谱。FGFR1 改变在 DNT 中的发生率为 58.1%～82.0%，多为酪氨酸激酶结构域内部串联重复，少数为错义单核苷酸变异和 *FGFR1-TACC* 融合。此外，*BRAF p.V600E*[19]、染色体 5～7 扩增、染色体 22 缺失[20-21]在 DNT 中也有报道。DNT 生长缓慢，CNS WHO 分级为 1 级，绝大多数的 DNT 患者手术切除后癫痫发作控制良好，少数患者存在复发[22]。

多结节和空泡状神经元肿瘤(multnodular and vacuolating neuronal tumor，MVNT)是一种在 CNS WHO 4th 修订版中新增的神经元良性肿瘤，多发生于颞叶、额叶或顶叶，部分患者以难治性癫痫起病[23]，影像学多表现为 FLAIR 和 T2WI 高信号的多发小结节影，镜下显示皮质深层或灰白质交界区的多个离散或融合的淡染结节。结节由中等大小的神经元组成，胞浆丰富、嗜酸，核仁明显，背景为纤细的神经毡[24]。肿瘤细胞表达 Olig2、MAP2、Syn，文献中报道了不同的分子学改变，主要为 MAPK 通路激活异常，包括 *MAP2K1*、*BRAF V600E* 和 *FGFR2* 等。有研究认为，如患者未表现出显著的临床症状，可定期随访，无须手术治疗；而对于 MVNT 导致的难治性癫痫，手术可明显改善癫痫发作[25]。

乳头状胶质神经元肿瘤(papillary glioneuronal tumor，PGNT)是一种 WHO 1 级胶质神经元肿瘤。部分学者认为 PGNT 是一种 LEAT 相关肿瘤，多见于青少年和年轻人，临床表现为癫痫发作的 PGNT 多发生于颞叶、额叶或顶叶[26]，其影像学多表现为脑室附近边界清晰囊实性病变。显微镜下，肿瘤呈双相分化，包括由扁平到立方的胶质细胞组成的假乳头状结构和乳头状间 Syn 阳性的神经细胞，乳头轴心为玻璃样变性的血管。Pages 等[27]发现，PGNT 存在 *SLC44A1-PRKCA* 融合，少数病例表现为 *Notch1-PRKCA* 融合[28]。Hou 等[28]发现，PGNT 具体独特的甲基化谱系。PGNT 预后通常较好，中位 5 年无进展生存率高于 80%[29]。患者手术切除后癫痫发作控制良好，个别患者手术治疗后仍存在癫痫发作[30]。

二、局限性胶质瘤

发生于儿童的多形性黄色星形细胞瘤(pleomorphic xanthoastrocytoma，PXA)临床多表现为全身性强直-痉挛性癫痫或复杂性部分癫痫发作[31]，影像学多表现为大脑皮质及软脑膜的囊实性占位。显微镜下，肿瘤细胞由梭形、上皮样、多形性及富含脂质的多核胶质细胞组成，常见核内假包涵体、脂化细胞及淋巴细胞浸润[32]，组织学分级为 WHO 2 级或 3 级。PXA 表达 GFAP、S100，多数病例存在 CD34 阳性表达，60%～80% 的患者存在 *BRAF p.V600E* 阳性，局部表达神经元相关标志物。PXA 均存在 MAPK 信号通路相关基因的改变，包括 *BRAF*、*NTRK1/2/3*、*RAF1* 和 *NF1*[33-34]。约 94% 的患者存在 *CDKN2A/B* 的纯合性缺失。PXA 预后相对较好，2 级和 3 级的 PXA 5 年总生存率分别为 90.4% 和 57.1%[35]。一项研究发现，长期癫痫相关的 PXA 患者术后均可获得 Engel Ⅰ级结局[36]。

PA 是一种生长缓慢的儿童型局限性低级别胶质瘤，约占 LEAT 的 16%[2, 37]。大多数 PA 位于小脑、间脑或视觉通路，临床表现为头痛或颅内压增高等症状[37]。发生于脑叶的 PA 患者临床多表现为癫痫发作，其中约半数患者发生于颞叶[38]。PA 的影像学改变多样，多呈界限清楚的囊性占位伴附壁结节。显微镜下，PA 主要由毛样及少突样细胞组成，但组织学模式多样，部分由双极细胞和 Rosenthal 纤维组成的致密区域和少突样细胞组成的疏松区域交错构成，部分病例仅表现为富含毛样细胞和 Rosenthal 纤维的致密模式，部分病例仅表现为少突胶质细胞瘤样的形态特点。间质常有微囊形成及黏液样变性。可见 Rosenthal 纤维、嗜酸性颗粒小体，也可见马蹄样多核细胞。PA 免疫组化显示 GFAP、S100 和 Olig2 弥漫强阳性，Ki67 指数低。此外，PA 存在 MAPK 通路改变，＞60% 的 PA 存在 *KIAA1549*::*BRAF* 融合[39-40]。PA 预后较好，部分难治性癫痫相关 PA 患者术后癫痫症状得以改善，部分患者术后出现迟发性癫痫发作[41]。

三、儿童型弥漫性低级别胶质瘤

MYB/MYBL1 改变的弥漫性星形细胞瘤(diffuse astrocytoma，MYB- or MYBL1-altered，DA，MYB/MYBL1-altered)是 CNS WHO 5th 中新定义的肿瘤类型，通常从儿童时期就诊断为药物难治性癫痫[3]。2004 年 Schramm 等[42]将难治性癫痫相关的弥漫性胶质瘤定义为同构性星形细胞瘤(isomorphic astrocytoma)，与其他弥漫性胶质瘤相比，该肿瘤具有更好的生存率和更低的复发率，但其缺乏对分子学特点的描述。近年来的研究发现，该肿瘤具有独特的甲基化谱及

分子特征，约77%的患者存在*MYB/MYBL*基因改变[43]，主要是拷贝数改变或*MYBL1-*或*MYB-*基因融合，这与儿童型低级别弥漫性胶质瘤中伴*MYB/MYBL1*改变的弥漫性星形细胞瘤密切相关。该肿瘤可发生于任何脑叶，更常见于颞叶。MRI显示T_1低信号、无强化、边界清楚的肿块，累及皮质和皮质下区域。显微镜下，肿瘤低密度、低增殖和弥漫性生长；细胞形态单一，呈卵圆形或梭形，形态较温和。肿瘤细胞表达GFAP，不表达Olig2和CD34，缺乏异柠檬酸脱氢酶(isocitrate dehydrogenase，*IDH*)和组蛋白3赖氨酸27(lysine 27 on histone H3，*H3K27*)突变。约89%的患者术后癫痫症状完全缓解，其余患者癫痫发作频率明显改善[43]。

血管中心型胶质瘤(angiocentric glioma，AG)被归类为儿童弥漫性低级别胶质瘤，是一种累及皮质和皮质下白质的弥漫性脑肿瘤。大部分AG发生于额颞叶[44]。绝大多数患者表现为难治性癫痫发作[45]。影像学检查显示，肿瘤边界清晰且无增强性[46-47]。显微镜下，肿瘤细胞围绕血管呈放射状排列，部分沿软脑膜下生长，部分呈“神经鞘瘤样”排列，细胞呈星形细胞形态，核分裂罕见，无微血管增生及坏死。肿瘤细胞表达GFAP，不表达Olig2，上皮膜抗原呈核旁点状或环状阳性，Ki67多小于5%[48]。多数AG存在*MYB*融合[19]，主要为*MYB-QKI*融合。AG是一类惰性生物学行为的肿瘤，手术治疗是其主要的治疗方式，超过90%的患者手术切除术后无明显癫痫发作[45]。

青少年多形性低级别神经上皮肿瘤(polymorphous low-grade neuroepithelial tumor of the young，PLNTY)多发生于10～20岁年轻人，主要发生于颞叶，多以癫痫起病[49]；镜下表现为少突样肿瘤细胞浸润性生长，部分病例混杂纤维星形、梭形或多形性胶质细胞，常见钙化。PLNTY肿瘤细胞表达GFAP、Olig2，但与少突胶质细胞瘤不同，*IDH1/2*常阴性，而免疫组化CD34呈弥漫强阳性表达，Ki67多小于2%。该肿瘤具有独特的甲基化谱，均存在MAPK信号通路激活异常，包括*BRAF p.V600E*突变、*FGFR3*、*FGFR2*基因融合等改变[49]。部分患者术后癫痫症状完全缓解，部分患者术后仍存在癫痫发作[49]。

四、其他与长期难治性癫痫相关的肿瘤

伴菊型团形成的胶质神经元肿瘤(rsette-forming glioneuronal tumor，RGNT)[50-51]、脑室外神经细胞瘤[52-53]，促纤维增生性婴儿节细胞胶质瘤/促纤维增生性婴儿星形细胞瘤(desmoplastic infantile ganglioglioma/desmoplastic infantile astrocytoma，DIG/DIA)[54]、少突胶质细胞瘤，*IDH*突变型伴1p/19q共缺失[3]、星形细胞瘤、*IDH*突变型、个别室管膜瘤[55]多以头痛及神经系统症状起病，仅少部分患者表现为难治性癫痫发作。

五、总结与展望

LEAT是一类具有形态学和分子遗传学多样性的肿瘤，占所有脑肿瘤的2%～5%[56]。LEAT临床表现复杂，多表现为复杂的局灶性发作或局灶性未意识改变发作[57]。目前认为LEAT癫痫发作类型与病变部位相关，多数LEAT发生于颞叶[58]。早期，LEAT的组织形态学及免疫组化特征存在较差，导致这类肿瘤的诊断较为困难。2021年CNS WHO 5th的发布推进了分子诊断在CNS肿瘤分类中的应用。分子学检测可协助标准化LEAT的诊断及分类，使对LEAT的认识更加明确。目前，根据肿瘤的分子学特征，LEAT可分为3类，第一类以*BRAFV600E*突变为主；第二类以*FGFR1*突变为主，包括DNT；另外一类是以*MYB*改变为特征的LEAT，主要包括DA、*MYB/MYBL*-altered。LEAT的分子分型在患者治疗及预后中的价值尚不清楚[3]。手术治疗是LEAT主要的治疗方式。与其他低级别脑肿瘤相比，这类肿瘤预后好，手术切除后无需辅助治疗，且多数LEAT患者术后无明显癫痫发作，故将其与其他低级别肿瘤分开可避免过度治疗[56]。ASM治疗是肿瘤相关癫痫的重要治疗手段，目前的研究发现，多数LEAT患者术后未使用或停用ASM，仍可保持无癫痫发作。然而，对于持续存在癫痫发作的患者，仍建议长期使用ASM[59]，但遗憾的是，关于LEAT研究多未详述ASM治疗方案。

本综述根据CNS WHO 5th分类及现有的LEAT研究对LEAT的肿瘤分类进行总结，期待未来能有更大规模、更完整的队列研究更深入地理解LEAT。

利益冲突 文章所有作者共同认可文章无相关利益冲突

作者贡献声明 资料收集、论文撰写为李卓，论文修订、审校为王军梅

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