·癫痫及发作性疾病·

癫痫外科常见病理类型体细胞突变研究进展

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【摘要】 癫痫是临床常见的神经系统疾病，结构性病因导致的癫痫手术切除病灶可治愈，一直是癫痫外科关注的重点。随着基因检测技术的发展，发现结构性病因可能由体细胞突变所致。本文综述皮质发育畸形、长期癫痫相关肿瘤、海马硬化和下丘脑错构瘤4种癫痫外科常见病理类型体细胞突变相关致病基因及其研究进展，以及对手术方案制定和手术预后的影响，以为癫痫外科治疗提供新的思路。

【关键词】 癫痫； 基因； 突变； 病理学； 综述

Research progress on common pathological types of somatic mutation in epilepsy surgery

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【Abstract】 Epilepsy is a common neurological disease in clinic. Epilepsy caused by structural causes can be cured by surgery, which has been the focus of attention in the field of epilepsy surgery. With the development of gene sequencing technology, more and more studies have found that structural etiology may be caused by somatic mutations of genes. In this paper, somatic mutation-related pathogenic genes of four common pathological types of epilepsy surgery, including malformation of cortical development (MCD), long-term epilepsy associated tumor (LEAT), hippocampal sclerosis (HS) and hypothalamic hamartoma (HH), were reviewed, and their effects on surgical protocol formulation and prognosis were reviewed, in order to provide a new idea for the treatment of epilepsy.

【Key words】 Epilepsy; Genes; Mutation; Pathology; Review

This study was supported by National Key Research and Development Program of China (No. 2021YFC2401201), and the National Natural Science Foundation of China (No. 82071457).

Conflicts of interest: none declared

癫痫是临床常见的神经系统疾病，全球大约5000万例患者[1]。根据病因分为结构性、基因性、代谢性、感染性、免疫性和病因不明性6种类型[2]，其中结构性病因导致的癫痫可通过手术切除病灶达到术后无发作之目的，一直是癫痫外科关注的重点。由于尚缺乏体细胞突变的无创性检测方法，临床将外周血检出种系突变导致的癫痫归因为基因性，将未检出种系突变但有明确致痫灶的癫痫归因为结构性。随着癫痫外科手术术前评估和手术技术的发展，以及全外显子组测序（WES）和全基因组测序（WGS）等基因检测技术的进步，部分结构性病因患者手术切除组织可检出致病性体细胞突变，提示结构性病因也可能是体细胞突变所致[3-5]。目前癫痫外科常见病理类型包括皮质发育畸形（MCD）、长期癫痫相关肿瘤（LEAT）、海马硬化（HS）、下丘脑错构瘤（HH）等，其中皮质发育畸形和长期癫痫相关肿瘤等病理类型与体细胞突变有关，但相关研究仅集中于单一病种或单个基因[3,6-7]。本文拟综述上述常见癫痫病理类型体细胞突变相关致病基因的致病机制及其对手术方案制定和手术预测的影响，以为癫痫外科治疗提供新的思路。

一、皮质发育畸形

皮质发育畸形是早发型难治性癫痫的主要病

doi：10.3969/j.issn.1672-6731.2023.02.008

基金项目：国家重点研发计划项目（项目编号：2021YFC2401201）；国家自然科学基金资助项目（项目编号：82071457）

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表1 皮质发育畸形分类[10]

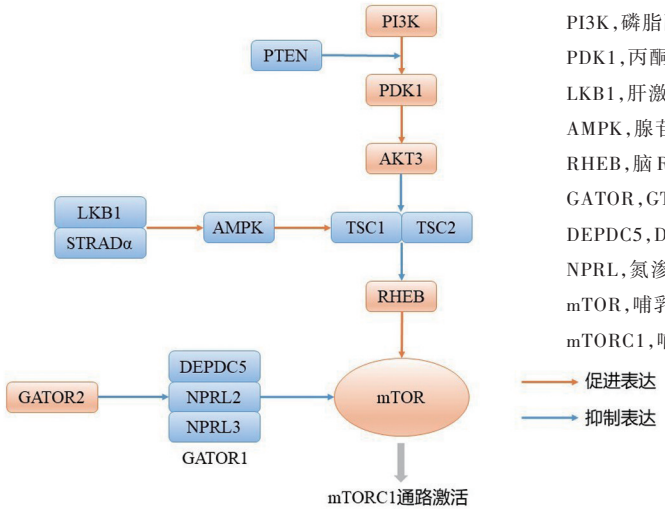
Table 1. Classification of MCD[10]

病因	MCD类型	形态学
神经细胞增殖分化障碍	小头畸形	小头畸形,小脑畸形,前脑无裂畸形等
	弥漫性/局灶性皮质生长过度	巨脑畸形,半侧巨脑畸形,多小脑回畸形,FCDⅡ型,TS
神经元迁移障碍	经典无脑回谱系	无脑回畸形,皮质下带状灰质异位等
	“鹅卵石”样畸形	多小脑回畸形,软脑膜胶质神经元异位等
	脑室旁灰质异位	结节型或线性脑室旁灰质异位
	皮质层状结构发育不良	FCDⅠ型
轴突通路形成障碍	胼胝体缺陷	胼胝体缺如、DCC等
白质病变	mMCD	mMCD伴过多异位神经元、MOGHE

MCD,malformation of cortical development,皮质发育畸形;mMCD,mild malformation of cortical development,轻度皮质发育畸形;FCD,focal cortical dysplasia,局灶性皮质发育不良;TS,tuberous sclerosis,结节性硬化症;DCC,dysgenesis of the corpus callosum,胼胝体发育不良;MOGHE,mild malformation of cortical development with oligodendroglial hyperplasia in epilepsy,轻度皮质发育畸形伴少突胶质细胞增生及癫痫

因,约40%儿童期发病的难治性癫痫系皮质发育畸形所致[8],约75%的皮质发育畸形患儿出现癫痫发作[9]。大脑皮质发育过程包括神经细胞增殖分化、神经元迁移、皮质结构构建与联系共3个阶段,不同阶段的发育异常可以导致不同类型的皮质发育畸形(表1)[10]。神经细胞增殖分化障碍主要导致小头畸形、弥漫性/局灶性皮质生长过度等;神经元迁移障碍导致无脑回畸形、“鹅卵石”样畸形、脑室旁灰质异位、局灶性皮质发育不良Ⅰ型(FCDⅠ)等;皮质结构构建与联系过程中轴突通路形成障碍导致胼胝体缺陷等[11-12]。2004年,Palmini等[13]对局灶性皮质发育不良进行分类时提出一类以白质内异位神经元增多为主要病理特征且无皮质神经元结构异常的白质病变,并命名为轻度皮质发育畸形(mMCD),但随后的各项研究样本量较小,其致痫性一直存有争议[14-15];2017年,Schurr等[16]发现了一种轻度皮质发育畸形伴白质内少突胶质细胞明显增生的病理改变,并命名为轻度皮质发育畸形伴少突胶质细胞增生及癫痫(MOGHE);2022年,国际抗癫痫联盟(ILAE)正式将二者归类为局灶性皮质发育不良[17]。如果皮质发育畸形患者致痫灶范围局限且术后不引起严重神经功能障碍,手术切除致痫灶可治愈。

近年来,皮质发育畸形相关致病基因研究进展迅速,体细胞突变类型主要包括两种,即导致皮质生长过度的磷脂酰肌醇3-激酶(PI3K)/丝氨酸/苏氨酸激酶3(AKT3)/哺乳动物雷帕霉素靶蛋白(mTOR)信号转导通路(简称mTOR通路)相关体细胞突变(图1)[3,6,18-21]以及导致MOGHE的UDP-半乳糖转运体(*UTR*)基因中*SLC35A2*基因体细胞突变[7,22]。mTOR通路中PI3K催化4,5-二磷酸磷脂酰肌醇(PIP2)生成3,4,5-三磷酸磷脂酰肌醇(PIP3),使下游AKT磷酸化,激活mTOR通路,调节细胞增殖、自噬和凋亡等,*PDK1*、*RHEB*、*GATOR2*基因可促进该通路激活,*PTEN*、*TSC1*、*TSC2*、*LKB1*、*STRADα*、*AMPK*、*GATOR1*复合体基因则发挥抑制通路激活的作用。mTOR通路基因变异最早见于巨脑畸形和半侧巨脑畸形患者脑组织[23-24],随后发现,病变范围更局限的皮质发育畸形如FCDⅡ型患者病变组织异形神经元和“气球”样细胞亦存在mTOR通路基因变异,并表现为mTOR通路过度激活[3,16]。mTOR通路相关体细胞突变主要有以下两种机制:(1)*mTOR*基因或能够激活mTOR通路的基因发生功能获得突变(GoF),使mTOR通路过度激活,神经细胞过度增殖,引起皮质病变,一次功能获得突变即可致病[18]。(2)能够抑制mTOR通路的基因发生功能失去突变(LoF),对mTOR通路的抑制作用减弱,导致mTOR通路过度激活,往往需要二次功能失去突变才导致皮质病变,通常为种系突变合并单核苷酸变异(SNV)[25-27]或等位基因杂合性缺失[16,20]等体细胞二次突变,可能是由于抑制mTOR通路的基因一次突变导致的表达异常不足以诱发皮质病变[10]。迄今已明确*AKT3*、*DEPDC5*、*MTOR*、*NPRL2*、*NPRL3*、*PIK3CA*、*RHEB*、*TSC1*、*TSC2*共9种常见体细胞突变可导致半侧巨脑畸形或FCDⅡ型,占此类患者的38%~63%[16-17,25],提示即使外周血未检出可能致病



PI3K，磷脂酰肌醇3-激酶；PTEN，同源性磷酸酶-张力蛋白；PDK1，丙酮酸脱氢酶激酶1；AKT3，丝氨酸/苏氨酸激酶3；LKB1，肝激酶B1；STRADα，STE20相关激酶衔接蛋白α；AMPK，腺苷酸活化蛋白激酶；TSC，结节性硬化复合体；RHEB，脑RAS同源蛋白；GATOR，GTP酶激活蛋白对RAS相关GTP结合蛋白激活因子；DEPDC5，DEP结构域结合蛋白5；NPRL，氮渗透调节器样蛋白；mTOR，哺乳动物雷帕霉素靶蛋白；mTORC1，哺乳动物雷帕霉素靶蛋白复合物1

图1　PI3K/AKT3/mTOR信号转导通路

Figure 1　PI3K/AKT3/mTOR pathway.

的种系突变，包含体细胞突变在内的基因变异仍是导致皮质发育畸形的主要原因之一。此外，*PTPN11*、*EEF2*、*NAV2*、*IRS1*、*ZNF337*等局灶性皮质发育不良相关体细胞突变见诸个案报道，但尚未得到广泛验证[5,28]。既往认为，*SLC35A2*基因体细胞突变是FCD Ⅰa型的典型变异[16,25,29-30]，但后续研究发现，此类患者皮质神经元无明显异型性改变或结构排列紊乱，而白质可见大量异位神经元和增生的少突胶质细胞，故存在*SLC35A2*基因体细胞突变的患者均重新分类为MOGHE[22]。*SLC35A2*基因编码的UTR蛋白主要参与蛋白质与鞘脂的糖基化过程，45%～100%的MOGHE患者可检测出*SLC35A2*基因体细胞突变[21-22]，但该突变不影响mTOR通路信号传导，提示糖基化障碍可能发挥重要作用，但具体作用机制尚待进一步探究[30-31]。

尽管皮质发育畸形的体细胞突变机制研究较为充分，但尚无大样本临床研究证实体细胞突变与手术预后之间存在关联[32]，手术方案的制定主要取决于病变部位和范围，累及双侧大脑半球的广泛皮质发育畸形通常无法手术切除，主要采取神经调控技术和胼胝体切开术等姑息性手术；累及单侧大脑半球或某一象限的皮质发育畸形可采取大脑半球离断术、后象限离断术等；范围更局限的病变则有望通过手术切除病灶实现术后无发作，如FCD Ⅱ型手术预后良好，约67.4%患者术后5年仍无癫痫发作[33]。而MOGHE病变主要位于额叶，术后无发作率与癫痫发病年龄、手术年龄和切除范围相关[34-35]。由于存在种系突变的二次功能失去突变（如*GATOR1*复合体基因和*TSC*基因突变）致皮质发育畸形患者手术预后良好，>50%患者术后无发作或发作频率减少>75%，因此认为，此类患者有明确病灶时手术切除是首选治疗方法[36]。而对于无手术适应证或手术切除效果欠佳的患者，mTOR抑制剂雷帕霉素作为靶向药物具有一定疗效[37]。

二、长期癫痫相关肿瘤

儿童期发病的脑肿瘤并接受手术治疗是癫痫的第2位病因，部分肿瘤生长相对缓慢不易发现，临床多以癫痫发作为首发症状，药物难以控制，手术全切除肿瘤后预后较好，称为癫痫相关肿瘤（EAT），其中难治性癫痫病史>2年者称为长期癫痫相关肿瘤[38]。此类肿瘤通常具有以下特征[38-39]：（1）以早发型难治性癫痫发作为主要症状。（2）多发生于双侧颞叶。（3）约80%的患儿恶性程度低（WHO Ⅰ级）。（4）通常为神经胶质与神经元混合性肿瘤，呈多种形态，如囊性变或结节状等。（5）无相同基因变异驱动，如*IDH1*突变或1p/19q共缺失等。目前尚无“长期癫痫相关肿瘤”的定义，2016年世界卫生组织（WHO）中枢神经系统肿瘤分类第四版修订版将神经节细胞胶质瘤（GG）、胚胎发育不良性神经上皮肿瘤（DNT）、多形性黄色瘤型星形细胞瘤（PXA）、血管中心型胶质瘤（AG）、同形弥漫性胶质瘤（IDG）、青年人多形性低级别神经上皮肿瘤（PLNTY）等均归为长期癫痫相关肿瘤[5,38]。虽有长期癫痫相关肿瘤体细胞突变基因的个案报道，但尚未在连续队列研究中予以系统性验证，这些基因变异是否普遍存在，尚待更高级别证据的支持[40]。

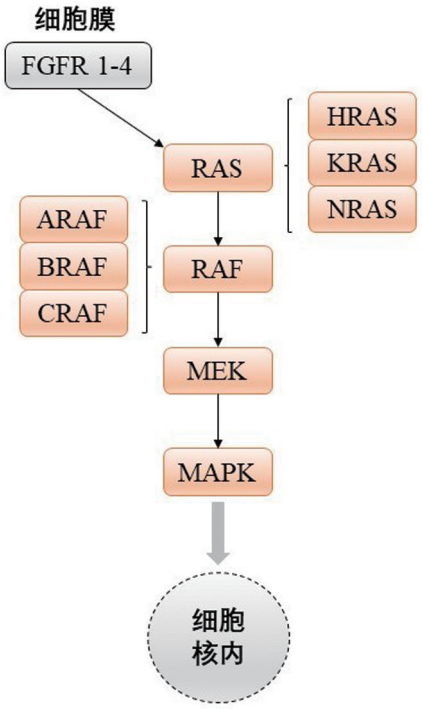


图2 RAS/RAF/MAPK信号转导通路

Figure 2 RAS/RAF/MAPK pathway.

FGFR，纤维母细胞生长因子受体；
RAS，大鼠肉瘤蛋白；
HRAS，Harvey大鼠肉瘤病毒癌基因同源物；
KRAS，Kirsten大鼠肉瘤病毒癌基因同源物；
NRAS，神经母细胞瘤大鼠肉瘤病毒癌基因同源物；
RAF，快速加速纤维肉瘤蛋白；
ARAF，v-RAF鼠类肉瘤3611病毒癌基因同源体；
BRAF，鼠类肉瘤滤过性毒菌致癌同源体B1；
CRAF，鼠类白血病病毒癌基因同源体1；
MEK，丝裂原激活蛋白激酶/细胞外信号调节激酶；
MAPK，丝裂原激活蛋白激酶

长期癫痫相关肿瘤体细胞突变主要发生于RAS/RAF/丝裂原激活蛋白激酶（MAPK）信号转导通路（图2），该通路中细胞外信号通过蛋白酪氨酸激酶（PTK）如纤维母细胞生长因子受体（FGFR）等激活RAS，活化的RAS激活AKT级联放大作用，募集胞质内RAF激酶至胞膜，RAF激酶磷酸化丝裂原激活蛋白激酶/细胞外信号调节激酶（MEK），激活MAPK，活化的MAPK转移至胞核并直接激活转录因子，参与细胞增殖、分化与凋亡的调节[41]。Qaddoumi等[42]按照体细胞突变类型将长期癫痫相关肿瘤分为3个亚组，即*BRAF*基因变异导致的神经节细胞胶质瘤样组、*FGFR1*基因变异导致的少突胶质细胞瘤样组以及*MYB*基因变异导致的星形胶质细胞瘤和血管中心型胶质瘤样组，其中，神经节细胞胶质瘤样组以*BRAF* V600E突变常见，最早见于恶性黑色素瘤[43]，随后在多形性黄色瘤型星形细胞瘤和神经节细胞胶质瘤中也发现该突变[5,44]。*BRAF* V600E突变蛋白主要表达于神经元，但部分也表达于神经胶质细胞，表明*BRAF*基因变异的神经干细胞仍可分化为神经元和神经胶质细胞[45]，可以解释长期癫痫相关肿瘤多为神经胶质与神经元混合的原因。*BRAF* V600E突变的致瘤性主要取决于神经胶质细胞改变，致痫性则与瘤内发育异常的神经元有关[46]；少突胶质细胞瘤样组的常见变异类型为*FGFR1*基因变异，最早见于毛细胞型星形细胞瘤[47]，亦有58.1%～82.0%的胚胎发育不良性神经上皮肿瘤患者存在该变异[5,42,48]，提示*FGFR1*基因变异是胚胎发育不良性神经上皮肿瘤的特征性改变。部分合并FCD Ⅲd型的青年人多形性低级别神经上皮肿瘤患者肿瘤组织可检出*FGFR2*基因体细胞突变，提示该突变是青年人多形性低级别神经上皮肿瘤的潜在分子学特征[5]。星形胶质细胞瘤和血管中心型胶质瘤样组以*MYB*基因变异为主，最早见于7例弥漫性星形细胞瘤、2例血管中心型胶质瘤和1例少突胶质细胞瘤患者[49]；随后一项纳入15例血管中心型胶质瘤的研究显示，14例存在*MYB*基因融合，其中13例为*MYB-QKI*融合[42]；约77%的同形弥漫性胶质瘤患者存在*MYB*基因变异，且主要为拷贝数变异（CNV）以及*MYBL1*和*MYB*基因融合[50]。此外，*KRAS*、*ADAM22*、*PRKCA*等基因体细胞突变也可能与长期癫痫相关肿瘤的发生相关[5,51]。

尽管长期癫痫相关肿瘤的分子学特征研究已有初步进展，但与术后无发作率是否存在关联性仍有待证实[52]。目前认为，长期癫痫相关肿瘤术后无发作率可达68.4%～80.0%，预后较好，且与发病年龄、病程、癫痫发作类型、手术切除范围有关[39,53-54]。

一项Meta分析纳入12项临床研究计193例*BRAF* V600E变异型和397例野生型长期癫痫相关肿瘤患者，结果显示，与野生型组相比，*BRAF* V600E变异型组发病年龄更早（$P=0.020$），但两组癫痫病程、肿瘤部位、术后无发作率等无明显差异[47]。*BRAF* V600E突变与神经节细胞胶质瘤复发速度呈正相关，与无进展生存期（PFS）呈负相关，提示该突变可能增加肿瘤复发率[55-56]。达拉非尼、曲美替尼和维莫非尼等BRAF激酶抑制剂对*BRAF* V600E变异型肿瘤有效，可能成为某些难以手术切除的神经节细胞胶质瘤的新型治疗方案[57-59]。

三、海马硬化

海马硬化系一种以海马星形胶质细胞增生及神经元丢失为病理改变的继发性疾病，通常继发于儿童期（4～7岁）高热惊厥、脑缺血、癫痫持续状态（SE）、脑炎等[60-62]。影像学主要表现为海马体积缩小、T_2WI海马细胞分层模糊、T_2WI和FLAIR成像高信号等。海马硬化致癫痫通常为难治性癫痫，手术治疗有效，术后无发作率达71%～90%[63-65]。尽管海马硬化自身可能与体细胞突变无关，但部分基因变异可增加癫痫患者海马硬化易感性，例如，*SCN1A*基因变异导致的反复发热诱发的癫痫发作可引起海马硬化，可能与高热和癫痫发作导致脑组织缺血、缺氧，海马神经元线粒体应激，进而引起继发性海马损伤有关[66-67]。包含*SCN1A*在内的离子通道相关基因变异导致的癫痫通常为全面性癫痫，手术效果较差[68]，因此，选择手术适应证时应鉴别海马硬化是导致癫痫发作的病因（可手术）还是基因突变致全面性癫痫长期发作导致的海马硬化（不可手术）。此外，部分体细胞突变引起的神经皮肤综合征如*KRAS*基因变异致皮脂腺痣综合征患者可能合并海马硬化，手术切除同样有效，术后无发作率可达73%[69]。

四、下丘脑错构瘤

下丘脑错构瘤是发生于下丘脑腹侧的先天性非进展性病变，临床罕见，发病率约为1/20万[70]。根据解剖结构分为下丘脑内型和下丘脑旁型，前者主要引起以痴笑性发作为主要表现的难治性癫痫发作；后者主要引起内分泌异常和性早熟，癫痫发作罕见[71-72]。下丘脑错构瘤致病基因体细胞突变主要涉及音猬因子（SHH）通路相关基因，SHH蛋白与其受体相结合活化跨膜蛋白，促进胶质瘤相关癌基因同源基因（*GLI*）的转移和表达，调控下游靶基因，参与细胞活性和组织稳态的调节，该通路相关基因如*GLI3*、*PRKACA*、*SMO*、*CREBBP*、*GLI2*等体细胞突变可导致下丘脑错构瘤[70,73]。SHH通路在下丘脑发育早期参与神经发生与细胞结构调节，该通路中基因变异导致邻近正常脑组织过度增殖，形成错构瘤组织[74]。此外，*GLI3*基因种系突变引起的Pallister-Hall综合征（PHS）也表现为下丘脑错构瘤，同时出现多指或并指、会厌裂、肛门闭锁、肾脏畸形等，其癫痫发作程度较单纯下丘脑错构瘤轻微[75]。手术治疗主要包括切除术以及射频热凝（RFTC）和激光间质热疗（LITT）等微创毁损术[76-77]，两种手术方法术后无发作率无显著差异（76.9%对69.2%，$P>0.05$）。但是由于下丘脑解剖结构复杂，切除术常引起邻近脑组织损伤而导致尿崩症、近记忆力减退、体重增加、甲状腺功能减退症等并发症[76]，且对于体积较大（最大径>20 mm）的下丘脑错构瘤，难以单次全切除，多次手术进一步增加并发症风险。微创毁损术可能是更好选择[76]，激光间质热疗临床预后良好[78-79]。首都医科大学附属北京天坛医院自2020年启动激光间质热疗临床试验以来，采用该技术治疗36例下丘脑错构瘤患者，术后无发作率达63.89%（23/36），无一例发生严重术后并发症。由于微创毁损术利用植入病灶深部的电极或光纤对肿瘤进行毁损消融而非直接切除，术中病理组织获取困难，不利于下丘脑错构瘤相关基因体细胞突变研究。我们团队前期研究发现，影响下丘脑错构瘤患者激光间质热疗临床预后的因素主要包括下丘脑错构瘤分型、体积、消融比例和离断率等[80]，尚无证据证实体细胞突变影响手术预后，体细胞突变尚无法作为制定下丘脑错构瘤手术方式及手术规划的主要影响因素。

综上所述，尽管皮质发育畸形、长期癫痫相关肿瘤、海马硬化和下丘脑错构瘤这4种癫痫外科常见病理类型体细胞突变研究取得长足进展，但仍存在以下局限性：（1）体细胞突变的基因种类和变异负荷与手术方式的选择、术后预后等临床关注点的关系仍不明确，即使是广泛应用基因检测技术的结节性硬化症也尚未明确基因变异种类（*TSC1*或*TSC2*）对术后无发作率的预测价值[32]。而体细胞突变与上述临床关注点的关系正是癫痫外科在基因相关研究中最为关注的因素之一。（2）由于目前尚缺乏术前体细胞突变检测技术，相关研究主要针对手术切除脑组织，导致体细胞突变对癫痫外科手术

适应证影响的研究产生选择偏倚。与症状学、神经影像学、神经电生理学等主要术前评估指标相比，基因体细胞突变尚不足以对手术适应证或手术术式的选择产生决定性影响，未来尚待进一步探究体细胞突变与临床特征、手术方式选择及手术预后的关系，为癫痫外科精准医疗提供参考。

利益冲突 无

参 考 文 献

[1] Falco - Walter J. Epilepsy: definition, classification, pathophysiology, and epidemiology[J]. Semin Neurol, 2020, 40: 617-623.

[2] Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, Lagae L, Moshé SL, Peltola J, Roulet Perez E, Scheffer IE, Zuberi SM. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology [J]. Epilepsia, 2017, 58:522-530.

[3] Moloney PB, Cavalleri GL, Delanty N. Epilepsy in the mTORopathies: opportunities for precision medicine[J]. Brain Commun, 2021, 3:fcab222.

[4] Ye Z, McQuillan L, Poduri A, Green TE, Matsumoto N, Mefford HC, Scheffer IE, Berkovic SF, Hildebrand MS. Somatic mutation: the hidden genetics of brain malformations and focal epilepsies[J]. Epilepsy Res, 2019, 155:106161.

[5] Bedrosian TA, Miller KE, Grischow OE, Schieffer KM, LaHaye S, Yoon H, Miller AR, Navarro J, Westfall J, Leraas K, Choi S, Williamson R, Fitch J, Kelly BJ, White P, Lee K, McGrath S, Cottrell CE, Magrini V, Leonard J, Pindrik J, Shaikhouni A, Boué DR, Thomas DL, Pierson CR, Wilson RK, Ostendorf AP, Mardis ER, Koboldt DC. Detection of brain somatic variation in epilepsy-associated developmental lesions[J]. Epilepsia, 2022, 63:1981-1997.

[6] D'Gama AM, Woodworth MB, Hossain AA, Bizzotto S, Hatem NE, LaCoursiere CM, Najm I, Ying Z, Yang E, Barkovich AJ, Kwiatkowski DJ, Vinters HV, Madsen JR, Mathern GW, Blümcke I, Poduri A, Walsh CA. Somatic mutations activating the mTOR pathway in dorsal telencephalic progenitors cause a continuum of cortical dysplasias[J]. Cell Rep, 2017, 21:3754-3766.

[7] Bonduelle T, Hartlieb T, Baldassari S, Sim NS, Kim SH, Kang HC, Kobow K, Coras R, Chipaux M, Dorfmüller G, Adle-Biassette H, Aronica E, Lee JH, Blumcke I, Baulac S. Frequent SLC35A2 brain mosaicism in mild malformation of cortical development with oligodendroglial hyperplasia in epilepsy (MOGHE)[J]. Acta Neuropathol Commun, 2021, 9:3.

[8] Kuzniecky RI. Magnetic resonance imaging in developmental disorders of the cerebral cortex[J]. Epilepsia, 1994, 35 Suppl 6: S44-56.

[9] Leventer RJ, Phelan EM, Coleman LT, Kean MJ, Jackson GD, Harvey AS. Clinical and imaging features of cortical malformations in childhood[J]. Neurology, 1999, 53:715-722.

[10] Juric-Sekhar G, Hevner RF. Malformations of cerebral cortex development: molecules and mechanisms[J]. Annu Rev Pathol, 2019, 14:293-318.

[11] Barkovich AJ, Dobyns WB, Guerrini R. Malformations of cortical development and epilepsy [J]. Cold Spring Harb Perspect Med, 2015, 5:a022392.

[12] Romero DM, Bahi - Buisson N, Francis F. Genetics and mechanisms leading to human cortical malformations[J]. Semin Cell Dev Biol, 2018, 76:33-75.

[13] Palmini A, Najm I, Avanzini G, Babb T, Guerrini R, Foldvary-Schaefer N, Jackson G, Lüders HO, Prayson R, Spreafico R, Vinters HV. Terminology and classification of the cortical dysplasias[J]. Neurology, 2004, 62(6 Suppl 3):S2-8.

[14] Mühlebner A, Gröppel G, Dressler A, Reiter-Fink E, Kasprian G, Prayer D, Dorfer C, Czech T, Hainfellner JA, Coras R, Blümcke I, Feucht M. Epilepsy surgery in children and adolescents with malformations of cortical development: outcome and impact of the new ILAE classification on focal cortical dysplasia[J]. Epilepsy Res, 2014, 108:1652-1661.

[15] Krsek P, Maton B, Korman B, Pacheco-Jacome E, Jayakar P, Dunoyer C, Rey G, Morrison G, Ragheb J, Vinters HV, Resnick T, Duchowny M. Different features of histopathological subtypes of pediatric focal cortical dysplasia[J]. Ann Neurol, 2008, 63: 758-769.

[16] Schurr J, Coras R, Rössler K, Pieper T, Kudernatsch M, Holthausen H, Winkler P, Woermann F, Bien CG, Polster T, Schulz R, Kalbhenn T, Urbach H, Becker A, Grunwald T, Huppertz HJ, Gil-Nagel A, Toledano R, Feucht M, Mühlebner A, Czech T, Blümcke I. Mild malformation of cortical development with oligodendroglial hyperplasia in frontal lobe epilepsy: a new clinico-pathological entity [J]. Brain Pathol, 2017, 27:26-35.

[17] Najm I, Lal D, Alonso Vanegas M, Cendes F, Lopes-Cendes I, Palmini A, Paglioli E, Sarnat HB, Walsh CA, Wiebe S, Aronica E, Baulac S, Coras R, Kobow K, Cross JH, Garbelli R, Holthausen H, Rössler K, Thom M, El-Osta A, Lee JH, Miyata H, Guerrini R, Piao YS, Zhou D, Blümcke I. The ILAE consensus classification of focal cortical dysplasia: an update proposed by an ad hoc task force of the ILAE diagnostic methods commission[J]. Epilepsia, 2022, 63:1899-1919.

[18] Baldassari S, Ribierre T, Marsan E, Adle-Biassette H, Ferrand-Sorbets S, Bulteau C, Dorison N, Fohlen M, Polivka M, Weckhuysen S, Dorfmüller G, Chipaux M, Baulac S. Dissecting the genetic basis of focal cortical dysplasia: a large cohort study [J]. Acta Neuropathol, 2019, 138:885-900.

[19] Lim JS, Kim WI, Kang HC, Kim SH, Park AH, Park EK, Cho YW, Kim S, Kim HM, Kim JA, Kim J, Rhee H, Kang SG, Kim HD, Kim D, Kim DS, Lee JH. Brain somatic mutations in MTOR cause focal cortical dysplasia type Ⅱ leading to intractable epilepsy[J]. Nat Med, 2015, 21:395-400.

[20] Jansen LA, Mirzaa GM, Ishak GE, O'Roak BJ, Hiatt JB, Roden WH, Gunter SA, Christian SL, Collins S, Adams C, Rivière JB, St-Onge J, Ojemann JG, Shendure J, Hevner RF, Dobyns WB. PI3K/AKT pathway mutations cause a spectrum of brain malformations from megalencephaly to focal cortical dysplasia [J]. Brain, 2015, 138(Pt 6):1613-1628.

[21] Mirzaa GM, Campbell CD, Solovieff N, Goold C, Jansen LA, Menon S, Timms AE, Conti V, Biag JD, Adams C, Boyle EA, Collins S, Ishak G, Poliachik S, Girisha KM, Yeung KS, Chung BHY, Rahikkala E, Gunter SA, McDaniel SS, Macmurdo CF, Bernstein JA, Martin B, Leary R, Mahan S, Liu S, Weaver M, Doerschner M, Jhangiani S, Muzny DM, Boerwinkle E, Gibbs RA, Lupski JR, Shendure J, Saneto RP, Novotny EJ, Wilson CJ, Sellers WR, Morrissey M, Hevner RF, Ojemann JG, Guerrini R, Murphy LO, Winckler W, Dobyns WB. Association of MTOR mutations with developmental brain disorders, including megalencephaly, focal cortical dysplasia, and pigmentary mosaicism[J]. JAMA Neurol, 2016, 73:836-845.

[22] Blümcke I, Coras R, Busch RM, Morita-Sherman M, Lal D, Prayson R, Cendes F, Lopes-Cendes I, Rogerio F, Almeida VS,

Rocha CS, Sim NS, Lee JH, Kim SH, Baulac S, Baldassari S, Adle-Biassette H, Walsh CA, Bizzotto S, Doan RN, Morillo KS, Aronica E, Mühlebner A, Becker A, Cienfuegos J, Garbelli R, Giannini C, Honavar M, Jacques TS, Thom M, Mahadevan A, Miyata H, Niehusmann P, Sarnat HB, Söylemezoglu F, Najm I. Toward a better definition of focal cortical dysplasia: an iterative histopathological and genetic agreement trial [J]. Epilepsia, 2021, 62:1416-1428.

[23] Lee JH, Huynh M, Silhavy JL, Kim S, Dixon-Salazar T, Heiberg A, Scott E, Bafna V, Hill KJ, Collazo A, Funari V, Russ C, Gabriel SB, Mathern GW, Gleeson JG. De novo somatic mutations in components of the PI3K-AKT3-mTOR pathway cause hemimegalencephaly[J]. Nat Genet, 2012, 44:941-945.

[24] Poduri A, Evrony GD, Cai X, Elhosary PC, Beroukhim R, Lehtinen MK, Hills LB, Heinzen EL, Hill A, Hill RS, Barry BJ, Bourgeois BF, Riviello JJ, Barkovich AJ, Black PM, Ligon KL, Walsh CA. Somatic activation of AKT3 causes hemispheric developmental brain malformations[J]. Neuron, 2012, 74:41-48.

[25] Sim NS, Ko A, Kim WK, Kim SH, Kim JS, Shim KW, Aronica E, Mijnsbergen C, Spliet WGM, Koh HY, Kim HD, Lee JS, Kim DS, Kang HC, Lee JH. Precise detection of low-level somatic mutation in resected epilepsy brain tissue [J]. Acta Neuropathol, 2019, 138:901-912.

[26] Lee WS, Stephenson SEM, Pope K, Gillies G, Maixner W, Macdonald-Laurs E, MacGregor D, D'Arcy C, Jackson G, Harvey AS, Leventer RJ, Lockhart PJ. Genetic characterization identifies bottom-of-sulcus dysplasia as an mTORopathy[J]. Neurology, 2020, 95:e2542-2551.

[27] Ribierre T, Deleuze C, Bacq A, Baldassari S, Marsan E, Chipaux M, Muraca G, Roussel D, Navarro V, Leguern E, Miles R, Baulac S. Second-hit mosaic mutation in mTORC1 repressor DEPDC5 causes focal cortical dysplasia-associated epilepsy[J]. J Clin Invest, 2018, 128:2452-2458.

[28] Zhang Z, Gao K, Liu Q, Zhou J, Li X, Lang N, Liu M, Wang T, Zhang J, Wang H, Dong Y, Ji T, Wang S, Liu X, Jiang Y, Cai L, Wu Y. Somatic variants in new candidate genes identified in focal cortical dysplasia type Ⅱ[J]. Epilepsia, 2020, 61:667-678.

[29] Sim NS, Seo Y, Lim JS, Kim WK, Son H, Kim HD, Kim S, An HJ, Kang HC, Kim SH, Kim DS, Lee JH. Brain somatic mutations in SLC35A2 cause intractable epilepsy with aberrant N-glycosylation[J]. Neurol Genet, 2018, 4:e294.

[30] Winawer MR, Griffin NG, Samanamud J, Baugh EH, Rathakrishnan D, Ramalingam S, Zagzag D, Schevon CA, Dugan P, Hegde M, Sheth SA, McKhann GM, Doyle WK, Grant GA, Porter BE, Mikati MA, Muh CR, Malone CD, Bergin AMR, Peters JM, McBrian DK, Pack AM, Akman CI, LaCoursiere CM, Keever KM, Madsen JR, Yang E, Lidov HGW, Shain C, Allen AS, Canoll PD, Crino PB, Poduri AH, Heinzen EL. Somatic SLC35A2 variants in the brain are associated with intractable neocortical epilepsy[J]. Ann Neurol, 2018, 83:1133-1146.

[31] Miller KE, Koboldt DC, Schieffer KM, Bedrosian TA, Crist E, Sheline A, Leraas K, Magrini V, Zhong H, Brennan P, Bush J, Fitch J, Bir N, Miller AR, Cottrell CE, Leonard J, Pindrik JA, Rusin JA, Shah SH, White P, Wilson RK, Mardis ER, Pierson CR, Ostendorf AP. Somatic SLC35A2 mosaicism correlates with clinical findings in epilepsy brain tissue [J]. Neurol Genet, 2020, 6:e460.

[32] Benova B, Jacques TS. Genotype-phenotype correlations in focal malformations of cortical development: a pathway to integrated pathological diagnosis in epilepsy surgery [J]. Brain Pathol, 2019, 29:473-484.

[33] Lamberink HJ, Otte WM, Blümcke I, Braun KPJ; European Epilepsy Brain Bank writing group, study group, European Reference Network EpiCARE. Seizure outcome and use of antiepileptic drugs after epilepsy surgery according to histopathological diagnosis: a retrospective multicentre cohort study[J]. Lancet Neurol, 2020, 19:748-757.

[34] Mendes Coelho VC, Morita-Sherman M, Yasuda CL, Alvim MMK, Amorim BJ, Tedeschi H, Ghizoni E, Rogerio F, Cendes F. Magnetic resonance imaging findings and clinical characteristics in mild malformation of cortical development with oligodendroglial hyperplasia and epilepsy in a predominantly adult cohort[J]. Epilepsia, 2021, 62:1429-1441.

[35] Gaballa A, Woermann FG, Cloppenborg T, Kalbhenn T, Blümcke I, Bien CG, Fauser S. Clinical characteristics and postoperative seizure outcome in patients with mild malformation of cortical development and oligodendroglial hyperplasia[J]. Epilepsia, 2021, 62:2920-2931.

[36] Baldassari S, Picard F, Verbeek NE, van Kempen M, Brilstra EH, Lesca G, Conti V, Guerrini R, Bisulli F, Licchetta L, Pippucci T, Tinuper P, Hirsch E, de Saint Martin A, Chelly J, Rudolf G, Chipaux M, Ferrand-Sorbets S, Dorfmüller G, Sisodiya S, Balestrini S, Schoeler N, Hernandez-Hernandez L, Krithika S, Oegema R, Hagebeuk E, Gunning B, Deckers C, Berghuis B, Wegner I, Niks E, Jansen FE, Braun K, de Jong D, Rubboli G, Talvik I, Sander V, Uldall P, Jacquemont ML, Nava C, Leguern E, Julia S, Gambardella A, d'Orsi G, Crichiutti G, Faivre L, Darmency V, Benova B, Krsek P, Biraben A, Lebre AS, Jennesson M, Sattar S, Marchal C, Nordli DR Jr, Lindstrom K, Striano P, Lomax LB, Kiss C, Bartolomei F, Lepine AF, Schoonjans AS, Stouffs K, Jansen A, Panagiotakaki E, Ricard-Mousnier B, Thevenon J, de Bellescize J, Catenoix H, Dorn T, Zenker M, Müller-Schlüter K, Brandt C, Krey I, Polster T, Wolff M, Balci M, Rostasy K, Achaz G, Zacher P, Becher T, Cloppenborg T, Yuskaitis CJ, Weckhuysen S, Poduri A, Lemke JR, Møller RS, Baulac S. The landscape of epilepsy-related GATOR1 variants[J]. Genet Med, 2019, 21:398-408.

[37] Vawter-Lee M, Franz DN, Fuller CE, Greiner HM. Clinical letter: a case report of targeted therapy with sirolimus for NPRL3 epilepsy[J]. Seizure, 2019, 73:43-45.

[38] Slegers RJ, Blumcke I. Low-grade developmental and epilepsy associated brain tumors: a critical update 2020 [J]. Acta Neuropathol Commun, 2020, 8:27.

[39] Blumcke I, Spreafico R, Haaker G, Coras R, Kobow K, Bien CG, Pfäfflin M, Elger C, Widman G, Schramm J, Becker A, Braun KP, Leijten F, Baayen JC, Aronica E, Chassoux F, Hamer H, Stefan H, Rössler K, Thom M, Walker MC, Sisodiya SM, Duncan JS, McEvoy AW, Pieper T, Holthausen H, Kudernatsch M, Meencke HJ, Kahane P, Schulze-Bonhage A, Zentner J, Heiland DH, Urbach H, Steinhoff BJ, Bast T, Tassi L, Lo Russo G, Özkara C, Oz B, Krsek P, Vogelgesang S, Runge U, Lerche H, Weber Y, Honavar M, Pimentel J, Arzimanoglou A, Ulate-Campos A, Noachtar S, Hartl E, Schijns O, Guerrini R, Barba C, Jacques TS, Cross JH, Feucht M, Mühlebner A, Grunwald T, Trinka E, Winkler PA, Gil-Nagel A, Toledano Delgado R, Mayer T, Lutz M, Zountsas B, Garganis K, Rosenow F, Hermsen A, von Oertzen TJ, Diepgen TL, Avanzini G; EEBB Consortium. Histopathological findings in brain tissue obtained during epilepsy surgery[J]. N Engl J Med, 2017, 377:1648-1656.

[40] Thom M, Blümcke I, Aronica E. Long-term epilepsy-associated tumors[J]. Brain Pathol, 2012, 22:350-379.

[41] Phi JH, Kim SK. Clinical pearls and advances in molecular researches of epilepsy-associated tumors [J]. J Korean Neurosurg Soc, 2019, 62:313-320.

[42] Qaddoumi I, Orisme W, Wen J, Santiago T, Gupta K, Dalton

JD, Tang B, Haupfear K, Punchihewa C, Easton J, Mulder H, Boggs K, Shao Y, Rusch M, Becksfort J, Gupta P, Wang S, Lee RP, Brat D, Peter Collins V, Dahiya S, George D, Konomos W, Kurian KM, McFadden K, Serafini LN, Nickols H, Perry A, Shurtleff S, Gajjar A, Boop FA, Klimo PD Jr, Mardis ER, Wilson RK, Baker SJ, Zhang J, Wu G, Downing JR, Tatevossian RG, Ellison DW. Genetic alterations in uncommon low-grade neuroepithelial tumors: BRAF, FGFR1, and MYB mutations occur at high frequency and align with morphology[J]. Acta Neuropathol, 2016, 131:833-845.

[43] Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, Teague J, Woffendin H, Garnett MJ, Bottomley W, Davis N, Dicks E, Ewing R, Floyd Y, Gray K, Hall S, Hawes R, Hughes J, Kosmidou V, Menzies A, Mould C, Parker A, Stevens C, Watt S, Hooper S, Wilson R, Jayatilake H, Gusterson BA, Cooper C, Shipley J, Hargrave D, Pritchard-Jones K, Maitland N, Chenevix-Trench G, Riggins GJ, Bigner DD, Palmieri G, Cossu A, Flanagan A, Nicholson A, Ho JW, Leung SY, Yuen ST, Weber BL, Seigler HF, Darrow TL, Paterson H, Marais R, Marshall CJ, Wooster R, Stratton MR, Futreal PA. Mutations of the BRAF gene in human cancer[J]. Nature, 2002, 417:949-954.

[44] Dougherty MJ, Santi M, Brose MS, Ma C, Resnick AC, Sievert AJ, Storm PB, Biegel JA. Activating mutations in BRAF characterize a spectrum of pediatric low-grade gliomas[J]. Neuro Oncol, 2010, 12:621-630.

[45] Koelsche C, Wöhrer A, Jeibmann A, Schittenhelm J, Schindler G, Preusser M, Lasitschka F, von Deimling A, Capper D. Mutant BRAF V600E protein in ganglioglioma is predominantly expressed by neuronal tumor cells[J]. Acta Neuropathol, 2013, 125:891-900.

[46] Blümcke I, Wiestler OD. Gangliogliomas: an intriguing tumor entity associated with focal epilepsies[J]. J Neuropathol Exp Neurol, 2002, 61:575-584.

[47] Jones DT, Hutter B, Jäger N, Korshunov A, Kool M, Warnatz HJ, Zichner T, Lambert SR, Ryzhova M, Quang DA, Fontebasso AM, Stütz AM, Hutter S, Zuckermann M, Sturm D, Gronych J, Lasitschka B, Schmidt S, Seker-Cin H, Witt H, Sultan M, Ralser M, Northcott PA, Hovestadt V, Bender S, Pfaff E, Stark S, Faury D, Schwartzentruber J, Majewski J, Weber UD, Zapatka M, Raeder B, Schlesner M, Worth CL, Bartholomae CC, von Kalle C, Imbusch CD, Radomski S, Lawerenz C, van Sluis P, Koster J, Volckmann R, Versteeg R, Lehrach H, Monoranu C, Winkler B, Unterberg A, Herold-Mende C, Milde T, Kulozik AE, Ebinger M, Schuhmann MU, Cho YJ, Pomeroy SL, von Deimling A, Witt O, Taylor MD, Wolf S, Karajannis MA, Eberhart CG, Scheurlen W, Hasselblatt M, Ligon KL, Kieran MW, Korbel JO, Yaspo ML, Brors B, Felsberg J, Reifenberger G, Collins VP, Jabado N, Eils R, Lichter P, Pfister SM; International Cancer Genome Consortium PedBrain Tumor Project. Recurrent somatic alterations of FGFR1 and NTRK2 in pilocytic astrocytoma[J]. Nat Genet, 2013, 45:927-932.

[48] Rivera B, Gayden T, Carrot-Zhang J, Nadaf J, Boshari T, Faury D, Zeinieh M, Blanc R, Burk DL, Fahiminiya S, Bareke E, Schüller U, Monoranu CM, Sträter R, Kerl K, Niederstadt T, Kurlemann G, Ellezam B, Michalak Z, Thom M, Lockhart PJ, Leventer RJ, Ohm M, MacGregor D, Jones D, Karamchandani J, Greenwood CM, Berghuis AM, Bens S, Siebert R, Zakrzewska M, Liberski PP, Zakrzewski K, Sisodiya SM, Paulus W, Albrecht S, Hasselblatt M, Jabado N, Foulkes WD, Majewski J. Germline and somatic FGFR1 abnormalities in dysembryoplastic neuroepithelial tumors[J]. Acta Neuropathol, 2016, 131:847-863.

[49] Zhang J, Wu G, Miller CP, Tatevossian RG, Dalton JD, Tang B, Orisme W, Punchihewa C, Parker M, Qaddoumi I, Boop FA, Lu C, Kandoth C, Ding L, Lee R, Huether R, Chen X, Hedlund E, Nagahawatte P, Rusch M, Boggs K, Cheng J, Becksfort J, Ma J, Song G, Li Y, Wei L, Wang J, Shurtleff S, Easton J, Zhao D, Fulton RS, Fulton LL, Dooling DJ, Vadodaria B, Mulder HL, Tang C, Ochoa K, Mullighan CG, Gajjar A, Kriwacki R, Sheer D, Gilbertson RJ, Mardis ER, Wilson RK, Downing JR, Baker SJ, Ellison DW; St. Jude Children's Research Hospital-Washington University Pediatric Cancer Genome Project. Whole-genome sequencing identifies genetic alterations in pediatric low-grade gliomas[J]. Nat Genet, 2013, 45:602-612.

[50] Wefers AK, Stichel D, Schrimpf D, Coras R, Pages M, Tauziède-Espariat A, Varlet P, Schwarz D, Söylemezoglu F, Pohl U, Pimentel J, Meyer J, Hewer E, Japp A, Joshi A, Reuss DE, Reinhardt A, Sievers P, Casalini MB, Ebrahimi A, Huang K, Koelsche C, Low HL, Rebelo O, Marnoto D, Becker AJ, Staszewski O, Mittelbronn M, Hasselblatt M, Schittenhelm J, Cheesman E, de Oliveira RS, Queiroz RGP, Valera ET, Hans VH, Korshunov A, Olar A, Ligon KL, Pfister SM, Jaunmuktane Z, Brandner S, Tatevossian RG, Ellison DW, Jacques TS, Honavar M, Aronica E, Thom M, Sahm F, von Deimling A, Jones DTW, Blumcke I, Capper D. Isomorphic diffuse glioma is a morphologically and molecularly distinct tumour entity with recurrent gene fusions of MYBL1 or MYB and a benign disease course[J]. Acta Neuropathol, 2020, 139:193-209.

[51] Hou Y, Pinheiro J, Sahm F, Reuss DE, Schrimpf D, Stichel D, Casalini B, Koelsche C, Sievers P, Wefers AK, Reinhardt A, Ebrahimi A, Fernández-Klett F, Pusch S, Meier J, Schweizer L, Paulus W, Prinz M, Hartmann C, Plate KH, Reifenberger G, Pietsch T, Varlet P, Pagès M, Schüller U, Scheie D, de Stricker K, Frank S, Hench J, Pollo B, Brandner S, Unterberg A, Pfister SM, Jones DTW, Korshunov A, Wick W, Capper D, Blümcke I, von Deimling A, Bertero L. Papillary glioneuronal tumor (PGNT) exhibits a characteristic methylation profile and fusions involving PRKCA[J]. Acta Neuropathol, 2019, 137:837-846.

[52] Xing H, Song Y, Zhang Z, Koch PD. Clinical characteristics of BRAF V600E gene mutation in patients of epilepsy-associated brain tumor: a meta-analysis[J]. J Mol Neurosci, 2021, 71:1815-1824.

[53] Mehrotra A, Singh S, Kanjilal S, Pal L, Paliwal VK, Sardhara J, Verma PK, Maurya VP, Bhaisora KS, Das KK, Srivastava AK, Jaiswal AK, Behari S. Factors affecting seizure outcome in long-term epilepsy associated tumors (LEATs) in children and young adolescents[J]. Clin Neurol Neurosurg, 2020, 197:106104.

[54] Pelliccia V, Deleo F, Gozzo F, Sartori I, Mai R, Cossu M, Tassi L. Early and late epilepsy surgery in focal epilepsies associated with long-term epilepsy-associated tumors[J]. J Neurosurg, 2017, 127:1147-1152.

[55] Chen X, Pan C, Zhang P, Xu C, Sun Y, Yu H, Wu Y, Geng Y, Zuo P, Wu Z, Zhang J, Zhang L. BRAF V600E mutation is a significant prognosticator of the tumour regrowth rate in brainstem gangliogliomas[J]. J Clin Neurosci, 2017, 46:50-57.

[56] Dahiya S, Haydon DH, Alvarado D, Gurnett CA, Gutmann DH, Leonard JR. BRAF(V600E) mutation is a negative prognosticator in pediatric ganglioglioma[J]. Acta Neuropathol, 2013, 125:901-910.

[57] Subbiah V, Lassen U, Élez E, Italiano A, Curigliano G, Javle M, de Braud F, Prager GW, Greil R, Stein A, Fasolo A, Schellens JHM, Wen PY, Viele K, Boran AD, Gasal E, Burgess P, Ilankumaran P, Wainberg ZA. Dabrafenib plus trametinib in patients with BRAFV600E-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial[J]. Lancet Oncol, 2020, 21:1234-1243.

[58] Garnier L, Ducray F, Verlut C, Mihai MI, Cattin F, Petit A, Curtit E. Prolonged response induced by single agent vemurafenib in a BRAF V600E spinal ganglioglioma: a case report and review of the literature[J]. Front Oncol, 2019, 9:177.
[59] Yau WH, Ameratunga M. Combination of BRAF and MEK inhibition in BRAF V600E mutant low-grade ganglioglioma[J]. J Clin Pharm Ther, 2020, 45:1172-1174.
[60] French JA, Williamson PD, Thadani VM, Darcey TM, Mattson RH, Spencer SS, Spencer DD. Characteristics of medial temporal lobe epilepsy. Ⅰ: results of history and physical examination[J]. Ann Neurol, 1993, 34:774-780.
[61] Davies KG, Hermann BP, Dohan FC Jr, Foley KT, Bush AJ, Wyler AR. Relationship of hippocampal sclerosis to duration and age of onset of epilepsy, and childhood febrile seizures in temporal lobectomy patients[J]. Epilepsy Res, 1996, 24:119-126.
[62] Chiang LM, Huang GS, Sun CC, Hsiao YL, Hui CK, Hu MH. Association of developing childhood epilepsy subsequent to febrile seizure: a population-based cohort study[J]. Brain Dev, 2018, 40:775-780.
[63] Di Gennaro G, Casciato S, Quarato PP, Mascia A, D'Aniello A, Grammaldo LG, De Risi M, Meldolesi GN, Romigi A, Esposito V, Picardi A. Acute postoperative seizures and long-term seizure outcome after surgery for hippocampal sclerosis[J]. Seizure, 2015, 24:59-62.
[64] Tugcu B, Gungor A, Akpinar A, Kinay D, Kuscu DY, Gül G, Kayrak N, Keskinkilic C, Akdemir H, Emel E. Outcome of surgical treatment of hippocampal sclerosis from relatively new epilepsy surgery center[J]. J Neurosurg Sci, 2016, 60:159-168.
[65] Pitskhelauri DI, Kudieva ES, Melikyan AG, Vlasov PA, Kamenetskaya MI, Zaitsev OS, Kozlova AB, Eliseeva NM, Shishkina LV, Danilov GV, Nagorskaya IA, Sanikidze AZ, Melnikova-Pitskhelauri TV, Pronin IN, Konovalov AN. Surgical treatment of drug-resistant epilepsy following hippocampal sclerosis[J]. Zh Vopr Neirokhir Im NN Burdenko, 2021, 85:31-40.
[66] Kasperaviciute D, Catarino CB, Matarin M, Leu C, Novy J, Tostevin A, Leal B, Hessel EV, Hallmann K, Hildebrand MS, Dahl HH, Ryten M, Trabzuni D, Ramasamy A, Alhusaini S, Doherty CP, Dorn T, Hansen J, Krämer G, Steinhoff BJ, Zumsteg D, Duncan S, Kälviäinen RK, Eriksson KJ, Kantanen AM, Pandolfo M, Gruber-Sedlmayr U, Schlachter K, Reinthaler EM, Stogmann E, Zimprich F, Théâtre E, Smith C, O'Brien TJ, Meng Tan K, Petrovski S, Robbiano A, Paravidino R, Zara F, Striano P, Sperling MR, Buono RJ, Hakonarson H, Chaves J, Costa PP, Silva BM, da Silva AM, de Graan PN, Koeleman BP, Becker A, Schoch S, von Lehe M, Reif PS, Rosenow F, Becker F, Weber Y, Lerche H, Rössler K, Buchfelder M, Hamer HM, Kobow K, Coras R, Blumcke I, Scheffer IE, Berkovic SF, Weale ME, Delanty N, Depondt C, Cavalleri GL, Kunz WS, Sisodiya SM; UK Brain Expression Consortium. Epilepsy, hippocampal sclerosis and febrile seizures linked by common genetic variation around SCN1A[J]. Brain, 2013, 136(Pt 10):3140-3150.
[67] Zhang Y, Li SQ, Chen J. The mechanisms of hippocampai mitochondrial stress and neuronal injury after thrombotic cerebral ischemia in Tree Shrews[J]. Zhong Feng Yu Shen Jing Ji Bing Za Zhi, 2007, 24:140-142.[张颖, 李树清, 陈静. 树鼩脑缺血后海马线粒体应激与神经元损伤机制研究[J]. 中风与神经疾病杂志, 2007, 24:140-142.]
[68] Stevelink R, Sanders MW, Tuinman MP, Brilstra EH, Koeleman BP, Jansen FE, Braun KP. Epilepsy surgery for patients with genetic refractory epilepsy: a systematic review[J]. Epileptic Disord, 2018, 20:99-115.
[69] Pepi C, de Palma L, Trivisano M, Pietrafusa N, Lepri FR, Diociaiuti A, Camassei FD, Carfi-Pavia G, De Benedictis A, Rossi-Espagnet C, Vigevano F, Marras CE, Novelli A, Bluemcke I, Specchio N. The role of KRAS mutations in cortical malformation and epilepsy surgery: a novel report of nevus sebaceous syndrome and review of the literature[J]. Brain Sci, 2021, 11:793.
[70] Cohen NT, Cross JH, Arzimanoglou A, Berkovic SF, Kerrigan JF, Miller IP, Webster E, Soeby L, Cukiert A, Hesdorffer DK, Kroner BL, Saper CB, Schulze-Bonhage A, Gaillard WD; Hypothalamic Hamartoma Writing Group. Hypothalamic hamartomas: evolving understanding and management[J]. Neurology, 2021, 97:864-873.
[71] Kerrigan JF, Parsons A, Tsang C, Simeone K, Coons S, Wu J. Hypothalamic hamartoma: neuropathology and epileptogenesis[J]. Epilepsia, 2017, 58 Suppl 2:22-31.
[72] Chan YM, Fenoglio-Simeone KA, Paraschos S, Muhammad L, Troester MM, Ng YT, Johnsonbaugh RE, Coons SW, Prenger EC, Kerrigan JF Jr, Seminara SB. Central precocious puberty due to hypothalamic hamartomas correlates with anatomic features but not with expression of GnRH, TGFalpha, or KISS1[J]. Horm Res Paediatr, 2010, 73:312-319.
[73] Hildebrand MS, Griffin NG, Damiano JA, Cops EJ, Burgess R, Ozturk E, Jones NC, Leventer RJ, Freeman JL, Harvey AS, Sadleir LG, Scheffer IE, Major H, Darbro BW, Allen AS, Goldstein DB, Kerrigan JF, Berkovic SF, Heinzen EL. Mutations of the sonic hedgehog pathway underlie hypothalamic hamartoma with gelastic epilepsy[J]. Am J Hum Genet, 2016, 99:423-429.
[74] Corman TS, Bergendahl SE, Epstein DJ. Distinct temporal requirements for Sonic hedgehog signaling in development of the tuberal hypothalamus[J]. Development, 2018, 145:dev167379.
[75] Boudreau EA, Liow K, Frattali CM, Wiggs E, Turner JT, Feuillan P, Sato S, Patsalides A, Patronas N, Biesecker LG, Theodore WH. Hypothalamic hamartomas and seizures: distinct natural history of isolated and Pallister-Hall syndrome cases[J]. Epilepsia, 2005, 46:42-47.
[76] Wang S, Zhao M, Li T, Zhang C, Zhou J, Wang M, Wang X, Liu Z, Ma K, Luan G, Guan Y. Stereotactic radiofrequency thermocoagulation and resective surgery for patients with hypothalamic hamartoma[J]. J Neurosurg, 2020, 134:1019-1026.
[77] Liu C, Zheng Z, Shao XQ, Li CD, Yang XL, Zhang C, Sang L, Xie F, Zhou F, Hu WH, Zhang K. Stereoelectroencephalography-guided radiofrequency thermocoagulation for hypothalamic hamartoma: electroclinical patterns and the relationship with surgical prognosis[J]. Epilepsy Behav, 2021, 118:107957.
[78] Mithani K, Neudorfer C, Boutet A, Germann J, Elias GJB, Weil AG, Donner E, Kalia S, Lozano AM, Drake JM, Widjaja E, Ibrahim GM. Surgical targeting of large hypothalamic hamartomas and seizure-freedom following MR-guided laser interstitial thermal therapy[J]. Epilepsy Behav, 2021, 116:107774.
[79] Gadgil N, Lam S, Pan IW, LoPresti M, Wagner K, Ali I, Wilfong A, Curry DJ. Staged magnetic resonance-guided laser interstitial thermal therapy for hypothalamic hamartoma: analysis of ablation volumes and morphological considerations[J]. Neurosurgery, 2020, 86:808-816.
[80] Yao Y, Wang X, Hu W, Zhang C, Sang L, Zheng Z, Mo J, Liu C, Qiu J, Shao X, Zhang J, Zhang K. Magnetic resonance-guided laser interstitial thermal therapy for hypothalamic hamartoma: surgical approach and treatment outcomes[J]. J Clin Med, 2022, 11:6579.

（收稿日期：2023-02-23）
（本文编辑：柏钰）