·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)儿童型弥漫性胶质瘤分类解读

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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)与既往分类最大的区别之一为,将儿童型弥漫性低级别胶质瘤和儿童型弥漫性高级别胶质瘤归为独立的肿瘤类型,这是由于儿童型弥漫性胶质瘤虽然与成人型在组织学形态上较为相似,但分子遗传学特征完全不同,不同分子遗传学特征的预后各异,因此需要不同的治疗策略。临床医师亟需了解这些好发于儿童的肿瘤类型的临床诊疗特点。本文拟根据新版肿瘤分类描述的病理学特征并结合文献,总结儿童型弥漫性胶质瘤的影像学和病理学诊断特征,以及临床表现、治疗和预后,从临床诊疗角度对儿童型弥漫性胶质瘤进行初步解读,以为临床同道提供建议。

【关键词】 神经胶质瘤; 中枢神经系统肿瘤; 指南; 世界卫生组织; 磁共振成像; 病理学; 儿童; 综述

Interpretation on pediatric-type diffuse gliomas 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) was released. One of the biggest differences between new edition tumors classification and the previous editions is that the pediatric-type diffuse low-grade gliomas and the pediatric-type diffuse high-grade gliomas are classified into independent tumor families. This change is based on the fact that although pediatric-type diffuse gliomas morphologically resemble their adult counterparts, while their molecular genetics features are completely different, and the prognosis of these tumors with different molecular genetics features is different accordingly, so different treatment strategies are needed. Physicians and surgeons need to know of the features of these pediatric-type diffuse gliomas. This paper reviews the existing literature, and the pathological reports and imaging data of our hospital, summarizes the imaging and pathological diagnostic features, as well as the clinical manifestations, prognostic features and treatment suggestions of these pediatric-type diffuse gliomas. This review will provide an annotation from the view of diagnosis and treatment on pediatric-type diffuse gliomas for the physicians and surgeons.

【Key words】 Glioma; Central nervous system neoplasms; Guidelines; World Health Organization; Magnetic resonance imaging; Pathology; Child; Review

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孙崇然与许晶虹对本文有同等贡献

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自20世纪70年代世界卫生组织(WHO)主持编写的中枢神经系统肿瘤分类第一版问世,至2021年6月WHO中枢神经系统肿瘤分类(第五版,以下简称新版肿瘤分类)发布,历经40余年,包括2016年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)在内共6个版本。新版肿瘤分类从肿瘤分类形式上看与第四版修订版较为相似,主要原因是后者已对中枢神经系统肿瘤的诊断方法进行重大调整,首次引入分子诊断标准,但此种调整并不完善。随后成立的中枢神经系统肿瘤分类分子信息与分类实践联盟-非WHO官方组织(cIMPACT-NOW)对中枢神经系统肿瘤分子诊断分型及时进行补充和说明,并发布7个不同方面的更新。新版肿瘤分类经过进一步调整并吸纳上述更新,形成一种组织学和分子特征相结合的诊断模式,这种模式有利于更精确地诊断已充分了解的肿瘤类型,且有效区别尚不明确的肿瘤类型;以及更客观地反映肿瘤的发生、发展机制和预后特征并更有效指导治疗。

对于神经上皮肿瘤而言,儿童型与成人型在组织学形态上较为相似,但分子表型完全不同,新版肿瘤分类特别指出,儿童型肿瘤系指主要发生于儿童的肿瘤,发病年龄是其生物学特征之一,但并非诊断标准。儿童型肿瘤同样可发生于成人,特别是青年。在精准医学背景下,治疗方法要求个体化和精准化,故不同肿瘤类型或分类的治疗必定存在差异。本文拟对新版肿瘤分类儿童型弥漫性胶质瘤的诊断、临床治疗、预后进行分类解读,以为临床同道提供诊断与治疗建议。

一、儿童型弥漫性胶质瘤的分类

由于儿童型弥漫性胶质瘤的发病机制、治疗靶点、预后均与成人型有很大不同,新版肿瘤分类将儿童型弥漫性胶质瘤单独分为两大类,即儿童型弥漫性低级别胶质瘤和儿童型弥漫性高级别胶质瘤(表1),并在第四版修订版基础上新增6种肿瘤类型,即**弥漫性星形细胞瘤,*MYB*或*MYBL1*变异型**;青年人多形性低级别神经上皮肿瘤;**弥漫性低级别胶质瘤,MAPK通路变异型**;**弥漫性半球胶质瘤,H3 G34突变型**;**弥漫性儿童型高级别胶质瘤,H3野生和IDH野生型**;婴儿型半球胶质瘤。同时修改了1种肿瘤类型,即**弥漫性中线胶质瘤,H3 K27变异型**,因有多种分子机制参与,故将H3 K27M突变修改为H3 K27变异。

二、儿童型弥漫性低级别胶质瘤

儿童型弥漫性胶质瘤虽然在组织学形态上与成人型有相似之处,但其发病部位和分子病理学特征与成人型有很大不同。参照既往WHO中枢神经系统肿瘤分类标准,此类肿瘤之预后差异较大。2020年,Ryall等[1]根据分子诊断指标,将儿童型低级别胶质瘤分为3种不同风险组:低风险组包括*BRAF*等变异或*NF1*变异驱动的肿瘤,随访10年几乎无进展,20年几乎无死亡,对于此类肿瘤推荐保守治疗;中风险组包括*BRAF* V600E突变不伴*CDKN2A*缺失,*FGFR1*单核苷酸变异(SNV),*IDH1* R132H突变或*MET*突变的肿瘤,此类肿瘤可持续进展,20年总生存率为81%,需多疗程治疗和更长期

表1 儿童型弥漫性胶质瘤的分类

Table 1. The classification of pediatric-type diffuse gliomas

英文名称	中文名称	CNS WHO分级
Pediatric-type diffuse low-grade gliomas	儿童型弥漫性低级别胶质瘤	
Diffuse astrocytoma, *MYB*- or *MYBL1*-altered	弥漫性星形细胞瘤,*MYB*或*MYBL1*变异型	1级
Polymorphous low-grade neuroepithelial tumor of the young	青年人多形性低级别神经上皮肿瘤	1级
Angiocentric glioma	血管中心型胶质瘤	1级
Diffuse low-grade glioma, MAPK pathway altered	弥漫性低级别胶质瘤,MAPK通路变异型	未分级
Pediatric-type diffuse high-grade gliomas	儿童型弥漫性高级别胶质瘤	
Diffuse midline glioma, H3 K27-altered	弥漫性中线胶质瘤,H3 K27变异型	4级
Diffuse hemispheric glioma, H3 G34-mutant	弥漫性半球胶质瘤,H3 G34突变型	4级
Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype	弥漫性儿童型高级别胶质瘤,H3野生和IDH野生型	4级
Infant-type hemispheric glioma	婴儿型半球胶质瘤	4级

CNS, central nervous system, 中枢神经系统; MAPK, mitogen-activated protein kinase, 丝裂原激活蛋白激酶; IDH, isocitrate dehydrogenase, 异柠檬酸脱氢酶

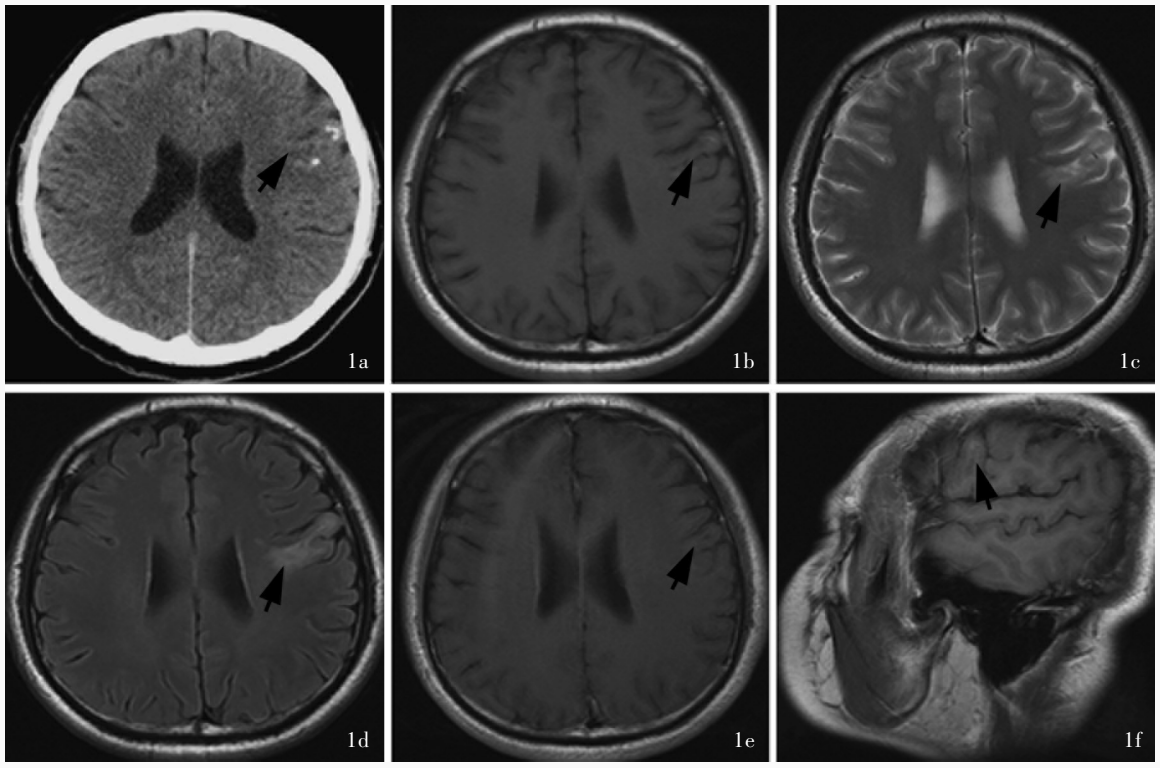


图1 男性患者，25岁，因反复面部抽搐6年入院，临床诊断为左侧额叶血管中心型胶质瘤。头部影像学检查所见 1a 横断面CT显示左侧额叶混杂密度影，病灶内可见钙化（箭头所示） 1b 横断面T_1WI显示病灶呈等或稍高信号（箭头所示） 1c 横断面T_2WI显示病灶呈高信号（箭头所示） 1d 横断面FLAIR成像显示病灶呈高信号（箭头所示） 1e，1f 横断面和矢状位增强T_1WI显示病灶强化不明显（箭头所示）

Figure 1 A 25 year-old male was admitted to the hospital for recurrent facial spasm for 6 years, the clinical diagnosis was angiocentric glioma of the left frontal lobe. Head MRI findings Axial CT showed mixed density lesion in left frontal lobe with calcification (arrow indicates, Panel 1a). Axial T_1WI showed isointensity or slight hyperintensity of the lesion (arrow indicates, Panel 1b). Axial T_2WI (Panel 1c) and FLAIR (Panel 1d) showed hyperintensity of the lesion (arrows indicate). Axial (Panel 1e) and sagittal (Panel 1f) enhanced T_1WI showed the enhancement of the lesion was not obvious (arrows indicate).

随访；高风险组包括*H3F3A* K27M突变或*BRAF* V600E突变伴*CDKN2A*缺失的肿瘤，此类肿瘤不可避免进展，患儿通常死于疾病本身，推荐积极治疗，并引入新的靶向药物。一项纳入289例儿童低级别胶质瘤患者的研究同样发现类似特点[2]。因此，新版肿瘤分类根据分子生物学标志物对儿童型弥漫性低级别胶质瘤进行分类。

1. 弥漫性星形细胞瘤，*MYB*或*MYBL1*变异型

此类肿瘤的影像学表现与成人型弥漫性低级别胶质瘤相似，呈浸润性生长，主要累及大脑半球，典型表现为：CT常见瘤内钙化灶；MRI呈T_1WI低信号、T_2WI和FLAIR成像高信号，增强扫描强化不明显，DWI扩散不受限；磁共振波谱（MRS）可见胆碱（Cho）峰升高，N-乙酰-天冬氨酸（NAA）峰降低[3]。**弥漫性星形细胞瘤，*MYB*或*MYBL1*变异型**是由星形细胞样细胞构成的弥漫浸润性肿瘤，其组织学形态无法与星形细胞瘤相鉴别，但是具有*MYB*或*MYBL1*变异且IDH野生。肿瘤细胞增殖指数低，属于CNS WHO 1级。*MYB*和*MYBL1*在儿童型弥漫性星形细胞瘤中有重要作用，发生*MYB*扩增的患儿预后较好，与未发生*MYB*扩增者相比，无进展生存期（PFS）更长，故将发生*MYB*扩增的肿瘤纳入低风险组[2]，并推荐此类患儿接受保守治疗[1]。

2. 血管中心型胶质瘤 此类肿瘤是一种发生在儿童和青年的相对罕见的神经上皮肿瘤类型，病程中常伴癫痫发作，部分患者特别是手术未全切除患者术后仍有癫痫发作[4]。大多数肿瘤位于幕上皮质及皮质下白质，常单发于一个脑叶，最常见于颞叶（39%），其次是额叶（30%）和顶叶（15%），发生于其他脑叶的可能性较低，也有发生于脑干（2%）和丘脑（1%）的报道[4]。CT表现多样，可呈低、高或混杂密度，部分可见钙化[5]；MRI呈T_1WI低、等或高信号，T_2WI高信号，增强扫描无强化或仅轻度强化，部分病灶可见囊性变（图1），DWI轻微扩散受限；MRS显

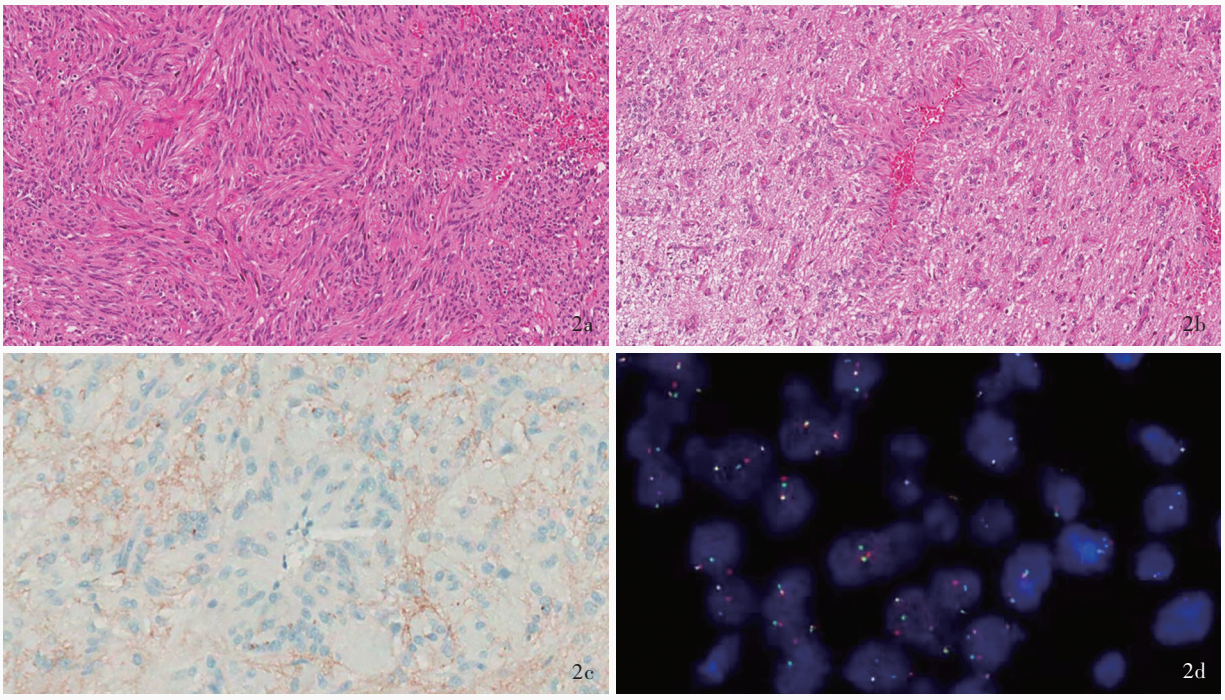
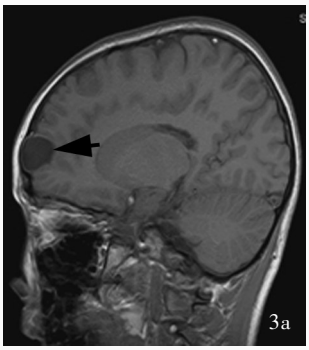


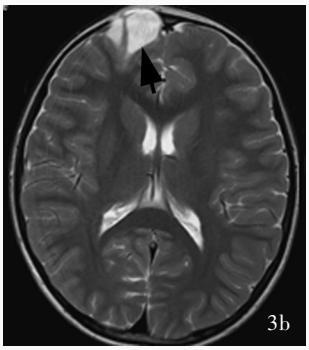
图2 男性患者，31岁，因癫痫发作入院，临床诊断为左侧额叶血管中心型胶质瘤，显微镜下切除肿瘤。术后病理学检查所见 2a 肿瘤细胞由形态一致的双极梭形细胞组成 HE染色 低倍放大 2b 血管周围可见假"菊形团"结构 HE染色 中倍放大 2c 肿瘤细胞胞核旁EMA呈点状阳性 免疫组化染色(EnVision二步法) 中倍放大 2d FISH显示MYB双色分离，提示MYB重排 荧光原位杂交(FISH)染色 高倍放大

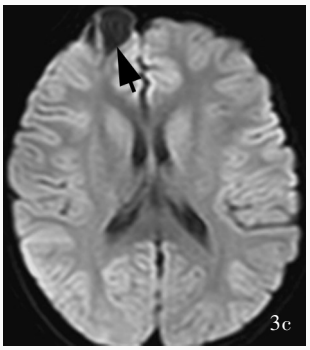
Figure 2 A 31 year-old male was admitted to the hospital for seizures, the clinical diagnosis was angiocentric glioma of the left frontal lobe. Microscopic resection of the tumor was performed. Pathological examination findings after operation The neoplasm was composed of monomorphous bipolar spindle cells (Panel 2a). HE staining low power magnified Perivascular pseudorosettes were seen (Panel 2b). HE staining medium power magnified The tumor cells exhibited dot-like cytoplasmic labelling for EMA (Panel 2c). Immunohistochemical staining (EnVision) medium power magnified *MYB* dual-color, break-apart FISH demonstrated *MYB* gene rearrangement (Panel 2d). FISH staining high power magnified

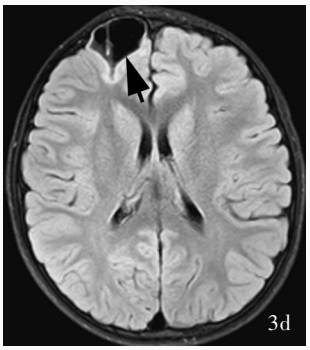
示NAA峰降低，Cho峰升高不明显。组织学形态相当于CNS WHO 1级，典型生长模式为，呈单形性、弥漫性浸润的双极梭形细胞以同心圆或假"菊形团"方式排列在皮质血管周围(图2)，肿瘤细胞形态较一致，胞核细长，染色质呈细颗粒状，核仁不明显；超微结构观察，纤毛和微绒毛填充的微腔由细长的中间连接包围，提示具有室管膜分化特征；免疫组化染色，肿瘤细胞Ki-67抗原标记指数较低(1%～5%)；标志性分子事件为*MYB-QKI*融合。治疗方法主要是外科手术，手术全切除可明显提高癫痫发作控制率[4]。Ampie等[4]发现，37例手术全切除的患者中仅1例术后癫痫发作复发，16例手术次全切除的患者中7例术后癫痫发作复发。由此可见，外科手术的目的除减轻肿瘤负荷外，还要控制癫痫发作，推荐参照致痫灶切除术标准实施手术。

3.青年人多形性低级别神经上皮肿瘤 青年人多形性低级别神经上皮肿瘤(PLNTY)亦为一种癫痫相关肿瘤。全基因组DNA甲基化分析显示，此类肿瘤具有独特的DNA甲基化特征，常发生*BRAF*突变或*FGFR2/3*融合[6]。除少数枕叶病变患者以头痛、头晕、视力障碍为首发症状外，大多数患者在明确诊断青年人多形性低级别神经上皮肿瘤前即已罹患1～21年的难治性癫痫[7]。肿瘤常呈膨胀性生长，钙化和囊性变常见，MRI表现为T_1WI低信号、T_2WI和FLAIR成像高信号，增强扫描局部强化；PWI可见病灶局部脑血容量(CBV)增多。典型影像学表现为病灶位于皮质，部分界限不清，CT呈颗粒样钙化，以及T_2WI"椒盐征"[6-9](图3)。青年人多形性低级别神经上皮肿瘤是胶质或胶质神经元分化的肿瘤，组织学形态表现为分化良好但不均匀的少突胶质细胞瘤样成分，伴梭形细胞、纤维样星形细胞和室管膜瘤样假"菊形团"成分，少突胶质细胞瘤样成分为其特征性表现(图4)；免疫组化染色，肿瘤细胞及其周围区域神经元CD34呈强阳性，丝裂原激活蛋白激酶(MAPK)信号转导通路异常激活[6,10]，属CNS WHO 1级；分子病理学检测，存在*BRAF* V600E突









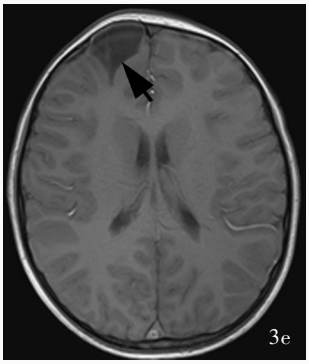
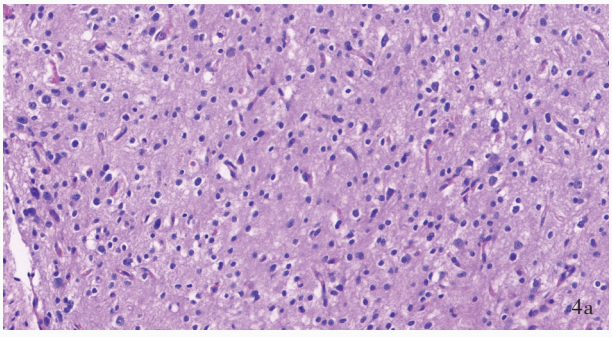
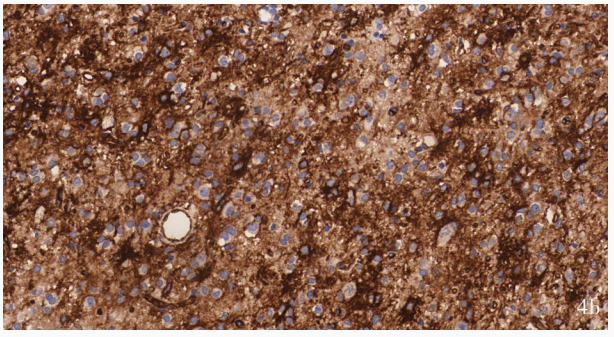
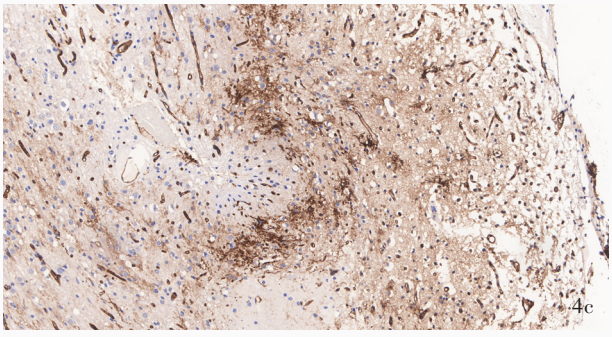


图3 男性患儿，8岁，因反复癫痫发作11个月入院。临床诊断为右侧额叶青年人多形性低级别神经上皮肿瘤。头部影像学检查所见 3a 矢状位T_1WI显示，右侧额叶异常低密度影，呈膨胀性生长（箭头所示） 3b 横断面T_2WI显示病灶呈高信号，其内可见一等信号分隔影（箭头所示） 3c 横断面DWI显示病灶呈低信号，其内可见一等信号分隔影（箭头所示） 3d 横断面FLAIR成像显示病灶呈低信号，其内可见一等信号分隔影（箭头所示） 3e 横断面增强T_1WI显示病灶无明显强化（箭头所示）

Figure 3 An 8 year-old male was admitted to hospital for recurrent seizures for 11 months, the clinical diagnosis was polymorphous low-grade neuroepithelial tumor of the young of the right frontal lobe. Head MRI findings Sagittal T_1WI showed the lesion was expanded with hypointensity in right frontal lobe (arrow indicates, Panel 3a). Axial T_2WI showed hyperintensity of the lesion and there was an isointensity separation shadow (arrow indicates, Panel 3b). Axial DWI (Panel 3c) and FLAIR (Panel 3d) showed hypointensity of the lesion could be seen inside (arrows indicate). Axial enhanced T_1WI did not show obvious enhancement of the lesion (arrow indicates, Panel 3e).







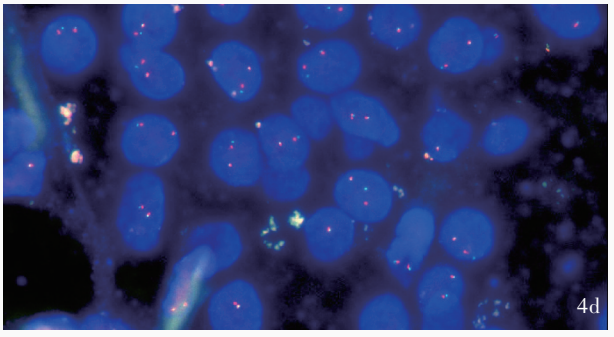
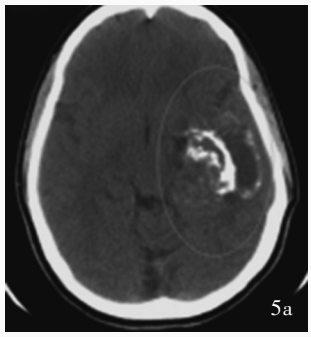
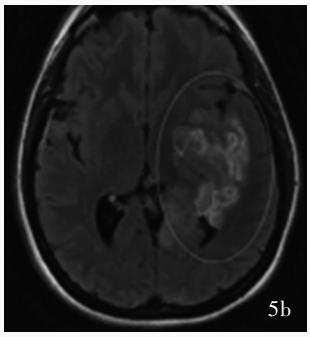


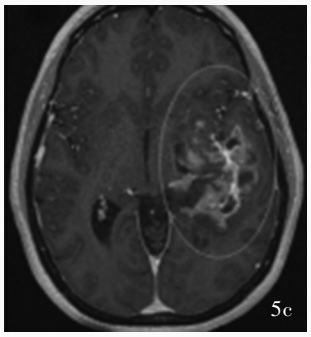
图4 图3患儿术后病理学检查所见 4a 肿瘤细胞呈少突胶质细胞样，可见薄壁血管 HE染色 中倍放大 4b 肿瘤细胞胞质CD34呈弥漫性阳性 免疫组化染色（EnVision二步法） 中倍放大 4c 肿瘤周围神经元CD34呈毛刺状阳性 免疫组化染色（EnVision二步法） 中倍放大 4d FISH显示*FGFR2*双色分离，提示*FGFR2*重排 FISH染色 高倍放大

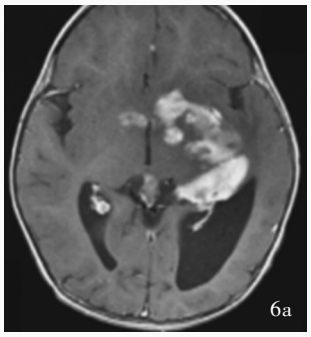
Figure 4 Pathological examination findings of Figure 3 patient after operation Tumor cells were composed of oligodendroglioma-like glial cell component with thin-walled vessels (Panel 4a). HE staining medium power magnified Tumor cells were intense CD34 immunoreactivity in both tumor cells (Panel 4b), and peripherally associated ramified neural elements (Panel 4c). Immunohistochemical staining (EnVision) medium power magnified *FGFR2* dual-color, break-apart FISH demonstrated *FGFR2* gene rearrangement (Panel 4d). FISH staining high power magnified

变或FGFR融合，常见融合基因有*FGFR2-KIAA1598*、*FGFR2-CTNNA3*和*FGFR3-TACC3*[6-7]。*BRAF* V600E突变持续激活BRAF激酶，从而使MAPK通路持续活化[11]；FGFR融合基因亦通过MAPK通路驱动增强下游信号，使细胞无限分裂、增殖，进而形成肿瘤[12]。有趣的是，青年人多形性低级别神经上









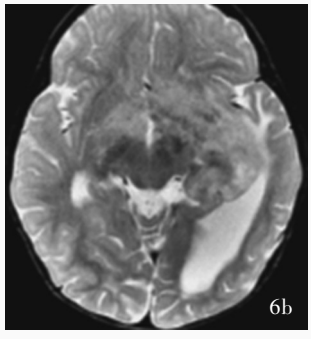


图5 皮质区*BRAF* V600E突变的**弥漫性低级别胶质瘤，MAPK通路变异型**的影像学特点[15] 5a 横断面CT显示，左侧颞岛枕叶混杂密度影，病灶内可见粗大钙化 5b 横断面FLAIR成像显示病灶呈不均匀高信号 5c 横断面增强T_1WI显示病灶呈明显不均匀强化 **图6** 间脑区*BRAF* V600E突变的**弥漫性低级别胶质瘤，MAPK通路变异型**的影像学特点[16] 6a 横断面增强T_1WI显示间脑区占位性病变，病灶内可见多发结节样明显强化 6b 横断面T_2WI显示病灶跨中线，呈浸润性生长，肿瘤周围水肿较轻

Figure 5 Imaging findings of a case with cortical **diffuse low-grade glioma, MAPK pathway altered** (with *BRAF* V600E mutation)[15] Axial CT showed mixed density in the left temporal insular occipital lobes with a massive calcification (Panel 5a). Axial FLAIR showed heterogeneous hyperintensity of the tumor (Panel 5b). Axial enhanced T_1WI showed heterogeneous enhancement of the tumor (Panel 5c). **Figure 6** Imaging findings of a case with diencephalic **diffuse low-grade glioma, MAPK pathway altered** (with *BRAF* V600E mutation)[16] Axial enhanced T_1WI indicated space occupying lesions in the diencephalon and the tumor showed multinodular with obvious enhancement (Panel 6a). Axial T_2WI indicated that the lesions showed invasive growth with mild peritumoral edema (Panel 6b).

皮肿瘤的*BRAF* V600E突变和FGFR融合相互排斥，即仅存在一种分子改变，最终导致MAPK通路异常激活。临床最易误诊为少突胶质细胞瘤，由于二者均存在癫痫病史，均位于大脑皮质浅层且伴钙化，组织学形态十分相似，但是青年人多形性低级别神经上皮肿瘤预后极好，而少突胶质细胞瘤属CNS WHO 2级或3级，预后较差。手术全切除是首选治疗方法，可明显改善癫痫发作。Gupta等[7]对8例青年人多形性低级别神经上皮肿瘤切除术后患者进行长达89个月的随访，发现仅1例术后出现1次癫痫发作。Tateishi等[13]收集1例有*BRAF* V600E突变的青年人多形性低级别神经上皮肿瘤患者术后标本，采用BRAF抑制剂达拉菲尼进行试验，发现达拉菲尼可适度抑制肿瘤细胞增殖活性，提示靶向药物可在手术无法切除区域有较好的应用价值。

4. 弥漫性低级别胶质瘤，MAPK通路变异型

MAPK信号转导通路对细胞的正常发育十分重要，但多种肿瘤均出现MAPK通路调节异常，脑胶质瘤*BRAF* V600E突变、*FGFR1*酪氨酸激酶结构域（TKD）重复和*FGFR1*突变可导致MAPK通路异常激活，是肿瘤预后不良的标志物。cIMPACT-NOW更新4将**弥漫性低级别胶质瘤，MAPK通路变异型**分为*FGFR1*酪氨酸激酶结构域重复、*FGFR1*突变、*BRAF* V600E突变，以及其他MAPK通路变异4种类型[14]。此类肿瘤的影像学改变可能与病变部位和组织学类型有关：位于大脑皮质的病灶内钙化较常见，肿瘤细胞形态与少突胶质细胞较为接近，T_1WI呈低信号、T_2WI呈高信号，增强扫描呈明显不均匀强化（图5）[15]；位于间脑的病灶多呈实性、分叶状，增强扫描呈明显均匀强化，无坏死、水肿和占位效应（图6）[16]。**弥漫性低级别胶质瘤，MAPK通路变异型**是一种罕见肿瘤，具有弥漫性、浸润性生长模式，组织学形态呈星形细胞瘤或少突胶质细胞瘤样。与血管中心型胶质瘤相比，缺少特征性围绕血管中心的生长方式、上皮膜抗原（EMA）点状阳性和*MYB*变异；与青年人多形性低级别神经上皮肿瘤相比，缺少肿瘤细胞CD34弥漫性强阳性。新版肿瘤分类对**弥漫性低级别胶质瘤，MAPK通路变异型**并未给出具体的WHO分级，主要原因为病例数较少，且缺乏足够的病程资料。Yang等[2]将*BRAF* V600E突变的**弥漫性低级别胶质瘤，MAPK通路变异型**纳入中风险组。Lassaletta等[17]认为靶向药物可以作为潜在的治疗方法，他们在接受BRAF抑制剂治疗的6例伴*BARF* V600E突变的儿童低级别胶质瘤患者中发现肿瘤细胞反应显著，可见49%～80%的肿瘤细胞减少。因此推荐此类患儿接受多疗程的治

疗和更长期的随访。

三、儿童型弥漫性高级别胶质瘤

儿童型弥漫性高级别胶质瘤通常具有肿瘤进展迅速、易对各种治疗产生抵抗的特点，因此此类患儿往往成为新的治疗模式的临床试验潜在对象，特别是免疫治疗。免疫治疗系通过刺激机体免疫系统，增强免疫反应以杀伤肿瘤细胞的方法，针对儿童型弥漫性胶质瘤的免疫治疗包括免疫检查点阻断、嵌合抗原受体T细胞（CAR-T）疗法和疫苗疗法[18]。免疫检查点是免疫系统中起抑制作用的调节分子，可防止免疫系统的过度损伤，肿瘤细胞过度表达免疫检查点分子，出现免疫逃逸现象，免疫检查点抑制剂可以在肿瘤微环境（TME）中阻断这一过程，恢复T淋巴细胞活化，发挥杀伤肿瘤细胞的作用。浙江大学医学院附属第二医院的基于体素的研究发现，儿童型弥漫性胶质瘤患者免疫检查点表达率与相应类型的成人型接近，特别是B7H3分子表达率接近60%，为儿童型弥漫性胶质瘤的免疫治疗提供一定的理论依据[19]。目前有多项临床试验正在开展中[20]。

1. **弥漫性中线胶质瘤，H3 K27变异型** **弥漫性中线胶质瘤，H3 K27变异型**的预后很差，2年生存率＜10%。此类肿瘤具有发生于中枢神经系统中线位置，呈弥漫性生长，具有胶质瘤病理学特征和H3 K27变异共4项特点，上述4项特点在诊断时缺一不可[21]。对各种临床治疗方法均不敏感，目前有较多关于靶向药物和细胞免疫治疗的研究，例如Imipridone ONC201和IDO1抑制剂Indoximod均具有早期临床活性[22]；CAR-T疗法具有较强的治疗潜力[23]。**弥漫性中线胶质瘤，H3 K27变异型**的MRI表现多样，常规MRI对判断H3 K27是否变异的价值有限，表观扩散系数（ADC）值通常呈中度降低（图7）。影像组学中的纹理分析有助于区分伴或不伴H3 K27变异[24-27]。组织学形态可见肿瘤细胞弥漫性浸润邻近及较远脑实质，核分裂象可见，但并非病理诊断的必要条件；此外还可见微血管增生及坏死（图8）。免疫组化染色，H3 K27M特异性较高，常伴H3 K27me3表达缺失，通过对比DNA甲基化谱、临床表现、病理学特征及预后等发现，**弥漫性中线胶质瘤，H3 K27变异型**与既往分类中的H3 K27M突变型十分相似（图9）[28]。研究显示，弥漫性中线胶质瘤高表达EZHIP/CXorf67，通过干扰多梳抑制复合物2（PRC2）活性而阻碍H3 K27me3甲基化；部分肿瘤还存在*EGFR*突变[29]。此外，还可见H3 K27I突变及H3.2 K27M突变的报道。基于此，新版肿瘤分类将**弥漫性中线胶质瘤，H3 K27M突变型**修改为**弥漫性中线胶质瘤，H3 K27变异型**[30]。由于此类肿瘤几乎不可避免地复发，患者可能需要接受再程放疗。Janssens等[31]对31例复发的弥漫性内生型脑桥胶质瘤（DIPG）患者行再程放疗，发现总生存期为13.7个月，与未行再程放疗的患者相比，中位无进展生存期相似，但是中位总生存期延长（13.7个月对10.3个月，$P=0.04$）；且再程放疗的生存获益与放疗结束和首次进展之间的时间间隔相关，时间间隔越长、生存获益越佳，因此推荐进展的弥漫性内生型脑桥胶质瘤患者应予以再程放疗。

2. **弥漫性半球胶质瘤，H3 G34突变型** **弥漫性半球胶质瘤，H3 G34突变型**是一种成熟组蛋白H3.3第34位发生错义突变的大脑半球弥漫性IDH野生型胶质瘤，通常发生于儿童和青年人[32]。其致病机制与成熟组蛋白H3.3发生错义突变相关，即第34位甘氨酸被精氨酸或缬氨酸取代（H3.3 G34突变）。颞叶和顶叶最常受累[33]，约占80%，病灶多位于额叶或颞岛叶皮质下，界限不清。头部CT呈等或稍高密度；MRI呈T_1WI等或低信号、T_2WI或FLAIR成像高信号，DWI扩散受限且呈高信号，增强扫描无强化或仅轻度强化；MRS显示Cho峰升高伴低的脂质乳酸（Lac）峰，肿瘤周围水肿较轻[34-36]（图10）。典型组织学形态为高级别的浸润性星形细胞瘤，核分裂象常见，伴微血管增生和（或）坏死；部分肿瘤细胞形态类似中枢神经系统胚胎性肿瘤，或可见排列一致且密集的小蓝圆细胞，无明显微血管增生或坏死[33]。其分子病理学特征为TP53突变、ATRX和Olig-2核表达缺失，O^6-甲基鸟嘌呤-DNA甲基转移酶（MGMT）甲基化（图11，12）。此类患者中位无进展生存期为9个月，中位总生存期为22个月，约88%患者发生局部肿瘤复发，小部分患者（8%）出现软脑膜广泛转移，MGMT甲基化是预后相对良好的生物学标志物，而癌基因（包括*PDGFRA*、*CCND2*、*CDK6*）扩增与预后不良显著相关[33]。研究显示，成人发生的**弥漫性半球胶质瘤，H3 G34突变型**患者中位总生存期与**胶质母细胞瘤，IDH野生型**相近，但较**弥漫性中线胶质瘤，H3 K27变异型**短[35-36]。

3. **弥漫性儿童型高级别胶质瘤，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**在DNA甲基化和细胞遗传学改变方面

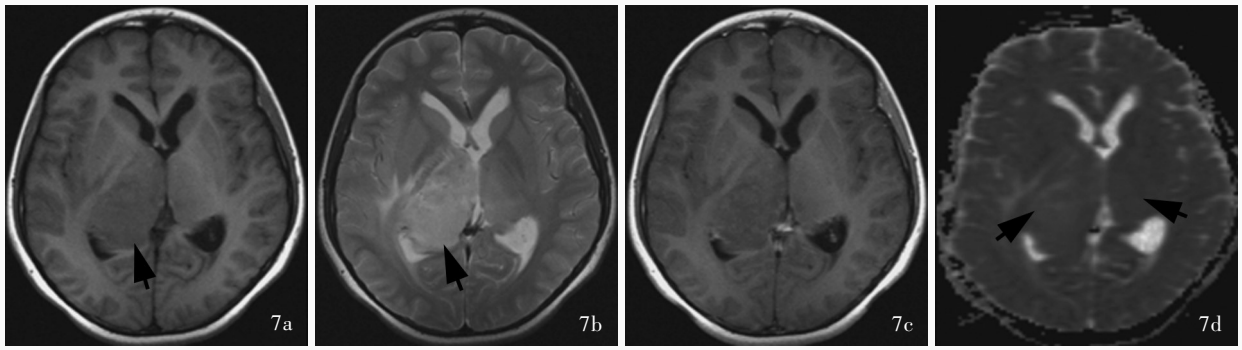


图7 男性患儿，9岁，主因头痛1个月伴幻视7 d入院。临床诊断为**弥漫性中线胶质瘤，H3 K27变异型**（右侧丘脑病变相对明显）。头部影像学检查所见 7a 横断面T_1WI显示双侧丘脑占位性病变，以右侧显著，呈稍低信号（箭头所示） 7b 横断面T_2WI显示病灶呈高信号（箭头所示） 7c 横断面增强T_1WI显示病灶强化不明显 7d 横断面ADC显示病灶呈稍高信号，右侧丘脑局部信号稍低（箭头所示）

Figure 7 A 9 year-old male was admitted to the hospital for headache for 1 month and vision hallucination for 7 d, the clinical diagnosis was right thalamic **diffuse midline glioma, H3 K27-altered**. Head MRI findings Axial T_1WI showed space occupying lesions in bilateral thalamus with slight hypointensity and right thalamus was prominent (arrow indicates, Panel 7a). Axial T_2WI showed hyperintensity of tumor (arrow indicates, Panel 7b). Axial enhanced T_1WI showed no obvious enhancement (Panel 7c). ADC map showed slight hyperintensity of the lesion and there was focal diffusion restriction in right thalamus (arrows indicate, Panel 7d).

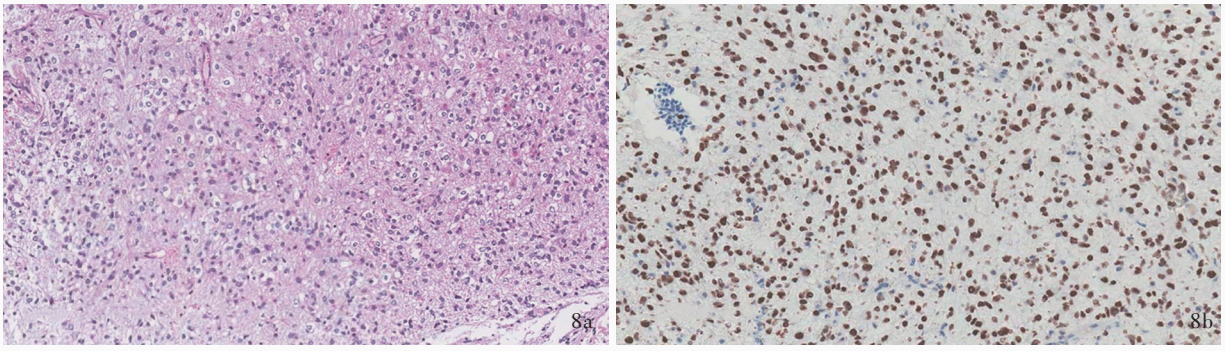


图8 男性患儿，9岁，因左侧腰痛20余天入院，影像学显示$T_{5\sim8}$水平髓内占位性病变，行开颅肿瘤切除术，术后病理诊断为**弥漫性中线胶质瘤，H3 K27变异型**。病理学检查所见 中倍放大 8a 肿瘤细胞密度中等，形态尚温和，未见明确微血管增生及坏死HE染色 8b 肿瘤细胞核H3 K27M呈弥漫性强阳性 免疫组化染色（EnVision二步法）

Figure 8 A 9 year-old male was admitted to the hospital for left backache for more than 20 d. Imaging showed intramedullary occupying lesion at T_{5-8} levels. Resection of the tumor was performed. The pathological diagnosis was **diffuse midline glioma, H3 K27-altered**. Pathological examination findings medium power magnified The diffusely infiltrating glioma showed medium cellularity with mild morphological abnormality, and microvascular hyperplasia or necrosis was not observed (Panel 8a). HE staining Tumor cells showed strong nucleus labelling for H3 K27M (Panel 8b). Immunohistochemical staining (EnVision)

具有显著的分子异质性。2016年的一项仍使用胶质母细胞瘤（GBM）命名的研究采用全基因组DNA甲基化分析的综合方法和其他检测方法进行突变和拷贝数变异验证，描述此类肿瘤的3种生物亚型，即儿童GBM_MYCN（*MYCN*扩增）、儿童GBM_RTK1（*PDGFRA*扩增）和儿童GBM_RTK2（*EGFR*扩增），不同的生物亚型预后差异显著，其中，儿童GBM_RTK2生存期更长，中位总生存期为44个月；儿童GBM_MYCN预后极差，其中位总生存期仅为14个月；儿童GBM_RTK1预后于上述二者之间[37]。**弥漫性儿童型高级别胶质瘤，H3野生和IDH野生型**的3种生物亚型与成人型之间未见任何重叠，故不同年龄阶段的胶质母细胞瘤系为“远亲”，而非“近亲”[38]。所有**弥漫性儿童型高级别胶质瘤，H3野生和IDH野生型**亚型中MGMT启动子甲基化频率较低，进一步提示**弥漫性儿童型高级别胶质瘤，H3野生和IDH野生型**的独特起源。

4. 婴儿型半球胶质瘤 根据现有的少量文献报道，婴儿型半球胶质瘤影像学特点大致可以归纳为：病灶位于一侧大脑半球，体积较大、形态不规则，CT呈稍高密度，MRI信号不均匀，囊性变或坏死、出血多见，增强扫描边缘呈不规则环状强化（图13）[39-40]。婴儿型半球胶质瘤发生于婴儿期，并且具有不同的组织学形态特征，主要包括高密度的小肥胖细胞，肿瘤细胞有丝分裂丰富、缺乏坏死[41]，可见中等程度的细胞增生、有丝分裂和坏死，肿瘤细胞

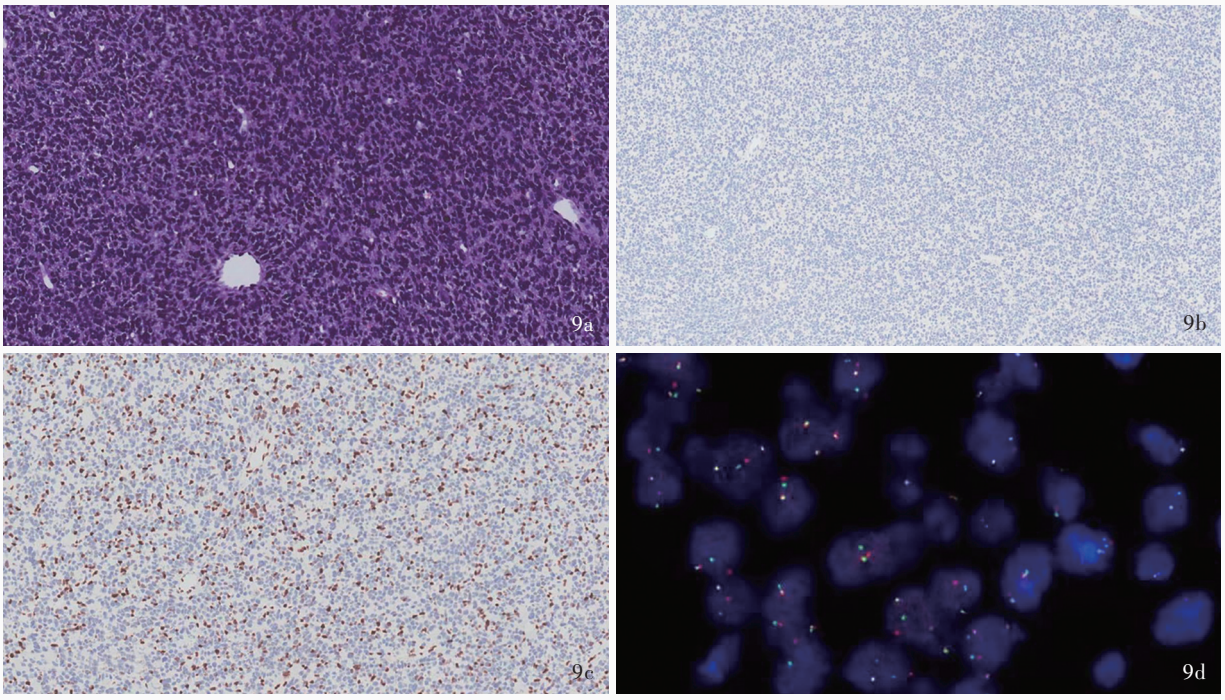


图9 男性患儿，3岁，主因言语障碍1个月入院，影像学检查显示双侧丘脑占位性病变，行立体定向组织活检术，病理诊断为**弥漫性中线胶质瘤，H3 K27变异型**。病理学检查所见 中倍放大 9a 肿瘤细胞密集生长，核质比较高 HE染色 9b 肿瘤细胞胞核H3 K27M呈阴性 免疫组化染色（EnVision二步法） 9c 肿瘤细胞胞核H3 K27me3表达缺失 免疫组化染色（EnVision二步法） 9d 肿瘤细胞胞核CXorf67呈阳性 免疫组化染色（EnVision二步法）

Figure 9 A 3 year-old male was admitted to the hospital for language impairment for one month. Imaging showed bilateral thalamic occupying lesion. The pathological diagnosis after stereotactic biopsy was **diffuse midline glioma, H3 K27-altered**. Pathological examination findings medium power magnified The tumor was composed of high density of small cell with hyperchromatic nuclei radio (Panel 9a). HE staining Tumor cells nucleus showed negative for H3 K27M (Panel 9b). Immunohistochemical staining (EnVision) Tumor cells nucleus showed loss of H3 K27me3 expression (Panel 9c). Immunohistochemical staining (EnVision) Tumor cells nucleus showed positive for CXorf67 (Panel 9d). Immunohistochemical staining (EnVision)

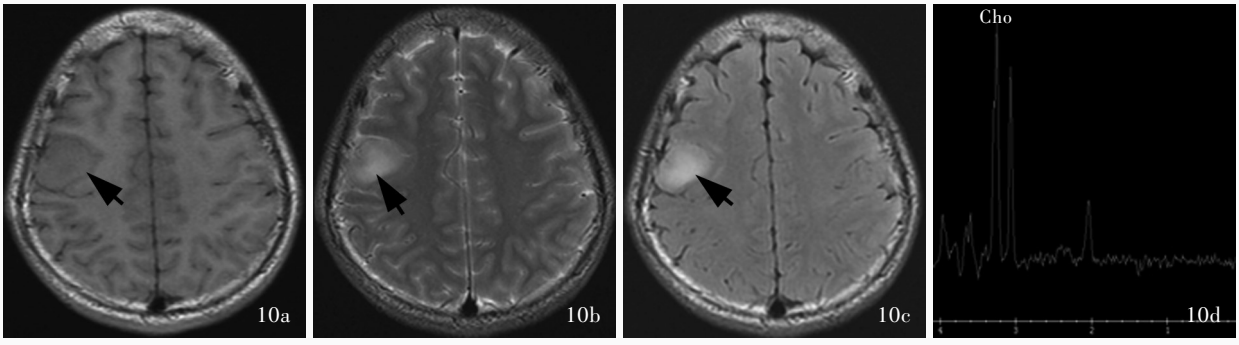


图10 男性患者，17岁，主因发作性肢体抽搐伴意识障碍入院。临床诊断为右侧额叶**弥漫性半球胶质瘤，H3 G34突变型**。头部影像学检查所见 10a 横断面T_1WI显示，右侧额叶占位性病变，呈稍低信号（箭头所示） 10b 横断面T_2WI显示病灶呈高信号（箭头所示） 10c 横断面FLAIR成像显示病灶呈高信号（箭头所示） 10d MRS显示Cho峰增高

Figure 10 A 17 year-old male was admitted to the hospital for paroxysmal convulsions with disturbance of consciousness. The clinical diagnosis was **diffuse hemispheric glioma, H3 G34-mutant** in the right frontal lobe. Head MRI findings Axial T_1WI showed a space occupying lesion in the right frontal lobe with slight hypointensity (arrow indicates, Panel 10a). Axial T_2WI showed hyperintensity of the tumor (arrow indicates, Panel 10b). Axial FLAIR showed hyperintensity of the tumor (arrow indicates, Panel 10c). MRS showed Cho peak increased (Panel 10d).

形态单一，缺乏明显的多形性，可见部分肿瘤细胞呈梭形[42-43]。婴儿型半球胶质瘤主要包括3个亚组，即大脑半球受体酪氨酸激酶（RTK）驱动的肿瘤，包括*ALK*/*ROS1*/*NTRK*/*MET*融合，组织学形态多呈高级别胶质瘤特征，预后一般；大脑半球*RAS*/*MAPK*驱动的肿瘤，术后临床干预最小且生存期较长；中线*RAS*/*MAPK*驱动的肿瘤，组织学形态多呈低级别胶质瘤伴*BRAF*变异特征，即使采用常规化疗，预后也

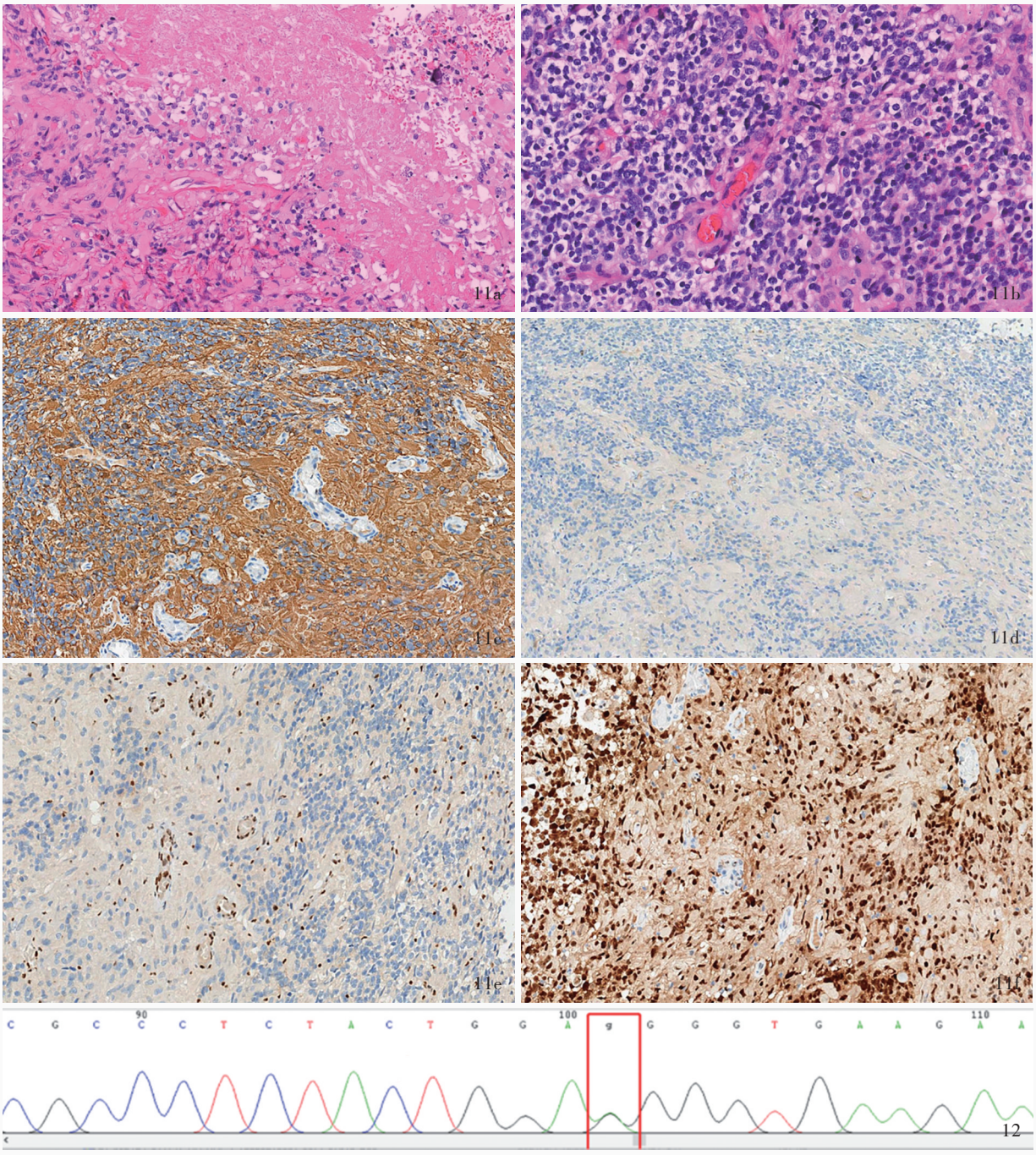


图11 男性患者，30岁，主因左下肢抽搐2个月入院，头部MRI显示右侧额颞叶占位性病变，临床诊断为低级别胶质瘤。行肿瘤大部切除术，术后病理诊断为**弥漫性半球胶质瘤，H3 G34突变型**。病理学检查所见 中倍放大 11a 肿瘤细胞呈高级别浸润性星形细胞瘤样 HE染色 11b 肿瘤细胞呈中枢神经系统胚胎性肿瘤样 HE染色 11c 肿瘤细胞GFAP呈弥漫性阳性 免疫组化染色（EnVision二步法） 11d 肿瘤细胞Olig-2呈阴性 免疫组化染色（EnVision二步法） 11e 肿瘤细胞胞核ATRX表达缺失 免疫组化染色（EnVision二步法） 11f 肿瘤细胞胞核P53呈弥漫性阳性 免疫组化染色（EnVision二步法） **图12** 图11患者H3F3A测序显示，鸟嘌呤（G）被腺嘌呤（A）取代，导致G34R突变（矩形区域所示）

Figure 11 A 30 year-old male was admitted to the hospital for left lower limb tic for 2 months. The clinical diagnosis was low-grade glioma, and the patient was treated with subtotal resection. The pathological diagnosis was **diffuse hemispheric glioma, H3 G34-mutant**. Pathological examination findings medium power magnified The tumor cells showed growth pattern of high-grade invasive astrocytoma (Panel 11a). HE staining The tumor cells showed central nervous system embryonal tumors histologically (Panel 11b). HE staining Tumor cells showed diffusely positive for GFAP (Panel 11c). Immunohistochemical staining (EnVision) Tumor cells showed negative for Olig-2 (Panel 11d). Immunohistochemical staining (EnVision) Tumor cells nucleus showed loss of ATRX expression (Panel 11e). Immunohistochemical staining (EnVision) Tumor cells nucleus showed diffusely positive for P53 (Panel 11f). Immunohistochemical staining (EnVision) **Figure 12** H3F3A sequencing of patient of Figure 11 showed that the nucleotide G was replaced with A, resulting in the G34R mutation (rectangular area indicates).

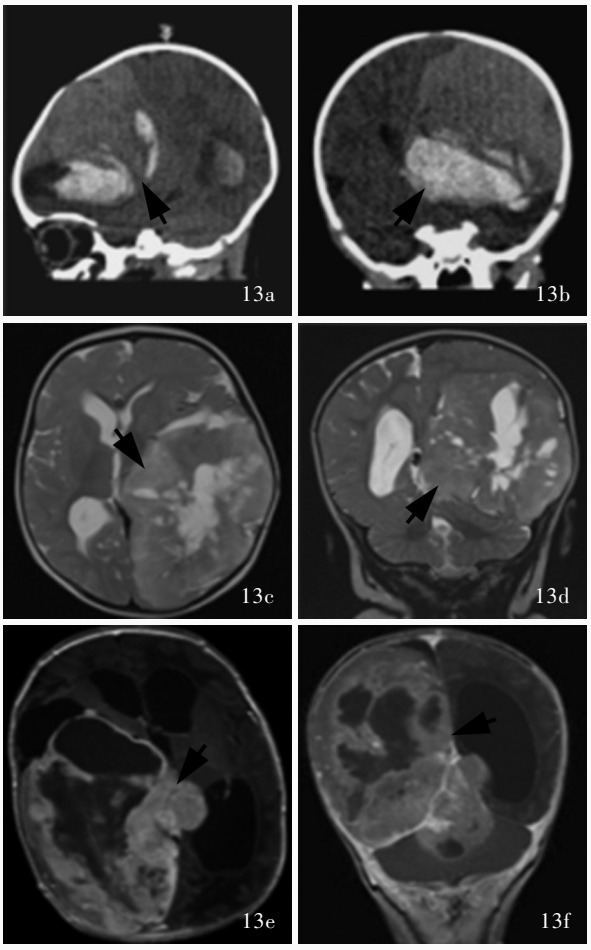


图13 婴儿型半球胶质瘤影像学特点(3例患者)[39] 13a,13b 1例矢状位和冠状位重建CT显示,左侧半球巨大占位性病变,呈稍高密度,病灶内可见出血(箭头所示) 13c,13d 1例横断面和冠状位T_2WI显示,左侧颞顶枕岛叶及左侧基底节丘脑区占位性病变,呈稍高信号,信号强度不均匀,内部多发囊性变或坏死(箭头所示) 13e,13f 1例横断面和冠状位增强T_1WI显示,右侧大脑半球、脑干及双侧小脑巨大占位性病变,呈明显强化,边缘不规则环形强化,病灶内坏死或囊性变区域未见强化(箭头所示)

Figure 13 Three cases of infant-type hemispheric glioma MRI findings [39] Sagittal (Panel 13a) and coronal (Panel 13b) CT of the first case showed large space-occupying lesion in the left hemisphere, slight high density with massive hemorrhage (arrows indicate). Axial (Panel 13c) and coronal (Panel 13d) T_2WI of the second case showed a space-occupying lesion was seen in the left temporo-parieto-occipito-insular and left basal ganglia thalamus. The hyperintensity with multiple cystic components or necrosis of the tumor could be seen (arrows indicate). Axial (Panel 13e) and coronal (Panel 13f) enhanced T_1WI of the third case showed large space-occupying lesions in the right cerebral hemisphere, brain stem, and bilateral cerebellum. Irregular ring-enhancement with necrosis or cystic formation could be seen (arrows indicate).

相对较差[39]。

综上所述,新版肿瘤分类新增儿童型低级别弥漫性胶质瘤和儿童型高级别弥漫性胶质瘤两大类,这是由于儿童型弥漫性胶质瘤虽与成人型在组织学形态上有很多相似之处,但驱动肿瘤发生发展的分子改变完全不同。儿童型弥漫性胶质瘤的命名仅提示肿瘤更常发生于儿童,但发病年龄并非诊断标准,少数成年患者仍可能罹患这些以"儿童型"命名的肿瘤。新版肿瘤分类结合组织病理学、肿瘤特殊位置以及肿瘤驱动基因或特征性分子改变,不仅可以更准确地判断预后,而且可以指导临床以及提示新的治疗靶点,开发更有针对性的抗肿瘤药物。

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利益冲突 无

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·小词典·

中英文对照名词词汇（四）

N-乙酰天冬氨酸 N-acetyl-aspartate（NAA）

异柠檬酸脱氢酶 isocitrate dehydrogenase（IDH）

异柠檬酸脱氢酶1/2 isocitrate dehydrogenase 1/2（IDH1/2）

婴儿原始黏液样间叶性肿瘤
primitive myxoid mesenchymal tumor of infancy（PMMTI）

荧光原位杂交 fluorescence in situ hybridization（FISH）

有多层菊形团的胚胎性肿瘤
embryonal tumor with multilayered rosettes（ETMR）

有毛细胞样特征的高级别星形细胞瘤
high-grade astrocytoma with piloid features（HGAP）

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
diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters（DGONC）

原始神经外胚层肿瘤
primitive neuroectodermal tumor（PNET）

整合酶相互作用分子1 integrase interactor-1（INI-1）

中枢神经系统原始神经外胚层肿瘤
central neuronal system primitive neuroectodermal tumor（CNS PNET）

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
the Consortium to Inform Molecular and Practical Approaches to Central Nervous System Tumor Taxonomy-Not Official WHO（cIMPACT-NOW）

肿瘤微环境 tumor microenvironment（TME）

肿瘤性疾病国际分类
The International Classification of Disease for Oncology（ICD-O）

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

总生存期 overall survival（OS）