·临床研究·

抗LGI1抗体相关边缘性脑炎临床分析

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【摘要】 **目的** 探讨抗富亮氨酸胶质瘤失活基因1(LGI1)抗体相关边缘性脑炎临床特点。**方法与结果** 2016年6月至2017年10月共诊断与治疗7例抗LGI1抗体相关边缘性脑炎病例,平均发病年龄为(48.29±15.09)岁。呈急性(4例)或亚急性(3例)发病,以癫痫发作和记忆障碍为主要表现,可伴有面-臂肌张力障碍发作(5例)、精神行为异常或性格改变(4例),或合并难治性低钠血症(2例)、胸腺瘤(1例);脑脊液(6例)或血清(7例)抗LGI1抗体呈阳性;头部MRI检查单侧或双侧颞叶内侧异常信号(6例),脑电图呈连续棘慢复合波和慢波(1例)。大剂量糖皮质激素序贯治疗(6例)有效。7例患者中2例失访,余5例遗留远期记忆障碍(3例)或近期与远期记忆障碍并存(2例),其中1例出院6个月后复发。**结论** 依据特异性临床表现如面-臂肌张力障碍发作、记忆障碍等,结合影像学及脑脊液检查结果可明确诊断;免疫抑制剂可有效改善临床症状与预后。

【关键词】 边缘叶脑炎; 肿瘤抑制蛋白质类; 抗体; 免疫疗法; 癫痫; 记忆障碍

Clinical analysis of patients with anti-leucine-rich glioma-inactivated 1 antibody-associated limbic encephalitis

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【**Abstract**】 **Objective** To investigate the clinical characteristics of anti-leucine-rich glioma-inactivated 1 (LGI1) antibody-associated encephalitis. **Methods and Results** From June 2016 to October 2017, a total of 7 patients with anti-LGI1 antibody-associated limbic encephalitis were diagnosed and treated, with an average age at onset (48.29±15.09) years. Patients presented acute (4 cases) or subacute onset (3 cases), with seizures and memory dysfunction as the main manifestations. It may be accompanied by faciobrachial dystonic seizures (FBDS, 5 cases), mental and behavioral abnormalities or personality changes (4 cases), or even combined with intractable hyponatremia (2 cases) or thymoma (one case). Serum anti-LGI1 antibody tests showed positive results in 7 cases, and cerebrospinal fluid (CSF) anti-LGI1 antibody tests showed positive results in 6 cases. MRI showed unilateral or bilateral medial temporal lobe abnormal signals (6 cases), and EEG showed continuous spike-slow waves or slow waves (one case). High-dose glucocorticoid sequential therapy was effective in 6 cases. During the follow-up period, 2 cases were lost, and the other 5 cases presented long-term memory disorder (3 cases) or long-term and short-term memory disorders (2 cases). Among them, one case relapsed 6 months after discharge. **Conclusions** According to specific clinical manifestations of patients (such as onset of FBDS, memory disorders, etc.), combined with imaging and CSF examination results, this disease can be clearly diagnosed. Immunosuppressive agents can effectively improve the clinical symptoms and prognosis.

【**Key words**】 Limbic encephalitis; Tumor suppressor proteins; Antibodies; Immunotherapy; Epilepsy; Memory disorders
Conflicts of interest: none declared

抗富亮氨酸胶质瘤失活基因1(LGI1)抗体相关边缘性脑炎为临床罕见的中枢神经系统自身免疫性疾病,主要累及海马、岛叶、杏仁核等边缘系统结构[1];临床表现为记忆力减退、精神行为异常、癫痫发作,以及面-臂肌张力障碍发作(FBDS)[2-3]。自2013年金丽日等[4]首次报告抗LGI1抗体相关边缘性脑炎后,该病即在国内引起关注,陆续有相关个案见诸文献报道。2016年6月至2017年10月中国

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医科大学附属第一医院神经内科共诊断与治疗7例抗LGI1抗体相关边缘性脑炎病例，笔者拟对其临床资料进行回顾分析，并结合近期相关文献探讨该病的临床特点，以为临床医师提供借鉴。

临床资料

一、一般资料

本组7例患者均为2016年6月至2017年10月经我院明确诊断并住院治疗的抗LGI1抗体相关边缘性脑炎病例，男性4例，女性3例；发病年龄22～63岁，平均（48.29±15.09）岁。多呈急性（4例）或亚急性（3例）发病，除1例主诉发病前有腹泻和感冒外，余6例均无明显诱因或前驱症状；首发症状以近记忆力减退（3例）、面-臂肌张力障碍发作（3例）或间断性头痛（1例）为主；7例患者病程中均出现癫痫发作，其中5例伴有面-臂肌张力障碍发作，分别累及左侧肢体（1例）、左上肢及面部（1例）、双侧上肢及面部（1例）或四肢同时受累（2例），2例伴有意识障碍、5例呈全面性强直-阵挛发作（GTCS）；7例患者发病后均出现记忆障碍，表现为近期（6例）和（或）远期（5例）记忆障碍；4例伴有精神行为异常或性格改变，例如短暂性失忆（1例）、胡言乱语及神志淡漠（1例）、抽搐前出现幻视或呓语（1例），以及幻视、幻听及性格改变（1例）。本组有3例患者入院后行简易智能状态检查量表（MMSE）评分，2例评分降低（22和19分）、1例正常（26分）。

二、实验室检查

1.脑脊液 （1）颜色与压力：本组患者脑脊液均无色透明，压力正常（6例）或略降低（1例）。（2）细胞计数：仅1例患者脑脊液白细胞计数轻度升高[18×10^6/L，（0～8）×10^6/L]，单核细胞比例0.17（0～1）、多核细胞比例0.83（0～1）。（3）生化：1例蛋白定量轻度升高[630 mg/L（120～600 mg/L）]，6例氯化物降低[109～118 mmol/L（120～132 mmol/L）]，有2例葡萄糖升高[5.80和4.70 mmol/L（2.20～3.90 mmol/L）]。（4）肿瘤标志物：本组无一例脑脊液中检出肿瘤细胞。（5）免疫学指标：6例患者抗LGI1抗体均呈阳性反应。其他自身免疫性脑炎抗体如抗N-甲基-D-天冬氨酸受体（NMDAR）抗体、抗γ-氨基丁酸B型受体（$GABA_BR$）抗体，以及抗Hu、Yo、Ri抗体等副肿瘤相关抗体均呈阴性反应。

2.血清学 （1）葡萄糖：本组有2例患者空腹葡萄糖水平升高，分别为8.48和6.30 mmol/L（3.90～6.10 mmol/L）。（2）有机化合物：2例病程中出现难治性低钠血症，血清钠平均水平分别为129.30 mmol/L（125.60～131.80 mmol/L）和130.80 mmol/L（120.20～135.30 mmol/L）。（3）免疫学指标：本组7例患者血清抗LGI1抗体均呈阳性反应，而其他自身免疫性脑炎抗体如抗NMDAR抗体、抗$GABA_BR$抗体，以及抗Hu、Yo、Ri抗体等副肿瘤相关抗体则均呈阴性反应。5例行血清抗甲状腺抗体检测，其中4例抗甲状腺球蛋白（TG）抗体和抗甲状腺过氧化物酶（TPO）抗体水平升高，平均水平分别为46.37 U/ml（9.43～99.31 U/ml）和235.16 U/ml（29.51～514.76 U/ml）。（4）肿瘤标志物：6例行血清肿瘤标志物筛查，1例血清癌胚抗原[CEA，5.46 ng/ml（0～4.30 ng/ml）]、糖类抗原199[CA199，27.09 U/ml（0～27 U/ml）]水平同时升高（左肺小结节）；1例神经元特异性烯醇化酶[NSE，23.73 ng/ml（0～16.30 ng/ml）]水平升高（右肺小结节）；1例曾因重症肌无力行胸腺瘤切除术，血清肿瘤标志物筛查糖类抗原125[CA125，52.28 U/ml（0～35 U/ml）]水平升高；1例CEA（7.07 ng/ml）水平升高；其余2例肿瘤标志物均于正常值范围。

三、辅助检查

1.影像学 （1）头部MRI：6例表现为单侧或双侧海马、颞叶异常信号，T_1WI呈等或低信号、T_2WI呈高信号、FLAIR成像呈高信号，但均未出现明显增强效应（图1～4）；余1例无异常所见。（2）胸部CT：5例行胸部CT检查，1例为左肺小结节、1例为右肺小结节，3例无异常所见。

2.脑电图 本组患者入院后均行脑电图检查，仅1例在检查过程中出现2次痫样放电，全部导联均由快波起始，波幅逐渐增高、频率增快，而后逐渐出现连续棘慢复合波和慢波；其余患者脑电图均无异常发现。

四、治疗与预后

本组7例患者中6例采用大剂量糖皮质激素序贯治疗，甲泼尼龙500 mg/d静脉滴注，连续治疗5～6 d，减至240 mg/d（3例）或120 mg/d（3例）；其中1例改为240 mg/d，治疗5 d后改为50 mg/d口服；5例治疗6 d后改为60 mg/d口服，持续服药6～24周，逐渐减至（每周减2.50或5 mg）停药。余1例采用小剂量糖皮质激素80 mg序贯治疗1 d。本组6例患者在接受激素治疗期间同时长期服用抗癫痫药物（AEDs），即左乙拉西坦0.50 g/d（2次/d）或丙戊酸钠500 mg/d（2次/d）或丙戊酰胺0.20 g/d（2次/d）或奥卡西平

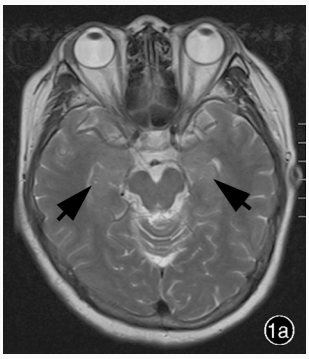
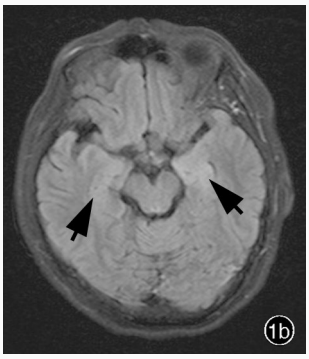
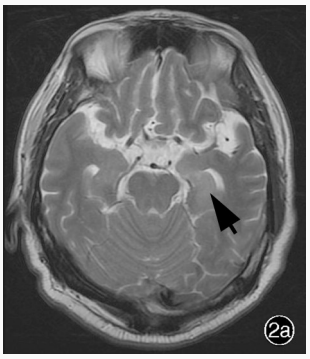
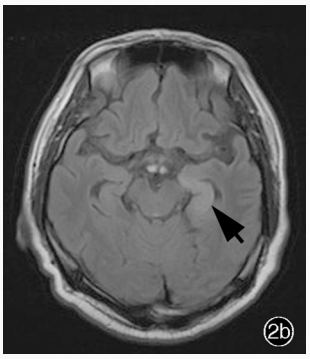

图1 女性患者，60岁。临床诊断为抗LGI1抗体相关边缘性脑炎。头部MRI检查所见 1a 横断面T_2WI显示左侧颞叶海马和海马旁回、右侧颞极稍高信号影（箭头所示） 1b 横断面FLAIR成像病变呈高信号（箭头所示） **图2** 男性患者，56岁。临床诊断为抗LGI1抗体相关边缘性脑炎。头部MRI检查所见 2a 横断面T_2WI显示左侧海马略高信号影（箭头所示） 2b 横断面FLAIR成像显示病变呈高信号（箭头所示）

Figure 1 Female patient, 60 years old, clinical diagnosis as anti-LGI1 antibody-associated limbic encephalitis. Brain MRI findings Axial T_2WI showed slightly high-intensity signals in hippocampus and parahippocampal gyrus of left temporal lobe and right temporal poles (arrows indicate, Panel 1a). Axial FLAIR showed lesions with high-intensity signal (arrows indicate, Panel 1b). **Figure 2** Male patient, 56 years old, clinical diagnosis as anti-LGI1 antibody-associated limbic encephalitis. Brain MRI findings Axial T_2WI showed slightly high-intensity signal of left hippocampus (arrow indicates, Panel 2a). Axial FLAIR showed lesion with high-intensity signal (arrow indicates, Panel 2b).

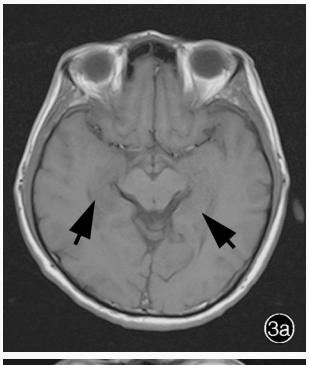
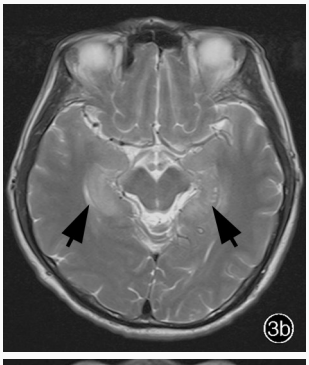
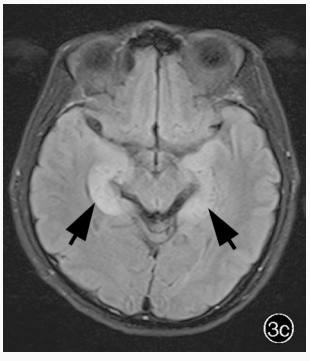
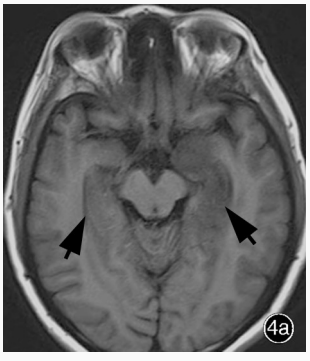
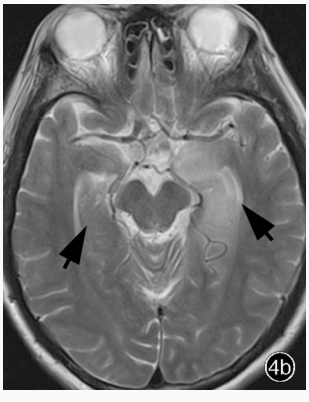
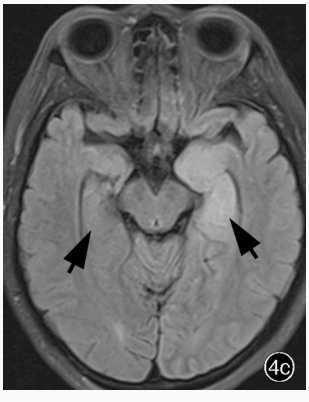

图3 男性患者，52岁。临床诊断为抗LGI1抗体相关边缘性脑炎。头部MRI检查所见 3a 横断面增强T_1WI显示，双侧颞叶海马稍肿胀，呈对称性低信号影（箭头所示），病灶无强化 3b 横断面T_2WI显示，双侧颞叶海马稍肿胀，呈对称性高信号影（箭头所示） 3c 横断面FLAIR成像病变呈高信号（箭头所示） **图4** 女性患者，52岁。临床诊断为抗LGI1抗体相关边缘性脑炎。头部MRI检查所见 4a 横断面T_1WI显示，左侧颞叶内侧海马肿胀，呈低信号影（箭头所示） 4b 横断面T_2WI显示，左侧颞叶内侧海马肿胀，呈高信号影（箭头所示） 4c 横断面FLAIR成像病变呈高信号（箭头所示）

Figure 3 Male patient, 52 years old, clinical diagnosis as anti-LGI1 antibody-associated limbic encephalitis. Brain MRI findings Axial contrast-enhanced T_1WI showed slightly swelling of bilateral temporal hippocampus and symmetrical low-intensity signals without enhancement (arrows indicate, Panel 3a). Axial T_2WI showed slightly swelling of bilateral temporal hippocampus with symmetrical high-intensity signals (arrows indicate, Panel 3b). Axial FLAIR showed lesions with high-intensity signals (arrows indicate, Panel 3c). **Figure 4** Female patient, 52 years old, clinical diagnosis as anti-LGI1 antibody-associated limbic encephalitis. Brain MRI findings Axial T_1WI showed slightly swelling of left medial temporal hippocampus with low-intensity signals (arrows indicate, Panel 4a). Axial T_2WI showed slightly swelling of left medial temporal hippocampus with high-intensity signals (arrows indicate, Panel 4b). Axial FLAIR showed lesions with high-intensity signals (arrows indicate, Panel 4c).

0.30 g/d（2次/d），其中3例单纯服用左乙拉西坦、余3例联合应用两种抗癫痫药物（丙戊酸钠+左乙拉西坦、丙戊酸钠+奥卡西平或丙戊酸钠+丙戊酰胺）。所有患者出院后均接受随访，其中2例失访，5例随访3～13个月，病情不同程度改善，但均遗留远期记忆障碍（3例）或近期与远期记忆障碍并存（2例）；其

中1例出院6个月后复发。

讨 论

Irani等[5]在2010年首次于96例抗钾离子通道抗体阳性患者脑组织提取物中分离出抗LGI1抗体，为一种跨突触蛋白黏附分子。在人体内，突触前蛋白解整合素-金属蛋白酶11（ADAM11）、ADAM23和突触后蛋白ADAM22形成复合体，抗LGI1抗体可与该复合体结合并破坏该结构，使突触前递质减少，进而影响神经元之间的兴奋性传递[6-7]。近期研究显示，可从约90%的抗LGI1抗体相关边缘性脑炎患者的体内检出特定的人类白细胞抗原（*HLA*）基因亚型（*HLA-DR7*、*HLA-DRB4*、*HLA-DQB*），而由*HLA*基因介导的免疫反应与抗LGI1抗体的产生有关[8-9]。自2010年以来，共报道300余例抗LGI1抗体相关边缘性脑炎病例[10]，其中荷兰发病率0.0083/万人年[11]、丹麦0.0063/万人年[12]。该类型脑炎好发于50岁以上的中老年人群，男性多于女性[13]，本组7例患者发病年龄为22～63岁，平均（48.29±15.09）岁，其中有5例年龄超过50岁，男女之比4∶3，与文献报道基本一致。

抗LGI1抗体相关边缘性脑炎呈急性或亚急性发病，首发症状以近期记忆力减退、面-臂肌张力障碍发作常见，偶有间断性头痛；病程中可伴癫痫发作（尤以面-臂肌张力障碍发作者好发）、记忆力减退、精神行为异常或难治性低钠血症[2-3]。癫痫发作形式呈多样化，面-臂肌张力障碍发作为其特征性症状，表现为单侧或双侧面部及四肢不自主运动，发作时间可持续数秒，每日发作频率最长者可达百余次[14]。对于抗LGI1抗体相关边缘性脑炎的诊断，面-臂肌张力障碍发作为早期典型症状，发生率为47%～71%[15-16]，具有诊断意义[17]。本组7例患者中3例以面-臂肌张力障碍发作为首发症状，有2例于病程中出现，主要表现为阵发性四肢或面部肌肉不自主运动，单纯偏侧肢体受累（1例）或四肢均受累（2例），亦可同时累及四肢及面部[左侧面部与上肢（1例）、面部与双侧上肢（1例）]。关于其发病机制目前尚存争议，可能与炎症累及基底节区有关，而面-臂肌张力障碍发作仅为锥体外系症状[18]；亦可能是癫痫发作的一种形式，因部分面-臂肌张力障碍发作患者发作期脑电图可见颞区棘波[19-21]，而最新临床研究认为这可能是额叶局部性癫痫发作[22]。对于病程中伴发面-臂肌张力障碍发作的抗LGI1抗体相关边缘性脑炎患者，抗癫痫药物治疗效果欠佳，应以免疫抑制剂作为首选治疗方案[23]，本组6例经左乙拉西坦、丙戊酸钠等抗癫痫药物治疗后均未能达到有效控制发作的效果，仍间断发作。记忆力减退是抗LGI1抗体相关边缘性脑炎的另一典型症状，其中40%的患者为首发症状，病因或与双侧海马亚区CA2/3区、CA4/DG区结构萎缩和硬化引起的语言及空间记忆障碍有关。此类患者大多伴认知功能障碍和肌阵挛型癫痫，易误诊为Creutzfeldt-Jakob病（CJD）[18,23-24]，经免疫抑制剂治疗仅35%的患者记忆力可恢复正常[12]。本组患者病程中均出现记忆力减退，其中5例预后不良（3例远期记忆障碍、2例近期与远期记忆障碍并存）。有2例患者于病程中出现难治性低钠血症，此也为抗LGI1抗体相关边缘性脑炎临床常见表现之一；其具体机制尚未阐明，已知下丘脑和肾小管均可以表达LGI1抗原，而抗LGI1抗体作用于上述靶器官可导致下丘脑抗利尿激素分泌增加、肾小管对水的重吸收减少，进而引起血清钠持续降低[25]。然而，低钠血症并非特异性症状，钠盐摄入量减少、腹泻或呕吐使体内钠盐大量丢失，以及甲状腺功能减退致内环境功能紊乱等均可导致持续性低钠血症。

抗LGI1抗体相关边缘性脑炎的非特异性表现以癫痫发作及自主神经功能障碍最为常见，根据文献报道并结合本组病例特点，笔者认为以下症状与体征常可在病程中出现：（1）头部电击样疼痛和心情莫名悲伤，每日可发作20～30次[26]。（2）频发性胸闷、不适，各项心脏检查均无异常发现，但发作期视频脑电图可见右侧颞叶异常放电[27]。（3）约25%的患者因炎症累及岛叶而出现自主神经功能障碍如严重的阵发性心动过缓[28-29]。（4）若抗LGI1抗体侵及周围神经系统则表现为周围神经损伤症状，如双侧下肢无力或麻木，肌电图检查可见以脱髓鞘特征为主的感觉运动性多发性神经病，患者对免疫抑制剂反应良好[30-31]。（5）皮肤黑色素细胞受累时可合并白癜风[32]。（6）抗LGI1抗体相关边缘性脑炎为自身免疫性疾病而非副肿瘤综合征（PNS）[33]，因此血清抗TG抗体及抗TPO抗体检测多呈阳性反应，本组有4例患者血清抗甲状腺抗体水平升高。（7）极少合并肿瘤，发生率低于10%，一般以小细胞肺癌或胸腺瘤常见[34]。本组7例患者中仅1例曾罹患胸腺瘤经手术切除，但该患者同时合并重症肌无力，目前尚无相关文献报道；2例胸部CT检查显示肺小结节

影，其中1例血清NSE（23.73 ng/ml）水平升高。

抗LGI1抗体相关边缘性脑炎的诊断与鉴别诊断以脑脊液和（或）血清抗LGI1抗体阳性为主要依据，一般脑脊液阳性检出率略高于血清（100%：88%）[14]；但也有文献报道，脑脊液抗LGI1抗体阳性检出率仅为53%[35]。一般情况下，脑脊液常规检查可无明显异常，或仅表现为白细胞计数轻度增高；本组患者中有6例脑脊液、7例血清抗LGI1抗体呈阳性反应，仅1例患者脑脊液白细胞计数轻度增高（18×10^6/L）、6例氯化物降低（109～118 mmol/L），可能与低血钠、低血氯有关。除外脑脊液和血清学各项化合物的变化，急性期影像学改变亦至关重要，约69%的患者可呈现特异性影像学异常[36]，即T_2WI和FLAIR成像呈单侧或双侧颞叶海马高信号，同时可见颞叶、额叶和小脑白质萎缩，后者可能与患者预后不良有关。另外，^{18}F-脱氧葡萄糖（^{18}F-FDG）PET显像亦是辅助诊断方法之一，患者在发病初期边缘系统病灶对放射性同位素^{18}F-FDG的摄取能力增强，而恢复期能力则逐渐减弱直至恢复至正常状态，可以作为疗效判断指标[37-38]；动脉自旋标记（ASL）可以通过脑血流量变化评价伴癫痫发作患者的预后[39-40]。

虽然迄今尚无明确的抗LGI1抗体相关边缘性脑炎的临床治疗指南，但首选大剂量糖皮质激素序贯治疗，同时辅以静脉注射免疫球蛋白（IVIg）或血浆置换（PE）等治疗方案已达成基本共识[41]。对于治疗1～2周仍无效的患者可考虑二线治疗方案，如利妥昔单抗和环磷酰胺。疗效评价应以患者临床症状改善作为判断指标，而血清与脑脊液抗LGI1抗体水平的变化不能反映疾病预后和转归[40-42]。

综上所述，对于呈急性或亚急性发病，临床表现为近期记忆力减退或面-臂肌张力障碍发作的患者，结合T_2WI和FLAIR成像单侧或双侧颞叶海马高信号，以及脑脊液和血清抗LGI1抗体阳性，则可明确诊断为抗LGI1抗体相关边缘性脑炎。同时应注意与Creutzfeldt-Jakob病，代谢性脑病（尿毒症、肝性脑病等），中毒性脑病（酒精中毒、一氧化碳中毒等）和自身免疫性疾病[干燥综合征（SS）、系统性红斑狼疮（SLE）等]等相鉴别。对于高度怀疑抗LGI1抗体相关边缘性脑炎的患者应尽早采用大剂量糖皮质激素序贯治疗并辅以静脉注射免疫球蛋白，控制疾病进程；免疫抑制剂可明显改善患者预后[12]。

利益冲突 无

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