·2021年WHO中枢神经系统肿瘤分类(第五版)解读·

2021年世界卫生组织中枢神经系统肿瘤分类(第五版)分子诊断指标解读

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【摘要】 2021年世界卫生组织中枢神经系统肿瘤分类(第五版,简称新版肿瘤分类)在组织学诊断的基础上引入一系列分子诊断指标,形成整合诊断及分层报告体系,并新定义多种肿瘤类型和亚型,反映出目前神经肿瘤相关领域对此类疾病遗传背景和临床特征的理解。本文综述新版肿瘤分类关键的分子诊断指标及相应检测方法,旨在为临床认识疾病、管理肿瘤患者提供帮助。

【关键词】 中枢神经系统肿瘤; 指南; 世界卫生组织; 分子生物学; 基因; 突变; 综述

Interpretation on the diagnostic molecular parameters in the 2021 WHO Classification of Tumors of the Central Nervous System (fifth edition)

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【Abstract】 The 2021 WHO Classification of Tumors of the Central Nervous System (fifth edition) introduces a series of molecular biomarkers and new types/subtypes, which highlight the importance of integrated diagnoses and layered reports. The new edition tumors classification is reflections of the understanding in this field at present. Herein, we review the key molecular diagnostics and detection techniques, aiming to facilitate better understanding and more appropriate management for the tumors of the central nervous system.

【Key words】 Central nervous system neoplasms; Guidelines; World Health Organization; Molecular biology; Genes; Mutation; Review

Conflicts of interest: none declared

随着病理学的发展和病理检测技术的进步,尤其是第二代测序技术(NGS)、全基因组甲基化测序(WGBS)等组学技术的提高,肿瘤遗传背景和发生发展机制逐渐清晰。越来越多的分子生物学标志物被证实在中枢神经系统(CNS)肿瘤分类、分型、分级、治疗和预后方面发挥重要作用。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(以下简称第四版修订版)首次在组织学形态的基础上引入分子表型,提出整合诊断的理念,旨在提高病理诊断的客观性和可重复性,完善个体化管理流程,促进临床试验、基础实验和流行病学研究的开展,并为优化资源配置、制定政策提供支持[1-2]。然而,第四版修订版是组织病理学和分子病理学整合后的首次尝试,许多暂定的肿瘤实体仍待进一步研究[2-3]。经过5年的实践和完善,2021年WHO中枢神经系统肿瘤分类(第五版,以下简称新版肿瘤分类)在整合最新研究进展与中枢神经系统肿瘤分子信息与分类实践联盟-非WHO官方组织(cIMPACT-NOW)7次更新的基础上,制定新的肿瘤分类体系和分级标准,重点推进分子诊断在中枢神经系统肿瘤分类中的应用[4]。本文拟对中枢神经系统肿瘤分子诊断指标进行解读,其中基因变异以斜体字表示,蛋白质和基因家族则以正体字表示(表1)[4]。尽管新版肿瘤分类并不推荐分子检测的具体方法,但本文对常用的分子检测技术进行简要介绍,为更好地理解分子检测提供帮助。

一、中枢神经系统常见肿瘤分子变异

1. 成人型弥漫性胶质瘤 IDH突变是成人型弥

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表1 不同中枢神经系统肿瘤的关键基因、分子及信号转导通路改变[4]

Table 1. Key diagnostic genes, molecules, pathways, and/or combinations in major primary CNS tumors[4]

肿瘤类型	关键基因及分子变异*
星形细胞瘤，IDH突变型	*IDH1*，*IDH2*，*ATRX*，*TP53*，*CDKNA/B*
少突胶质细胞瘤，IDH突变和1p/19q共缺失型	*IDH1*，*IDH2*，染色体1p/19q，*TERT*启动子，*CIC*，*FUBP1*，*NOTCH1*
胶质母细胞瘤，IDH野生型	IDH野生，*TERT*启动子，第7号染色体和第10号染色体，*EGFR*
弥漫性星形细胞瘤，*MYB*或*MYBL1*变异型	*MYB*，*MYBL1*
血管中心型胶质瘤	*MYB*
青年人多形性低级别神经上皮肿瘤	*BRAF*，FGFR家族
弥漫性低级别胶质瘤，MAPK通路变异型	*FGFR1*，*BRAF*
弥漫性中线胶质瘤，H3 K27变异型	H3 K27，*TP53*，*ACVR1*，*PDGFRA*，*EGFR*，*EZHIP*
弥漫性半球胶质瘤，H3 G34突变型	H3 G34，*TP53*，*ATRX*
弥漫性儿童型高级别胶质瘤，H3野生和IDH野生型	IDH野生，H3野生，*PDGFRA*，*MYCN*，*EGFR*（DNA甲基化谱）
婴儿型半球胶质瘤	NTRK家族，*ALK*，*ROS*，*MET*
毛细胞型星形细胞瘤	*KIAA1549-BRAF*，*BRAF*，*NF1*
有毛细胞样特征的高级别星形细胞瘤	*BRAF*，*NF1*，*ATRX*，*CDKN2A/B*（DNA甲基化谱）
多形性黄色瘤型星形细胞瘤	*BRAF*，*CDKN2A/B*
室管膜下巨细胞型星形细胞瘤	*TSC1*，*TSC2*
脊索样胶质瘤	*PRKCA*
星形母细胞瘤，*MN1*变异型	*MN1*
神经节细胞胶质瘤	*BRAF*
胚胎发育不良性神经上皮肿瘤	*FGFR1*
有少突胶质细胞瘤样特征和核簇的弥漫性胶质神经元肿瘤	第14号染色体（DNA甲基化谱）
乳头状胶质神经元肿瘤	*PRKCA*
形成菊形团的胶质神经元肿瘤	*FGFR1*，*PIK3CA*，*NF1*
黏液样胶质神经元肿瘤	*PDGFRA*
弥漫性软脑膜胶质神经元肿瘤	*KIAA1549-BRAF*，1p（DNA甲基化谱）
多结节和空泡状神经元肿瘤	MAPK信号转导通路
小脑发育不良性神经节细胞瘤（Lhermitte-Duclos病）	*PTEN*
脑室外神经细胞瘤	FGFR（*FGFR1-TACC1*融合基因），IDH野生
幕上室管膜瘤	*ZFTA*，*RELA*，*YAP1*，*MAML2*
后颅窝室管膜瘤	H3 K27me3，*EZHIP*（DNA甲基化谱）
脊髓室管膜瘤	*NF2*，*MYCN*
髓母细胞瘤，WNT活化型	*CTNNB1*，*APC*
髓母细胞瘤，SHH活化型	*TP53*，*PTCH1*，*SUFU*，*SMO*，*MYCN*，*GLI2*（DNA甲基化谱）
髓母细胞瘤，非WNT/非SHH活化型	*MYC*，*MYCN*，*PRDM6*，*KDM6A*（DNA甲基化谱）
非典型性畸胎样/横纹肌样肿瘤	*SMARCB1*，*SMARCA4*
有多层菊形团的胚胎性肿瘤	C19MC，*DICER1*
中枢神经系统神经母细胞瘤，*FOXR2*活化型	*FOXR2*
有*BCOR*内部串联重复的中枢神经系统肿瘤	*BCOR*
松果体区促纤维增生性黏液样肿瘤，*SMARCB1*突变型	*SMARCB1*
脑膜瘤	*NF2*，*AKT1*，*TRAF7*，*SMO*，*PIK3CA*； *KLF4*，*SMARCE1*，*BAP1*； H3 K27me3； *TERT*启动子，*CDKN2A/B*
孤立性纤维性肿瘤	*NAB2-STAT6*
脑膜黑色素细胞肿瘤	*NRAS*（弥漫性）； *GNAQ*，*GNA11*，*PLCB4*，*CYSLTR2*（局限性）

续表1

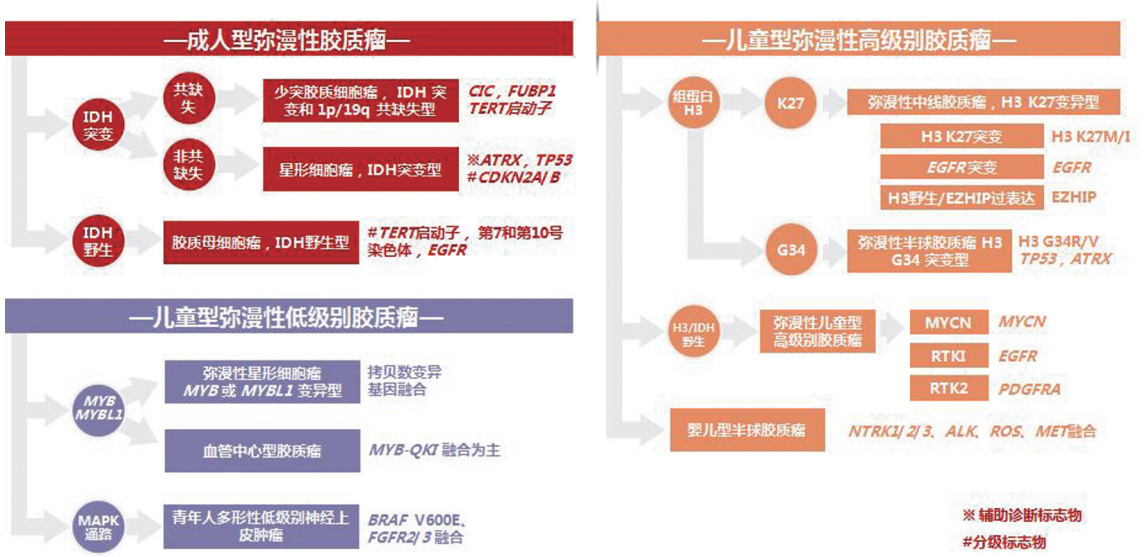
肿瘤类型	关键基因及分子变异*
牙釉质细胞瘤型颅咽管瘤	*CTNNB1*
乳头状型颅咽管瘤	*BRAF*

*In this column, molecules that are definitional (including for those that are wildtype) are listed before others; for those tumor types without specific definitional changes, more commonly altered genes and molecules are listed before others. Most types have characteristic methylome patterns, but "(methylome)" is only listed for those types for which methylome testing offers particular diagnostic guidance,其中一些是诊断所必须,一些尽管不是诊断所必须,但是肿瘤的典型分子病理学特征。诊断性分子标志物列在最前面;对于无诊断性分子标志物的肿瘤类型,最常见的分子变异列在最前面。大多数肿瘤均有特征性DNA甲基化谱,"(DNA甲基化谱)"表示甲基化检测对于此类肿瘤具有特定的诊断意义。H3 is a gene family (eg, *H3F3A*, *HIST1H3B*), H3代表一个基因家族(包括*H3F3A*,*HIST1H3B*等)。IDH, isocitrate dehydrogenase,异柠檬酸脱氢酶;FGFR, fibroblast growth factor receptor,纤维母细胞生长因子受体;MAPK, mitogen-activated protein kinase,丝裂原激活蛋白激酶;NTRK, neurotrophin receptor kinase,神经营养因子受体酪氨酸激酶

漫性胶质瘤的重要诊断标志物。脑胶质瘤最常见的IDH突变为*IDH1*基因第132位密码子突变(以R132H突变最常见,其他包括R132C、R132S、R132G和R132L等),其余为*IDH2*基因第172位密码子突变(包括R172G、R172M和R172W等)及其他少见密码子突变(如*IDH1* R49等)[5-7]。IDH突变的弥漫性胶质瘤若伴1p/19q共缺失,则诊断为**少突胶质细胞瘤,IDH突变和1p/19q共缺失型**;其中,*TERT*启动子突变、*NOTCH1*突变、*FUBP1*突变和*CIC*突变是此种类型胶质瘤的常见分子特征[8];IDH突变但是不伴1p/19q共缺失的弥漫性胶质瘤,诊断为**星形细胞瘤,IDH突变型**;*ATRX*突变、*TP53*突变是此种类型胶质瘤的典型分子变异,也是重要的辅助诊断标志物[7-9];而*CDKN2A/B*纯合性缺失是此种类型肿瘤的分级标志物,有*CDKN2A/B*缺失的IDH突变型星形细胞瘤诊断为**星形细胞瘤,IDH突变型,CNS WHO 4级**[4,9](图1)。组织学形态表现为坏死或微血管增生的IDH野生型弥漫性胶质瘤,则诊断为**胶质母细胞瘤,IDH野生型**[1,4];组织学形态呈CNS WHO 2级或3级的IDH野生型弥漫性星形细胞瘤,如果有*EGFR*扩增、第7号染色体扩增/第10号染色体缺失(+7/−10)、*TERT*启动子突变上述3种分子变异之一,也可诊断为**胶质母细胞瘤,IDH野生型**[10],同时这3种分子变异也是此类肿瘤预后相关的分子生物学标志物[10]。

2. 儿童型弥漫性低级别胶质瘤 新版肿瘤分类首次引入儿童型弥漫性低级别胶质瘤的概念,组织学形态表现为弥漫性低级别胶质瘤,主要发生于儿童,亦可见于成人,通常有癫痫病史[11]。分子变异分为*MYB*或*MYBL1*变异型和丝裂原激活蛋白激酶(MAPK)通路变异型两大类[4]。(1)*MYB*或*MYBL1*变异型:*MYB*是含MYB/SANT结构域转录因子家族的基因之一,在控制造血及其他祖细胞增殖和分化中发挥重要作用,在白血病和实体肿瘤中扮演原癌基因的角色[12]。*MYBL1*基因的作用与之类似[12]。*MYB*或*MYBL1*变异形式包括基因拷贝数变异和基因融合(*MYB*伴侣基因有*QKI*、*ESR1*、*MMP16*、*MAML2*、*PCDHGA1*等,*MYBL1*伴侣基因有*RAD51B*、*MAML2*、*ZFHX4*、*TOX*等)[12-15]。尽管研究显示,*MYB*或*MYBL1*变异的低级别胶质瘤具有相似的DNA甲基化谱(DNA methylome patterns),但尚待多中心大样本研究进一步证实[14]。新版肿瘤分类结合组织学形态和分子特征将*MYB*或*MYBL1*变异型肿瘤分为**弥漫性星形细胞瘤,*MYB*或*MYBL1*变异型**和血管中心型胶质瘤(*MYB-QKI*融合常见)两种类型[4]。(2)MAPK通路变异型:MAPK信号转导通路是真核细胞重要的信号转导系统,通过三级激酶级联反应转导细胞外信号,参与细胞生长、分化、凋亡等多种生理过程,与肿瘤发生发展密切相关[12]。胶质瘤MAPK通路相关基因变异包括*NF1*、*BRAF*、*FGFR1*、*CRAF*、*NTRK*、*PTPN11*、*ROS1*等[12]。青年人多形性低级别神经上皮肿瘤(PLNTY)的分子变异包括*BRAF* V600E、*FGFR3-TACC3*融合、*FGFR2-CTNNA3*融合、*FGFR2-KIAA1598*融合[16-17]。**弥漫性低级别胶质瘤,MAPK通路变异型**的常见分子变异包括*FGFR1*酪氨酸激酶结构域(TKD)重复、*FGFR1*突变、*FGFR1*融合,以及*BRAF* V600E突变、*BRAF*融合、*BRAF*插入突变[18]。由于MAPK通路变异型肿瘤中部分分子变异缺乏特异性,故组织学形态和免疫组化染色等经典病理诊断方法和结果十分重要。

3. 儿童型弥漫性高级别胶质瘤 (1)组蛋白H3变异型:H3是参与真核细胞染色质结构的5个主要



IDH，isocitrate dehydrogenase，异柠檬酸脱氢酶；MAPK，mitogen-activated protein kinase，丝裂原激活蛋白激酶；RTK，receptor tyrosine kinase，受体酪氨酸激酶

图1 弥漫性胶质瘤分子遗传学特征

Figure 1 The genetic alterations of diffuse gliomas.

组蛋白之一，其序列变异和修饰状态在基因的动态和长期调控中发挥重要作用。新版肿瘤分类新增**弥漫性中线胶质瘤，H3 K27变异型**，进一步拓展弥漫性中线胶质瘤的定义[4]。根据分子变异分为3种亚型，即H3 K27突变型[19-20]（包括H3 K27M和H3 K27I）、*EGFR*突变型[21-22]（多累及丘脑）、H3野生伴EZHIP过表达型[23]。H3 K27突变发生于H3.3（编码基因*H3F3A*）和H3.1（编码基因*HIST1H3B/C*），其中*H3F3A*突变率约为*HIST1H3B/C*的3倍，且预后更差[20]。*TP53*突变、*ACVR1*突变、*PPM1D*突变和*PDGFRA*扩增等分子变异是H3 K27突变型弥漫性中线胶质瘤的常见分子遗传学特征[1]。另一携带组蛋白H3变异的肿瘤是**弥漫性半球胶质瘤，H3 G34突变型**，主要发生于大脑半球，表现为组蛋白H3.3第34位甘氨酸（Gly）被精氨酸（Arg）或缬氨酸（Val）取代的错义突变（H3.3 G34R/V）[24-25]。胶质瘤H3.3 G34突变主要发生于*H3F3A*基因，常伴*ATRX*突变、*TP53*突变[24]。（2）H3野生和IDH野生型：**弥漫性儿童型高级别胶质瘤，H3野生和IDH野生型**好发于儿童和青年，具备高级别肿瘤组织学特征，但分子病理学特征表现为IDH野生型、组蛋白H3野生型。根据DNA甲基化特征可以分为儿童型高级别胶质瘤RTK1型、儿童型高级别胶质瘤RTK2型和儿童型高级别胶质瘤MYCN型，其中，RTK2型伴高频率的*EGFR*扩增和*CDKN2A/B*纯合性缺失，预后较好；MYCN型伴高频率的*MYCN*扩增和*ID2*扩增，预后最差；RTK1型伴高频率*PDGFRA*扩增[26]。（3）婴儿型半球胶质瘤：主要发生于婴幼儿，位于大脑半球，分子遗传学特征为受体酪氨酸激酶（RTK）家族变异，主要包括NTRK家族基因（*NTRK1/2/3*）融合、*ROS1*融合、*MET*融合、*ALK*融合[28-29]。

4. 局限性星形细胞胶质瘤　毛细胞型星形细胞瘤最常见的分子变异是*KIAA1549-BRAF*融合（>70%），其他变异包括其他形式的*BRAF*融合（伴侣基因为*FAM131B*、*RNF130*等）、*BRAF* V600E突变、*NF1*突变、*FGFR1*变异（包括突变、融合或内部串联重复）等[1]。多形性黄色瘤型星形细胞瘤最常见的是*BRAF* V600E突变，其他变异包括*CDKN2A/B*纯合性缺失、第3和7号染色体获得等[1]；由于多形性黄色瘤型星形细胞瘤亦可部分携带*TERT*启动子突变[11]，因此诊断IDH野生型且仅*TERT*启动子突变肿瘤时，须注意组织学诊断的准确性。室管膜下巨细胞型星形细胞瘤发病与多发性硬化密切相关，故常伴*TSC1*和*TSC2*突变[1]。脊索样胶质瘤最常见的分子变异为*PRKCA* D463H突变[29-30]，部分肿瘤还可携带*BRAF* V600E突变[31]。有毛细胞样特征的高级别星形细胞瘤是新版肿瘤分类新定义的肿瘤，具有特征性DNA甲基化谱，但是组织学特征无特异性。

部分肿瘤表现出间变性和毛细胞样组织学特征，同时伴高频率MAPK通路基因变异（包括*BRAF*突变和融合、*NF1*突变、*FGFR1*突变和融合、*KRAS*突变），*CDKN2A/B*纯合性缺失和*ATRX*突变[32-34]。具有典型星形母细胞瘤组织学形态的肿瘤，若携带*MN1*变异（*MN1-BEND2*融合和*MN1-CXXC5*融合，常伴染色体22q和X染色体大量杂合性缺失），则可诊断为**星形母细胞瘤，*MN1*变异型**[35-37]。

5.胶质神经元和神经元肿瘤　MAPK通路相关基因变异是多种胶质神经元和神经元肿瘤的典型分子病理学特征。神经节细胞胶质瘤最常见的分子变异是*BRAF* V600E突变（20%～60%）[1]，还涉及多种*BRAF*融合（伴侣基因包括*MACF1*、*AGK*、*GNAI1*、*KIAA1549*、*FXR1*）[1,18]。胚胎发育不良性神经上皮肿瘤*FGFR1*酪氨酸激酶结构域重复、*FGFR1*突变和*FGFR1-TACC1*融合常见[18]，同时可检测到*BRAF* V600E突变或融合、*PDGFRA*突变等[18,38-39]。形成菊形团的胶质神经元肿瘤以*FGFR1*突变最常见（突变形式包括N546K和K656E），伴*PIK3CA*突变、*NF1*突变，偶见*PTPN11*突变[40]。弥漫性软脑膜胶质神经元肿瘤常见*KIAA1549-BRAF*融合和第1号染色体短臂缺失[41]，基于其DNA甲基化特征可以分为两种亚型，MC-1型（1p/19q共缺失比例较高）和MC-2型（伴染色体1q获得）[42]。其中，MC-2型无进展生存期（PFS）和总生存期（OS）较差，可能与染色体1q获得有关[43]。多结节和空泡状神经元肿瘤的典型分子变异也与MAPK通路相关，包括*BRAF*突变、*MAP2K1*变异（突变和阅读框内缺失）以及*FGFR2-INA*融合[44]。脑室外神经细胞瘤主要特征为*FGFR1-TACC1*融合（60%），亦可见*FGFR3-TACC3*融合和*FGFR1-EVI5*融合[45]。其他常见分子变异包括乳头状胶质神经元肿瘤常见的*PRKCA*融合（主要为*SLC44A1-PRKCA*融合，偶见*NOTCH1-PRKCA*融合）[46-47]以及小脑发育不良性神经节细胞瘤（Lhermitte-Duclos病）的*PTEN*胚系变异[1]。新版肿瘤分类新增的两种类型肿瘤中，黏液样胶质神经元肿瘤伴*PDGFRA* K385突变（K385L/I）[48-49]，其DNA甲基化特征与胚胎发育不良性神经上皮肿瘤相似；有少突胶质细胞瘤样特征和核簇的弥漫性胶质神经元肿瘤也是具有特征性DNA甲基化谱的肿瘤，伴第14号染色体单体，常发生于儿童[50]。

6.室管膜肿瘤　室管膜肿瘤的分子特征与其解剖部位、年龄等因素密切相关[51]。幕上室管膜瘤以融合基因为主要特征，可分为*ZFTA*融合阳性型和*YAP1*融合阳性型。*ZFTA*（*C11orf95*）的融合方式主要为*ZFTA-RELA*融合，导致核因子-κB（NF-κB）信号转导通路过度激活，预后相对较差[52-53]；其他融合方式包括*ZFTA-MAML2*，*ZFTA-NCOA1*等，*ZFTA*融合阳性的幕上室管膜瘤有相似的DNA甲基化特征[52]。*YAP1*融合的方式主要为*YAP1-MAMLD1*融合，部分为*YAP1-FAM118B*融合，*YAP1*融合阳性型主要发生于儿童（<3岁），预后相对较好[54-55]。非*ZFTA*非*YAP1*融合的幕上室管膜瘤比例较低，部分伴*MAML2 - ASCL2*、*MARK2 - ADCY3*、RTN3 - *NCOA1*、*MTMR3-NCOA3*等融合，部分缺乏典型分子病理学特征（组织学形态表现为伸长细胞型室管膜瘤或星形母细胞瘤）[54,56]。后颅窝室管膜瘤表现为特征性DNA甲基化谱，可分为PFA组和PFB组[57]。PFA组主要发生于婴幼儿，多数具有间变性特征，预后较差，组蛋白H3 K27me3表达缺失、CXorf67过表达；PFB组主要发生于大龄儿童或者成人，预后相对较好，组蛋白H3 K27me3表达正常[58-59]。染色体1q获得也是后颅窝室管膜瘤预后不良的生物学标记之一[51]。脊髓室管膜瘤中有一类以*MYCN*扩增为特征，具有很强的侵袭性和转移能力，预后较差[60]。由于脊髓室管膜瘤是2型神经纤维瘤病的特征性病变之一，故常伴*NF2*变异[1]。

7.胚胎性肿瘤　第四版修订版已对髓母细胞瘤进行分子分型，新版肿瘤分类延续这一分子分型体系，并予以更详细阐释[1,4]。WNT活化型最常见的分子变异为*CTNNB1*突变和第6号染色体单体，其次为*DDX3X*、*SMARCA4*、*KMT2D*、*TP53*、*PIK3CA*、*CSNK2B*等突变，APC胚系变异与该亚型的发生具有一定相关性[1,61]。SHH活化型的常见分子变异为*TP53*、*PTCH1*、*SUFU*、*SMO*等突变，*MYCN*、*GLI1*、*GLI2*等扩增，第9号染色体长臂、第10号染色体长臂、第17号染色体短臂缺失，以及*TERT*启动子突变等[61]。非WNT/非SHH活化型的常见分子变异为*MYC*、*MYCN*、*OTX2*等扩增，*GFI1*、*GFI1B*、*PRDM6*激活，*SMARCA4*、*KBTBD4*、*CTDNEP1*、*KMT2D*、*KDM6A*、*ZMYM3*、*KMT2C*、*KMT2D*等突变。基于DNA甲基化特征，SHH活化型分为α、β、γ、δ共4种亚型，非WNT/非SHH活化型分为8种亚型，不同亚型临床特征及驱动基因有所不同[62]。其他中枢神经系统胚胎性肿瘤中，非典型性畸胎样/横纹肌样肿瘤（AT/RT）典型分子变异为*SMARCB1*或*SMARCA4*

突变，基于DNA甲基化特征将*SMARCB1*突变的肿瘤分为3种亚型，即AT/RT-TYR型、AT/RT-SHH型和AT/RT-MYC型[63]。有多层菊形团的胚胎性肿瘤的典型分子变异为*C19MC*扩增[染色体19q13.42，涵盖一簇微小RNA(miRNA)，约90%]、*DICER1*突变(约5%)、*MIR17HG*扩增(miRNA17～92簇)[1,64-65]。**中枢神经系统神经母细胞瘤，*FOXR2*活化型**的组织学形态表现为神经母细胞瘤或节细胞神经母细胞瘤(GNB)，分子病理学特征为染色体重排致*FOXR2*过表达(包括重复、缺失、易位、线粒体基因插入等，部分产生*FOXR2*相关融合基因)，常伴染色体1q获得，具有独特的DNA甲基化特征[66]。有*BCOR*内部串联重复的中枢神经系统肿瘤典型的分子病理学特征为*BCOR*基因外显子15内部串联重复[66-67]。

8.脑膜瘤　脑膜瘤是最常见的原发性颅内肿瘤，其分子变异与性别、肿瘤解剖部位等具有一定相关性[68]。约60%的脑膜瘤可检出*NF2*变异，包括移码突变、等位基因失活、错义突变等[1,69]。非*NF2*变异的脑膜瘤较复杂，包括Hedgehog信号转导通路变异(*SMO*、*SUFU*、*PRKAR1A*、*PTCH1/2*等)、磷脂酰肌醇3-激酶(PI3K)信号转导通路变异(*PTEN*、*AKT1*、*PIK3CA*、*PIK3R1*等)、染色体重塑复合物变异(*SMARCB1*、*SMARCE1*、*ARID1A*、*PBRM1*等)及其他基因变异(*KLF4*、*BAP1*、*POLR2A*、*DMD*等)[70]。部分分子病理学特征与脑膜瘤组织学亚型相关，例如*TRAF7*和*KLF4*突变是分泌型脑膜瘤的分子生物学标志物[70]，*TRAF7*、*POLR2A*、*ATK1*突变是内皮型脑膜瘤的标志物[69-70]，*SMARCE1*突变是透明细胞型脑膜瘤的标志物[71]，*BAP1*和*PBRM1*突变是横纹肌样型脑膜瘤和乳头状型脑膜瘤的标志物[72-73]。另一部分与肿瘤恶性程度有关，如组蛋白H3 K27me3表达缺失与脑膜瘤复发密切相关[74-75]，*TERT*启动子突变和*CDKN2A/B*纯合性缺失是CNS WHO 3级脑膜瘤的分子生物学标志物[76-77]。此外，染色体1p、6q、9p、10、14q、18q、22q缺失，染色体1q、9q、12q、15q、20q获得以及某些基因(如*NRDG2*、*MEG3*、*PDGFR*等)DNA甲基化水平或表达变化也与脑膜瘤的发生发展密切相关[1,70]。基于DNA甲基化特征，脑膜瘤分为两组6型，其中，A组包括benign-1型、benign-2型、benign-3型和intermediate A型，B组包括intermediate B型、malignant型，不同亚型的解剖部位、驱动基因和临床预后等有所差异[78]。值得注意的是，发生于儿童的脑膜瘤有不同的分子病理学特征，除与肿瘤易感综合征相关的分子变异外，*YAP1*融合可能与部分*NF2*野生型儿童脑膜瘤有关[79]。

9.中枢神经系统其他肿瘤　**松果体区促纤维增生性黏液样肿瘤，*SMARCB1*突变型**发生于松果体区。免疫组化染色，胞核整合酶相互作用分子1(INI-1)表达缺失、而表达上皮膜抗原(EMA)和CD34，分子病理学特征为*SMARCB1*缺失(纯合性或杂合性缺失)或移码突变，与AT/RT-MYC型具有相似的DNA甲基化特征[80]。孤立性纤维性肿瘤的典型分子变异为*NAB2-STAT6*融合。免疫组化染色，胞核表达信号传导与转录激活因子6(STAT6)[1]。弥漫性脑膜黑色素细胞肿瘤包括脑膜黑色素细胞增生症和脑膜黑色素瘤病，*NRAS*(常见突变位点为Q61)突变频率较高[81]；局限性脑膜黑色素细胞肿瘤包括脑膜黑色素细胞瘤和脑膜黑色素瘤，则可检测到*GNAQ*(常见突变位点为Q209)、*GNA11*(常见突变位点Q209)、*CYSLTR2*(常见突变位点L129)、*PLCB4*(常见突变位点D630)、*BAP1*、*EIF1AX*、*SF3B1*等突变[82-83]。牙釉质细胞瘤型颅咽管瘤以*CTNNB1*突变为特征(约95%)，乳头状型颅咽管瘤以*BRAF* V600E突变为特征(81%～95%)，二者具有特征性DNA甲基化谱，新版肿瘤分类将上述肿瘤归为不同类型[4,84]。

二、常用分子病理学检测技术

中枢神经系统分子病理学检测应选择同类方法中结果稳定、重复性佳、特异性高的技术，同时亦应考虑样本量、肿瘤异质性、检测项目多少等，综合选择适宜的检测方法。检测过程中须严格参照国家卫生健康委员会制订的《肿瘤个体化治疗检测技术指南(试行)》进行标准化操作和质量控制。

1.免疫组化染色　免疫组化染色是一种经济、便捷、稳定的检测技术，利用抗体与组织内抗原的特异性结合，对抗原进行定性、定位和相对定量检测，是临床实践最常用的分子病理学检测方法[7]。除鉴别肿瘤起源、明确分化方向、判断增殖活性外，其在分子诊断方面的应用还包括：(1)直接反映分子变异类型和位点，如应用IDH1 R132H(H09)、BRAF V600E(VE1)、H3 K27M、H3 G34R、H3 G34V等突变特异性抗体。(2)通过编码蛋白表达水平或模式反映该基因变异，如胞核ATRX表达缺失、胞核β-catenin阳性、胞核STAT6阳性、胞核INI-1表达缺失等。(3)通过相关蛋白的表达推断基因变异，如L1细胞黏附分子(L1CAM)阳性与*ZFTA-RELA*融合、

LIN28A弥漫性阳性与*C19MC*扩增、H3 K27me3表达缺失与**后颅窝室管膜瘤，PFA组**等。由于NGS等其他高通量分子检测技术耗时长、费用高、对样本和检测设备要求较高，通过寻找不同免疫组化指标替代其他分子检测方法仍是目前病理学研究的方向之一。例如，对于**星形细胞瘤，IDH突变型**，免疫组化染色，胞核ATRX表达缺失和（或）P53弥漫性强阳性（>10%），可在不进行1p/19q检测的情况下明确诊断[7,9]。

2. 荧光原位杂交　荧光原位杂交（FISH）系通过荧光标记的DNA探针与胞核内DNA靶序列杂交，并在荧光显微镜下观察分析其结果的分子细胞遗传学技术，可对基因缺失、基因扩增、基因重排（断裂-分离探针）、基因融合（融合探针）等进行检测。FISH技术空间定位精确，敏感性和特异性较好，可检测隐匿或微小的染色体畸变和复杂核型，目前广泛应用于临床。中枢神经系统肿瘤的一些重要分子改变，如1p/19q共缺失、*EGFR*扩增、*MN1*重排、*KIAA1549-BRAF*融合等均可行FISH检测，但该项技术对操作和结果判读要求较高，且成本昂贵，通量低，故需多个分子诊断指标联合分析时，局限性较大。同时，整合FISH检测结果时还应注意潜在的假阳性或假阴性结果，如染色体1p/19q FISH探针仅覆盖1p36和19q13区域，无法区分部分缺失和整臂缺失[85]；小于探针长度的*CDKN2A*微小缺失无法经FISH检出，可能出现假阴性结果[86]。

3. Sanger测序、焦磷酸测序及其他基于聚合酶链反应的检测技术　（1）Sanger测序：系经典的DNA序列分析方法，可检测已知和未知的变异位点，包括少见的突变形式和确切的突变类型，如点突变、片段缺失，被认为是基因分型的“金标准”。但敏感性较低，等位基因突变率>20%方可检出且通常要求肿瘤细胞比例≥50%。（2）焦磷酸测序（pyrosequencing）：系一种可定量检测样品中单核苷酸突变水平的方法，适用于对已知短序列进行重测序分析，在表观遗传学研究中逐渐成为数据分析的“金标准”[87]，检测灵敏度为10%，重复性和精确性可与Sanger测序媲美，且通量较高，但缺点是无法对长片段进行分析。（3）其他基于聚合酶链反应（PCR）的检测技术：扩增阻滞突变系统（ARMS）-PCR、高分辨率熔解曲线（HRM）、数字PCR（digital PCR）、荧光实时定量PCR等，目前已用于中枢神经系统肿瘤*TERT*启动子突变、IDH突变、1p/19q共缺失、*MGMT*启动子甲基化等的检测[88-89]。NanoString数字化基因分析系统（NanoString nCounter Technology）系通过对探针上颜色分子条形码标记直接探测、计数以实现多重定量检测的技术，敏感性和准确性与荧光实时定量PCR相当，通量高，操作流程便捷[90]。该项技术通过对髓母细胞瘤核心基因表达进行检测，从而快速、稳定进行肿瘤分子分型，是目前髓母细胞瘤分子诊断的重要方法。

4. 第二代测序技术　NGS亦称大规模平行测序，可高通量地检测分析肿瘤驱动基因变异或治疗靶点，给患者带来治疗和生存获益。该项技术用于中枢神经系统肿瘤的分子诊断可以一次性获得覆盖基因组特定区域（启动子、外显子、内含子等）的高通量数据，同时可以检测多种基因变异形式（突变、插入或缺失、重排、拷贝数变异等）[91]。然而，传统NGS仅覆盖部分常见融合基因，无法检测所有可能出现的基因融合。因此，mRNA第二代测序（next-generation mRNA sequencing）有助于发现肿瘤诊断、分类和靶向治疗重要的、少见的、新的融合基因[92]。检测过程中采用的NGS技术平台应符合技术诊断标准，达到有效测序深度要求，遵循标准化检测流程，纳入必需的分子指标、试剂和方法以进行严格的管理和质控、对每个基因变异位点进行明确的注释和合理的遗传咨询[91]。

5. DNA甲基化谱　基于DNA甲基化特征的分析已经成为中枢神经系统肿瘤分类的重要方法之一，不仅可获得肿瘤的甲基化信息，还可获得拷贝数变异（扩增、缺失、基因融合等）。当与其他标准技术（如组织学）共同应用时，DNA甲基化分析是脑和脊髓肿瘤分类的有效辅助方法，尤其对于特征不显著、罕见的肿瘤类型和亚型[4,93]。与其他诊断技术一样，判读检测结果时须考虑组织学特征（如肿瘤细胞数目和纯度）。新版肿瘤分类假定几乎所有（但是并非所有）肿瘤类型均具有特征性DNA甲基化谱。

三、结论

新版肿瘤分类反映了目前知识背景下相关领域专家对中枢神经系统肿瘤的理解，应视为中枢神经系统肿瘤分类的一个阶段。相信新版肿瘤分类正式发布后，随着新型检测技术的大规模应用，一定会发现越来越多与肿瘤相关的新的分子变异；同时，随着相关临床试验的开展，我们对中枢神经系统肿瘤分类体系的理解也将更加深刻。希望这些

变化及其解释可以为神经病理学家和神经肿瘤学家的临床实践提供指导,从而使患者获益。

利益冲突 无

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下期内容预告 本刊2021年第10期报道专题为脑小血管病，重点内容包括：β淀粉样蛋白两种结局：淀粉样脑血管病与阿尔茨海默病；脑小血管病影像学标志物与认知功能障碍相关性研究——基于上海社区老年队列；常染色体显性遗传性脑动脉病伴皮质下梗死和白质脑病病理学特点及分子发病机制；脑白质高信号与近期单发皮质下梗死预后相关性研究；可独立行走的脑小血管病患者跌倒风险相关危险因素分析