·临床研究·

MRI阴性的局灶性皮质发育不良临床特征分析

俱京涛 陈昕 刘佳宾 胡永生 王雷明 陈楠

【摘要】 **目的** 对比分析MRI阳性与MRI阴性的局灶性皮质发育不良(FCD)临床特征、病理学类型及预后。**方法与结果** 纳入2015年1月至2021年6月在首都医科大学宣武医院行致痫灶切除术的局灶性皮质发育不良患者共96例。根据术前FLAIR成像有无异常表现分为MRI阳性组(39例)和MRI阴性组(57例)。MRI阴性组FCD Ⅱ A型比例高于MRI阳性组($\chi^2=8.370$,$P=0.004$)。两组癫痫发作类型差异具有统计学意义(Fisher确切概率法:$P=0.037$),其中MRI阴性组完全性失神发作(Fisher确切概率法:$P=0.036$)和多种类型发作(Fisher确切概率法:$P=0.036$)比例高于MRI阳性组局灶性知觉性发作患者比例,MRI阴性组完全性失神发作(校正$\chi^2=4.728$,$P=0.030$)和多种类型发作(校正$\chi^2=4.728$,$P=0.030$)比例高于MRI阳性组局灶性知觉障碍性发作患者比例。MRI阴性组术后癫痫发作比例高于MRI阳性组($\chi^2=9.013$,$P=0.003$)。**结论** MRI阴性的局灶性皮质发育不良患者术后2年癫痫发作比例高于MRI阳性局灶性皮质发育不良患者,FCD Ⅱ A型在MRI阴性患者中比例高于MRI阳性患者,MRI阴性患者多以完全性失神发作和多种类型发作为主。

【关键词】 皮质发育畸形; 癫痫; 磁共振成像; 病理学; 预后

Clinical characteristics analysis of focal cortical dysplasia with negative MRI

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【**Abstract**】 **Objective** To comparative analysis of clinical characteristics, pathological types, and prognosis of focal cortical dysplasia (FCD) with positive and negative MRI. **Methods and Results** A total of 96 patients with FCD who underwent epileptic foci resection surgery at Xuanwu Hospital, Capital Medical University from January 2015 to June 2021 were selected. According to the presence of abnormal imaging findings in preoperative FLAIR imaging, patients were divided into MRI positive group ($n=39$) and MRI negative group ($n=57$). The proportion of FCD Ⅱ A in the MRI negative group was higher than that in the MRI positive group ($\chi^2=8.370$, $P=0.004$); there was a statistically significant difference in the types of epileptic seizures between the 2 groups (Fisher′s exact probability: $P=0.037$). Among them, the MRI negative group had a higher proportion of complete loss of consciousness seizures (Fisher′s exact probability: $P=0.036$) and multiple types of seizures (Fisher′s exact probability: $P=0.036$) than the MRI positive group, with a higher proportion of patients with focal perceptual seizures. The MRI negative group had a higher proportion of complete loss of consciousness seizures (adjusted $\chi^2=4.728$, $P=0.030$) and multiple types of seizures (adjusted $\chi^2=4.728$, $P=0.030$) than the MRI positive group, with a higher proportion of patients with focal perceptual deficit seizures. The proportion of postoperative epileptic seizures in the MRI negative group was higher than that in the MRI positive group ($\chi^2=9.013$, $P=0.003$). **Conclusions** The proportion of epileptic seizures in MRI negative FCD patients 2 years after surgery is higher than that in MRI positive FCD patients. The proportion of FCD Ⅱ A in MRI negative FCD patients is higher than that in MRI positive FCD patients. MRI negative FCD patients mainly have complete loss of consciousness seizures and multiple types of seizures.

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局灶性皮质发育不良(FCD)是耐药性癫痫(DRE)的主要原因之一。MRI阴性的局灶性皮质发育不良患者无明确影像学证据,术前诊断困难,难以精准定位致痫灶,导致手术治疗效果不佳[1-2]。尽管随着神经影像技术的发展,MRI阴性的局灶性皮质发育不良检出率有所提高[3-4],但仍有高达40%的FCDⅡ型和85%的FCDⅠ型常规MRI无明确阳性征象[5]。因此,术前明确MRI阴性的局灶性皮质发育不良临床特征,包括性别、发病年龄、病程、发病部位、癫痫发作类型及其与术后病理学类型、预后的关系将有助于术前诊断、预后评估及后期病理学特征研究。本研究回顾分析首都医科大学宣武医院经术后病理证实的96例局灶性皮质发育不良患者的临床表现、病理学类型、影像学特征,通过对比MRI阳性与MRI阴性患者,明确MRI阴性的局灶性皮质发育不良临床特征,以为预后评估以及后期病理学特征研究提供参考依据。

资料与方法

一、临床资料

1.纳入标准 (1)药物治疗无效或癫痫控制欠佳。(2)经临床多学科综合评估后,接受神经外科致痫灶切除术,并经术后病理证实为局灶性皮质发育不良。(3)术前均行常规头部MRI检查。(4)术后2年随访资料包括癫痫发作控制情况、发作类型、发作频率、抗癫痫发作药物(ASM)使用情况等资料完整。

2.排除标准 (1)同时伴其他致痫性疾病,如肿瘤、颅脑创伤、脑梗死等。(2)病理类型为FCDⅢ型。(3)同时患有其他严重系统性疾病,如血液系统疾病,代谢性及中毒性疾病等。(4)临床资料不完整或失访。

3.一般资料 根据上述纳入与排除标准,选择于2015年1月至2021年6月在首都医科大学宣武医院神经外科行致痫灶切除术的局灶性皮质发育不良患者共96例,男性54例,女性42例;发病年龄1~47岁,中位年龄8.84(1.30,38.00)岁;病程6个月至33年,中位病程8.50(4.00,13.00)年。

二、研究方法

1.局灶性皮质发育不良影像学分类 (1)MRI检查:所有患者术前均采用3.0T Verio超导型磁共振扫描仪(德国Siemens公司)进行常规头部MRI检查,由2位10年以上工作经验的神经影像科医师对所有已经病理证实为局灶性皮质发育不良患者的MRI图像进行重新判读,着重关注FLAIR成像,如意见不一致,由第3位具有20年工作经验的神经影像学专家共同研判,经协商达成一致。①FLAIR成像。重复时间(TR)9000 ms、回波时间(TE)93 ms、反转时间(TI)2500 ms,翻转角(FA)90°,扫描视野(FOV)240 mm×240 mm,矩阵320×320,激励次数(NEX)为2次,层厚5 mm、层间距为2 mm,共扫描23层,覆盖颅底至颅顶全部脑组织。②T_2WI。重复时间为2200 ms、回波时间89 ms,反转时间100 ms,翻转角90°,扫描视野240 mm×240 mm,矩阵320×320,激励次数1次,层厚为5 mm、层间距为0.8 mm,共扫描23层,覆盖颅底至颅顶全部脑组织。(2)影像学分类:MRI阴性的局灶性皮质发育不良定义为FLAIR成像未见颅内阳性征象。MRI阳性的局灶性皮质发育不良定义为常规MRI检查或FLAIR成像呈现典型征象如局限性累及皮质及皮质下异常信号,皮质增厚、灰白质分界不清及皮质下结构异常、T_2WI或FLAIR成像信号增高伴或不伴“Transmantal征”[6](图1)。(3)病变部位分类:MRI阳性的局灶性皮质发育不良采用上述影像学检查进行术前致痫灶定位。MRI阴性的局灶性皮质发育不良一部分术前采用UIH-uMI510扫描仪(上海联影医疗科技股份有限公司)行^{18}F-FDG PET显像或采用306通道脑磁图MEG仪(瑞典Elekta公司)行头部静息态脑磁图检查以进行致痫灶定位,另一部分患者术中采用皮质脑电图或立体定向脑电图(SEEG)进行定位切除(图2)。病变部位均视为手术切除部位,均为目测确定,分别为额叶、顶叶、枕叶、颞叶、多脑叶分布(病变部位≥1个脑叶)。

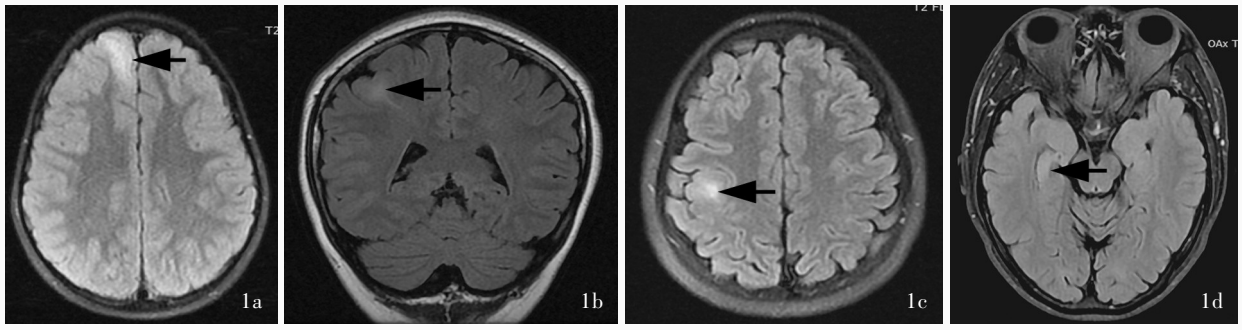

图1　MRI阳性的局灶性皮质发育不良患者头部MRI检查所见　1a　横断面抑脂FLAIR成像显示右侧额叶皮质局限性增厚，呈高信号（箭头所示）　1b　冠状位FLAIR成像显示右侧顶叶白质楔形高信号（箭头所示），底部位于皮质，尖端向侧脑室体部放射，呈典型“Transmantal征”　1c　横断面抑脂FLAIR成像显示右侧顶叶皮质局限性高信号（箭头所示）　1d　横断面抑脂FLAIR成像显示右侧海马斑片样高信号（箭头所示）

Figure 1　Imaging findings of FCD patient with positive MRI　Axial fat suppression FLAIR showed localized thickening of the right frontal cortex, with hyperintensity (arrow indicates, Panel 1a). Coronal FLAIR showed a wedge-shaped hyperintensity in the white matter of the right parietal lobe (arrow indicates), with the bottom located in the cortex and the tip radiating towards the body of the lateral ventricle, presenting a typical "Transmantal sign" (Panel 1b). Axial fat suppression FLAIR showed localized hyperintensity in the right parietal cortex (arrow indicates, Panel 1c). Axial fat suppression FLAIR showed patchy hyperintensity in the right hippocampus (arrow indicates, Panel 1d).

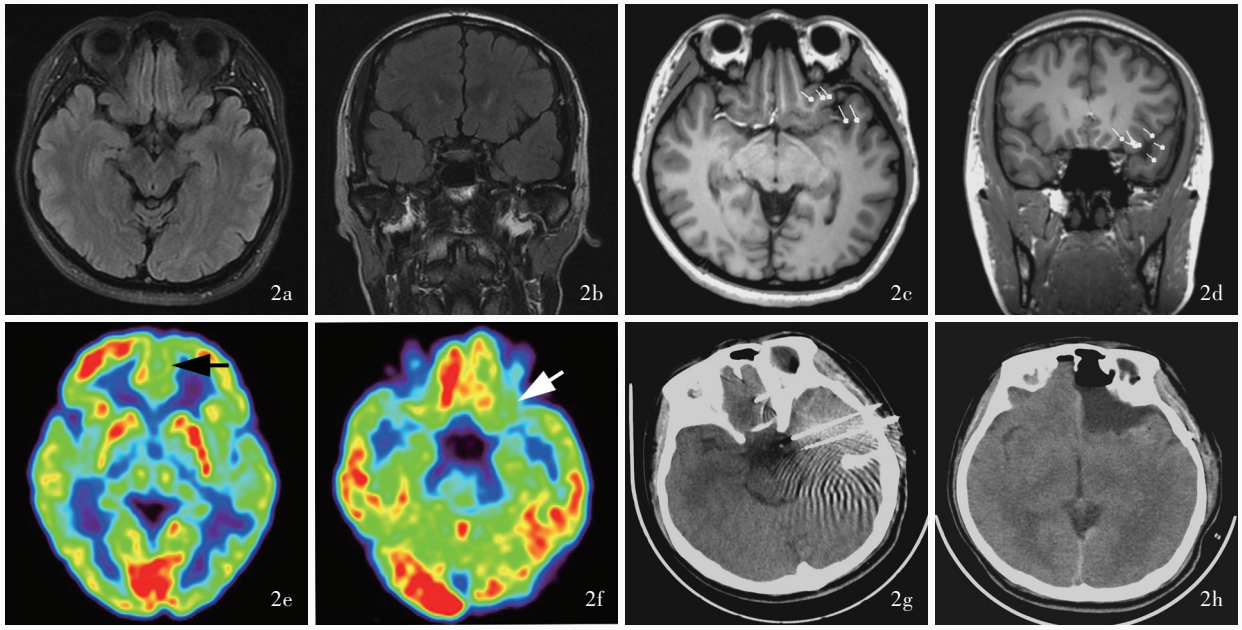

图2　女性患者，手术年龄27岁，临床诊断为癫痫，拟行致痫灶切除术，术前行脑磁图、^{18}F-FDG PET及SEEG定位，病变位于左侧前额叶底部，手术经左侧颞叶入路，切除致痫灶。手术前后影像学检查所见　2a，2b　横断面抑脂和冠状位FLAIR成像未见明显异常　2c，2d　脑磁图在横断面和冠状位T_1WI上定位显示偶极子簇位于左侧额叶底部　2e，2f　横断面^{18}F-FDG PET显示左侧额叶及左侧额叶底部局灶性低代谢区（箭头所示）　2g，2h　横断面CT显示SEEG植入及致痫灶切除术后改变

Figure 2　A female patient, aged 27 at the time of surgery. The clinical diagnosis was epilepsy, and a surgical resection of epileptic foci was considered. Preoperative MEG, ^{18}F-FDG PET, and SEEG were performed for localization. The lesion was located at the bottom of the left frontal lobe, and surgery was performed through the left temporal approach to remove the epileptic foci. The imaging findings before and after the surgery　Axial fat suppression and coronal FLAIR showed no significant abnormalities (Panel 2a, 2b). MEG showed dipole clusters located at the bottom of the left frontal lobe in both axial and coronal T_1WI (Panel 2c, 2d). Axial ^{18}F-FDG PET showed localized hypometabolic zone in the left frontal lobe and the bottom of the left frontal lobe (arrows indicate; Panel 2e, 2f). Axial CT showed changes after SEEG implantation and epileptic foci resection surgery (Panel 2g, 2h).

2.临床及病理学分类　（1）癫痫发作类型：由我院癫痫中心经验丰富的两位神经外科医师按照2016年国际抗癫痫联盟（ILAE）新癫痫发作分类基本版[7-8]将癫痫发作类型分为局灶性知觉性发作、局灶性知觉障碍性发作、完全性动作性发作、完全性失神发作和多种类型发作模式，若意见不一致，共同协商确定。（2）术后病理学分类：按照《局灶性皮质发育不良的国际共识分类——2018年的重要更

表1 MRI阳性组与MRI阴性组患者临床资料的比较

Table 1. Comparison of clinical data between MRI positive group and MRI negative group

观察指标	MRI阳性组（n=39）	MRI阴性组（n=57）	χ^2或Z值	P值
性别[例(%)]			0.659	0.417
男性	20(51.28)	34(59.65)		
女性	19(48.72)	23(40.35)		
发病年龄[$M(P_{25},P_{75})$,岁]	8.00 (2.00,14.00)	10.00 (5.50,14.50)	788.000	0.159
病程[$M(P_{25},P_{75})$,年]	7.00 (2.00,13.00)	9.00 (5.00,14.75)	812.497	0.229
病理学类型[例(%)]			8.528	0.036
FCDⅠ型	16(39.02)	25(60.98)	0.009	0.923
ⅠA型	10(38.46)	16(61.54)		
ⅠB型	6(40.00)	9(60.00)		
FCDⅡ型	23(41.82)	32(58.18)	8.370	0.004
ⅡA型	6(22.22)	21(77.78)		
ⅡB型	17(60.71)	11(39.28)		
癫痫发作类型[例(%)]			—	0.037
局灶性知觉性发作	7(17.95)	4(7.02)		
局灶性知觉障碍性发作	17(43.59)	15(26.32)		
完全性动作性发作	11(28.21)	18(31.58)		
完全性失神发作	2(5.13)	10(17.54)		
多种类型发作	2(5.13)	10(17.54)		
病变部位[例(%)]			—	0.851
额叶	16(41.03)	29(50.88)		
顶叶	5(12.82)	7(12.28)		
枕叶	1(2.56)	2(3.51)		
颞叶	11(28.21)	11(19.30)		
多脑叶分布	6(15.38)	8(14.04)		
预后[例(%)]			9.013	0.003
术后无癫痫发作	31(79.49)	28(49.12)		
术后癫痫发作	8(20.51)	29(50.88)		

—，Fisher's exact probability，Fisher确切概率法。Mann-Whitney U test for comparison of age of onset and duration, and χ^2 test for comparison of others，发病年龄和病程的比较采用Mann-Whitney U检验，其余指标的比较采用χ^2检验。FCD，focal cortical dysplasia，局灶性皮质发育不良

新》[9]，分为FCDⅠ型（ⅠA型、ⅠB型、ⅠC型）和FCDⅡ型（ⅡA型、ⅡB型）。

3. 预后评估　随访至术后2年，根据Engel分级进行预后评估[10]，Ⅰ级，术后无癫痫发作；Ⅱ级，癫痫发作频率减少>90%；Ⅲ级，癫痫发作频率减少50%～90%；Ⅳ级，癫痫发作频率减少<50%。EngelⅠ级为术后无癫痫发作，EngelⅡ～Ⅳ级为术后癫痫发作。

4. 统计分析方法　采用SPSS 26.0统计软件进行数据处理与分析。计数资料以相对数构成比（%）或率（%）表示，采用χ^2检验或Fisher确切概率法。正态性检验行P-P图检验，呈非正态分布的计量资料以中位数和四分位数间距[$M(P_{25},P_{75})$]表示，采用Mann-Whitney U检验。以$P\leq0.05$为差异有统计学意义。

结　果

本组96例患者根据术前MRI检查结果（尤其是FLAIR成像）分为有明显阳性征象组（MRI阳性组，39例）和无明显阳性征象组（MRI阴性组，57例）。两组病理学分类差异有统计学意义（P=0.036，表1），其中FCDⅠA亚型和FCDⅠB亚型比例组间差异无统计学意义（P=0.923），MRI阴性组FCDⅡA亚型比例高于MRI阳性组（P=0.004）；两组癫痫发作类型比较差异亦具有统计学意义（P=0.037，表1），其中MRI阴性组完全性失神发作（Fisher确切概率法：P=0.036）和多种类型发作（Fisher确切概率法：P=0.036）比例高于MRI阳性组，局灶性知觉性发作患者比例，MRI阴性组完全性失神发作（校正χ^2=4.728，P=0.030）和多种类型发作比例（校正χ^2=4.728，P=0.030）高于MRI阳性组局灶性知觉障碍性发作患者比例。MRI阴性组术后癫痫发作比例高于MRI阳性组（P=0.003，表1）。而性别、发病年龄、病程、病变部位组间差异无统计学意义（均P>0.05，表1）。

讨　论

由于MRI阴性的局灶性皮质发育不良在影像学上无异常改变，其诊断、术前定位及手术切除范围一直是临床面临的难题。因此，术前明确MRI阴性的局灶性皮质发育不良临床特征及其与术后病理学类型、预后的关系将有助于术前对其诊断及预后评估。目前对于如何提高MRI阴性的FCD检出率的研究较多，如超高场强MRI、MRI新序列及后处理技术均可以不同程度提高检出率[11-13]，但对于MRI阴性与MRI阳性的局灶性皮质发育不良之间临床特征差异的报道较少。本研究通过对MRI阴性与MRI阳性局灶性皮质发育不良患者临床特征的对比发现：二者性别、发病年龄、病程、病变部位无明显差异，而在病理学类型及癫痫发作类型上存在差异，且MRI阴性患者预后差于及MRI阳性患者。

研究显示，MRI阴性的局灶性皮质发育不良患者发病年龄较MRI阳性患者晚[14]，但本研究显示，两组患者发病年龄差异无统计学意义，可能原因为本研究排除FCDⅢ型患者，FCDⅢ型为FCDⅠA型合并海马硬化等疾病，常被归类为MRI阳性；也可能由于检查技术进步导致部分MRI阴性患者被检出。此外，本研究未发现两组病变部位存在差异。既往研究认为，FCDⅠ型多发生于颞叶、FCDⅡ型位于颞叶外，影像学技术的进步提高了FCDⅠ型的检出率[11]，使FCDⅠ型在MRI阴性患者中的比例下降，致痫灶位于颞叶的FCDⅠ型在MRI阳性患者中比例增加，另外本研究排除了FCDⅢ型患者，这可能减少FCDⅠ型患者比例，导致致痫灶位于颞叶的比例下降，是本研究两组患者病变部位无明显差异的原因。

研究发现，85%的FCDⅠ型和40%的FCDⅡ型患者MRI无明显阳性征象[5]，本研究有差异的病理学类型仅体现在FCDⅡ型，MRI阴性组FCDⅡA型比例高于MRI阳性组。FCDⅡA型患者病变体积往往较小并且倾向位于额叶或者脑沟底部[15]，并且额叶髓鞘成熟较晚[16]，相对于FCDⅡB型发病年龄较早[17]，此类病变在FLAIR成像上对比度降低，难以从常规序列中检出，故表现为MRI阴性。

本研究发现，MRI阴性组完全性失神性发作和多种发作模式比例较MRI阳性组高，而MRI阴性组病理学类型以FCDⅡA型为主。有研究认为，癫痫发作主要是因为皮质兴奋性过度所致[18]，癫痫发作沿大脑皮质水平扩散或由皮质-丘脑-皮质回路双向激活[19]，MRI阳性的局灶性皮质发育不良患者病变较为局限，表现为局部皮质增厚或萎缩，皮质及皮质下异常信号，尤其是“Transmantal征”，皮质及皮质下结构分界不清等，所引起的皮质过度兴奋性传导大多较为局限，而“气球”样细胞在一定程度上又抑制癫痫发作[20-21]。众所周知，“气球”样细胞多存在于MRI阳性FCDⅡB型患者中，如“Transmantal征”，从而导致MRI阳性的局灶性皮质发育不良患者癫痫发作类型以局灶性发作为主，脑电图常可捕捉到局灶性节律性放电，而邻近胼胝体及扣带回病变较易将冲动传导至双侧大脑半球[22]，引起全面性或多种复杂类型发作。较小的FCDⅡA型病变（大多数为MRI阴性病变）倾向位于额叶或邻近扣带回，同时较多的FCDⅠ型及FCDⅡA型病变可能存在癫痫网络，冲动传导具有不定向性，常同时累及多个脑区（平均每例患者>3个脑区），导致癫痫发作模式复杂多样[23]；脑电图通常无特异性[24]，可能导致不同的病理学类型倾向不同发作模式。最近文献报道，FCDⅡA型与FCDⅡB型发作期脑电图存在明显差异，在FCDⅡA型中，节律性慢波和快速活动的癫痫发作模式最为常见，重复尖峰/尖波模式是FCDⅡB型最为常见的发作模式[25]，同时也说明FCDⅡA型与FCDⅡB型在发作模式上存在差异，这可能是全面性发作及多种形式发作与MRI阴性征象关系密切的原因。

研究显示，MRI阴性是局灶性皮质发育不良患者预后不良的危险因素之一[1-2]，本研究亦发现，与MRI阳性患者相比，MRI阴性患者术后癫痫发作比例较高。近期文献报道，FCDⅠA型患者术后预后较好，可能与FCDⅠA型和FCDⅡA型病变体积一般较小，易手术切除有关[26-27]。本研究图2所示1例青年女性患者，以完全性失神发作为主，MRI未见任何阳性征象，术前经脑磁图、^{18}F-FDG PET及SEEG进行定位，术中以皮质脑电图定位进行致痫灶切除，术后病理学类型明确为FCDⅡA型，术后2年随访，预后为EngelⅢ级。可能是由于FCDⅡA型可存在≥1个致痫灶或异常癫痫网络，导致完全性失神发作及致痫灶手术切除不完全导致预后不良。

本研究尚存局限性：将切除部位视为病变部位，由于术后切除部位发生形变，可能导致致痫灶定位的精准性下降。综上所述，MRI阴性与MRI阳性的局灶性皮质发育不良患者性别、发病年龄、病程、病变部位无明显差异，MRI阴性患者术后2年癫痫发作比例高于MRI阳性患者，FCDⅡA型在MRI阴性患者中比例高于MRI阳性患者，MRI阴性患者多以完全性失神发作和多种类型发作为主。

利益冲突 无

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