·综述·

胶质瘤分级及分子遗传学标志物相关磁共振成像研究进展

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【摘要】 近年来胶质瘤病理学和影像学诊断均有显著进展。胶质瘤分级和分子遗传学标志物既是重要的预后预测因素,又可以指导治疗策略的制定。本文主要介绍应用扩散加权成像、扩散张量成像、扩散峰度成像、动态对比增强磁共振成像、灌注成像和磁共振波谱等新型MRI技术进行胶质瘤分级和分子遗传学标志物检测方面的新进展。分子遗传学标志物联合上述新型MRI技术可以更精确地对胶质瘤进行诊断和分级,并无创性检测胶质瘤分子特征,从而提高对患者预后评价的准确性,更好地指导个体化治疗。

【关键词】 神经胶质瘤; 生物学标记; 磁共振成像; 综述

Research progress of MRI in glioma grading and molecular genetic biomarkers

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【Abstract】 The pathological and imaging diagnosis of glioma has significantly evolved in recent years. Glioma grading, together with a number of molecular genetic biomarkers, has been recognized as an important prognostic and predictive factor, which can also guide the treatment strategy of glioma. This article highlights the research progress of MRI for noninvasively grading and molecular characterization of gliomas, including diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), diffusion kurtosis imaging (DKI), dynamic contrast-enhanced MRI (DCE-MRI), perfusion-weighted imaging (PWI) and magnetic resonance spectroscopy (MRS). The multiparametric imaging data analysis could improve imaging diagnosis, introduce the potential to noninvasively detect underlying molecular features of glioma, finally improve the accuracy of prognosis prediction and guide the individual-based treatment for glioma patients.

【Key words】 Glioma; Biological markers; Magnetic resonance imaging; Review

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胶质瘤是一组具有神经胶质细胞表型特征的神经上皮组织肿瘤的总称,是临床最常见的颅内原发性肿瘤。2016年世界卫生组织(WHO)中枢神经系统肿瘤分类根据组织学形态将胶质瘤分为WHO Ⅰ~Ⅳ级,其中Ⅰ级为良性、Ⅱ级为交界性、Ⅲ级为低度恶性、Ⅳ级为高度恶性,国际上认为Ⅰ和Ⅱ级为低级别胶质瘤(LGGs),Ⅲ和Ⅳ级为高级别胶质瘤(HGGs)。2016年WHO中枢神经系统肿瘤分类明显改进,首次将分子遗传学标志物应用于中枢神经系统肿瘤的分类和分型,突出体现胶质瘤分子遗传学变异的同源性,使临床诊断更加客观,对指导个

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体化治疗和提高预后评价精确性具有重要意义。头部MRI是非侵入性诊断颅内病变(包括不同级别胶质瘤)的重要方法。传统头部MRI的诊断精确性不甚理想,扩散加权成像(DWI)、扩散张量成像(DTI)、灌注成像(PWI)和磁共振波谱(MRS)等新型MRI技术已应用于临床,并能进行多参数MRI的联合分析,从而对胶质瘤分级和分子遗传学变异特征进行更为准确的评价。本文拟就近年胶质瘤分级和分子遗传学标志物相关MRI研究进展进行简要概述。

一、胶质瘤分级与传统MRI

胶质瘤分级直接与预后相关,是制定治疗方案的重要决定因素。对于高级别胶质瘤,手术切除程度是影响预后的独立因素,如果可行,强烈推荐手术全切除肿瘤[1];而低级别胶质瘤的治疗相对保守,部分患者早期可能考虑仅通过影像学检查密切随访观察。尽管组织病理学诊断是胶质瘤诊断和分级的"金标准",但是对于无症状性和肿瘤位于重要脑功能区的患者,MRI作为非侵入性检查技术对指导胶质瘤诊断、分级和治疗具有重要作用。同时,由于同一胶质瘤中可能同时包含高级别和低级别组织学成分,MRI可以提供高级别成分的定位和定量信息,从而有助于引导组织活检术、手术切除和放射治疗等。传统MRI通过对比增强区域与坏死区域以鉴别诊断高级别和低级别胶质瘤[2]。有研究显示,近20%的低级胶质瘤存在对比增强区域,而1/3未显示对比增强区域的胶质瘤可能是高级别胶质瘤[3],因此,传统MRI鉴别诊断低级别与高级别胶质瘤的准确度仅为55%~83%。为弥补传统MRI的不足,DWI、DTI、PWI、MRS等多参数新型MRI技术通过分析胶质瘤细胞组成、有丝分裂活性、微血管增殖和坏死等特性,从而更精确地进行肿瘤分级[4]。

二、胶质瘤分级与多参数MRI

1. DWI DWI序列用于测量水分子的布朗运动,其中最常测量的表观扩散系数(ADC)可以反映组织内水分子的流动性。在肿瘤分级方面,最初的研究结果显示,肿瘤细胞密度与ADC值呈负相关,即ADC值较高区域对应较低的细胞密度和较低的肿瘤级别,故低级别胶质瘤ADC值显著高于高级别胶质瘤[5]。但此对应关系并非绝对,例如,高级别胶质瘤中与肿瘤相关、并存的其他多种组织学形态特征如水肿、坏死、出血、囊性变或黏液变性等也可影响水分子扩散程度,肿瘤周围水肿引起的组织受压也可使肿瘤ADC值降低。近年在测量ADC值的单指数模型基础上出现双指数模型和拉伸指数模型,双指数模型测量ADC值、真ADC值、假ADC值和灌注分数,拉伸指数模型测量水分子扩散异质性指数和扩散分布系数,从而增加ADC值对肿瘤分级的准确性[6]。

2. DTI DTI序列用于测量水分子的扩散速度和方向。DTI图像参数包括平均扩散率(MD)、纯各向同性组分(p)、纯各向异性组分(q),其中,胶质瘤细胞密度越高、MD值越低;此外,还包括平面各向异性常数(CP)和球形各向异性常数(CS)。部分各向异性(FA)是评价组织微结构的重要指标,可用于定性诊断不同类型肿瘤。DTI同样可以用于高级别与低级别胶质瘤的鉴别诊断。Smitha等[6]报告,高级别和低级别胶质瘤的纯各向同性组分和MD值存在显著差异,其在受试者工作特征曲线(ROC曲线)中的灵敏度分别为93.9%和91.8%。

3. 扩散峰度成像 扩散峰度成像(DKI)作为DTI序列的延伸,可以测量复杂的组织内非高斯分布的水分子扩散运动,包括MD值、扩散异性指数和平均峰度等。同时采用DWI的双指数和拉伸指数模型以及DKI对胶质瘤进行测量和分析,发现各样本ADC值、真ADC值、灌注分数、水分子扩散异质性指数、扩散分布系数和MD值与胶质瘤级别呈正相关,而假ADC值和平均峰度与胶质瘤级别呈负相关,其中尤以水分子扩散异质性指数和平均峰度受胶质瘤级别的影响最显著[7],提示二者在胶质瘤分级中有良好的应用前景。

4. 动态对比增强MRI 动态对比增强MRI(DCE-MRI)是静脉注射对比剂钆-二乙三胺五醋酸(Gd-DTPA)等后获得的动态高时间分辨力T_1WI图像,其药代动力学参数包括血管内外容量转移常数(Ktrans)、血管外细胞外间隙容积比(Ve)、血管内外转移速度常数(Kep),这些参数可以反映血-脑屏障完整性、肿瘤血管灌注与通透性,故与肿瘤级别相关。研究显示,高级别胶质瘤由于局部血-脑屏障破坏致血管通透性增强,Ktrans值较低级别胶质瘤高,但对于二者鉴别诊断的Ktrans阈值尚无定论[8];该项研究还显示,高级别胶质瘤Ve值亦高于低级别胶质瘤[8]。然而,由于DCE-MRI图像的获取受对比剂种类、图像分析方法等因素的影响,故其对胶质瘤分级的实用性尚有限。

5. PWI PWI序列包括磁敏感加权成像(SWI)

与动脉自旋标记(ASL)。动态磁敏感增强灌注成像(DSC-MRI)系快速经静脉注射对比剂Gd-DTPA后测量一定时间内肿瘤组织内信号衰减程度以评价相对脑血容量(rCBV)。T_2WI显示对比剂首次通过肿瘤组织时信号强度降低,而后恢复。随时间改变的T_2信号强度称为T_2相关度,与对比剂剂量和达到的血药浓度呈正相关。通过对动态参数T_2相关度的测量可以评价兴趣区(ROI)相对脑血容量或肿瘤组织相对肿瘤血容量(rTBV),后者可以反映肿瘤血管增殖情况。血管增殖是判断胶质瘤分级的重要特征,故相对肿瘤血容量与胶质瘤级别呈正相关关系。ASL应用于动脉可以作为内源性示踪剂测量脑血流量(CBF)。Cebeci等[9]采用DSC-MRI共测量20例高级别胶质瘤和13例低级别胶质瘤患者的相对脑血容量和相对脑血流量(rCBF),并采用ASL测量相对信号强度(rSI)、脑血流量和相对脑血流量,结果显示,高级别胶质瘤患者上述指标均高于低级别胶质瘤患者,且相对脑血容量与ASL测量的相对脑血流量密切相关。由于该方法可以反映肿瘤血管增殖情况,其在胶质瘤分类和分级诊断中的应用潜力值得关注。

6. MRS 氢质子磁共振波谱(^{1}H-MRS)检测的代谢产物包括N-乙酰天冬氨酸(NAA)、胆碱(Cho)、肌酸(Cr)、乳酸(Lac)和脂质(Lip)等。N-乙酰天冬氨酸主要由神经元内线粒体产生,其波峰下降提示神经元功能障碍、数目减少或能量代谢障碍。胆碱主要反映神经元胞膜磷脂代谢水平。肌酸反映神经元和神经胶质细胞的能量利用和储存。乳酸仅出现于组织无氧酵解时。脂质提示组织凝固性坏死。N-乙酰天冬氨酸峰降低和胆碱峰升高的特征性表现以及乳酸峰和脂质峰的存在,与胶质瘤级别和侵袭性呈正相关,但MRS单独用于胶质瘤诊断的精确性有限。MRS、DWI和PWI联合应用可以将WHO Ⅱ和Ⅲ级少突胶质细胞瘤的诊断灵敏度提高至82%,精确度提高至84%[2]。

三、胶质瘤的分子遗传学标志物与MRI

2016年WHO中枢神经系统肿瘤分类的更新使胶质瘤的诊断进入分子诊断时代,其特征性分子遗传学标志物包括1p/19q-共缺失、异柠檬酸脱氢酶1/2(*IDH1/2*)基因突变等,目前MRI研究主要集中于影像学指标与分子遗传学标志物的关联性。

1. 1p/19q-共缺失与MRI 准确识别胶质瘤的1p/19q-共缺失对治疗有指导意义,1p/19q-共缺失患者放射治疗和药物化疗后无进展生存期(PFS)和总生存期更长。研究显示,存在1p/19q-共缺失的低级别少突胶质细胞瘤患者存在较高的最大相对脑血容量(rCBVmax),提示1p/19q-共缺失与少突胶质细胞瘤血管生成增多有关[2,10]。Kapoor等[11]的研究显示,1p/19q-共缺失的低级别胶质瘤患者相对肿瘤血容量增加;与1p/19q未缺失或仅19q缺失的胶质瘤相比,1p/19q-共缺失或仅1p缺失的胶质瘤相对肿瘤血容量更高,血管内皮生长因子(VEGF)mRNA、CD31 mRNA和CD105 mRNA表达水平更高。采用DCE-MRI分析1p/19q-共缺失的间变性少突胶质细胞瘤(WHO Ⅲ级)的研究显示,肿瘤体积越大、对比增强效应越明显,染色体9p和细胞周期蛋白依赖性激酶抑制基因2A(*CDKN2A*)缺失,血管生成相关基因表达水平升高[12]。Jenkinson等[13]采用^{1}H-MRS检测1p/19q-共缺失的少突胶质细胞瘤患者,结果显示,其Cho/Cr比值高于1p/19q未缺失患者,但差异未达到统计学意义。研究显示,相对脑血容量联合^{1}H-MRS[包括NAA/Cr、Cho/Cr、肌醇(mI)/Cr、Lac/Cr]诊断少突胶质细胞瘤有无1p/19q-共缺失的灵敏度为82.6%、特异度为64.7%、准确度达72%[10]。亦有研究显示,有或无1p/19q-共缺失的肿瘤在DWI、PWI或MRS中并未显示出明显差异,而且影像学对1p/19q-共缺失的误诊率高达40%[7]。上述研究结论差异较大,可能是由于不同研究者采用不同MRI序列和图像分析方法,特定的肿瘤级别和类型如是否为纯少突胶质细胞瘤或混合性肿瘤,以及不同表皮生长因子受体(*EGFR*)基因突变等。因此,胶质瘤1p/19q-共缺失与MRI之间的关系尚待进一步深入研究。

2. *IDH1/2*基因突变与MRI 在相同组织学类型的胶质瘤中,*IDH1/2*突变型预后明显优于野生型。*IDH*基因突变改变生物酶功能,消耗α-酮戊二酸和还原型烟酰胺腺嘌呤二核苷酸磷酸(NADPH)而产生致癌代谢物2-羟基戊二酸(2-HG)。采用质谱分析法检测手术切除的胶质瘤标本,可以检出较高水平的2-羟基戊二酸。目前通过MRS使无创性原位检测2-羟基戊二酸成为可能[14]。术前采用^{1}H-MRS可以在*IDH1*基因突变的肿瘤组织中检出2-羟基戊二酸,且该原位测值与体外质谱分析法测值呈正相关[15]。*IDH*基因突变还参与胶质瘤的发生、发展和新生血管形成过程。Kickingereder等[16]采用MRI测量初始治疗的73例低级别胶质瘤患者和WHO Ⅲ级

间变性胶质瘤患者相对脑血容量，结果显示，与野生型患者相比，*IDH1/2*突变型患者相对脑血容量下降，提示*IDH1/2*基因突变使胶质瘤血管生成减少，符合其对预后较好的提示作用；同时，相对脑血容量的测量准确预测87.67%患者（64/73）的*IDH1/2*基因突变。有研究进一步证实，*IDH1*突变型与野生型胶质瘤的标准化脑血容量（nCBV）不同，且前者ADC值更高[17]。

3.其他分子遗传学标志物与MRI　胶质瘤其他分子遗传学标志物包括EGFR、同源性磷酸酶-张力蛋白（PTEN）、Ki-67抗原、O^6-甲基鸟嘌呤-DNA-甲基转移酶（MGMT）甲基化等。采用DSC-MRI测量胶质母细胞瘤患者标准化相对肿瘤血容量（nTBV），可以在一定程度上预测上述标志物在胶质瘤中的表达水平：（1）MGMT甲基化阴性的胶质母细胞瘤患者标准化相对肿瘤血容量高于MGMT甲基化阳性患者。（2）EGFR阳性的胶质母细胞瘤患者中*PTEN*基因缺失亚组标准化相对肿瘤血容量高于*PTEN*基因正常亚组。（3）Ki-67抗原标记指数与胶质瘤标准化相对肿瘤血容量呈正相关[18]。*EGFR*Ⅷ是胶质母细胞瘤最常见的*EGFR*基因突变类型，占胶质母细胞瘤的25%～35%，并可加速胶质瘤的新生血管形成。DCE-MRI显示，与EGFRⅧ阴性的胶质母细胞瘤相比，EGFRⅧ阳性的胶质母细胞瘤呈现出更明显的强化和衰减，对评价EGFRⅧ分子靶向药物治疗效果具有潜在的应用价值[19]。

综上所述，随着近年新型MRI技术的发展和多种技术联合应用方法的建立，可以无创性对胶质瘤分级进行更准确地评价，并可对其特异性分子遗传学变异特征进行更深入地分析，从而有助于胶质瘤的诊断、分级和鉴别诊断及分子靶向药物治疗前疗效评价。目前该领域大量工作尚待开展，将胶质瘤分子遗传学变异特性与多种影像学新技术紧密结合，是未来胶质瘤分子诊断与治疗时代影像学发展的必然趋势。

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Encyclopedia of Computational Neuroscience published

Encyclopedia of Computational Neuroscience (ISBN: 978-1-4614-6674-1, eBook ISBN: 978-1-4614-6676-5) was published by Springer-Verlag New York in 2015. The editors of this book are Dieter Jaeger (Department of Biology, Emory University) and Ranu Jung (Department of Biomedical Engineering, Florida International University).

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