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抗LGI1抗体相关脑炎一例病例报道并文献复习

刘　悦[1]，李翠萍[2]，田新涛[3]，张晓蒙[1]，杨绍楠[1*]

[1]青岛大学附属医院神经内科，山东　青岛
[2]青岛大学附属医院重症医学科，山东　青岛
[3]青岛大学附属医院泌尿外科，山东　青岛

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摘　要

自身免疫性脑炎是一种罕见的神经系统炎症性疾病，自2005年首次报道了N-甲基-D-天冬氨酸(NMDA)抗体脑炎后，已经描述了数量惊人的新型致病抗体。根据抗体不同，自身免疫性脑炎分为不同类型，抗富亮氨酸胶质瘤灭活1 (LGI1)抗体相关性脑炎是自身免疫性脑炎的一种亚型，以急性或亚急性认知障碍、面－臂肌张力障碍发作、癫痫、精神障碍和低钠血症为特征。我们报道了一例抗LGI1抗体相关脑炎合并桥本甲状腺炎的病例。由于自身免疫性脑炎的临床和影像学表现呈多样性，常给诊断带来挑战。在这篇文章中，我们讨论了该类自身免疫性脑炎的相关特征及其他合并疾病，提高神经科医生对该类自身免疫性脑炎的认识，对早期诊断、治疗甚至预后都具有重要意义。

关键词

自身免疫性脑炎，桥本甲状腺炎，LGI1，免疫治疗

Antibody LGI1 Autoimmune Encephalitis: A Case Report and Literature Review

Yue Liu[1], Cuiping Li[2], Xintao Tian[3], Xiaomeng Zhang[1], Shaonan Yang[1*]

[1]Department of Neurology, The Affiliated Hospital of Qingdao University, Qingdao Shandong
[2]Department of Critical Care Medicine, The Affiliated Hospital of Qingdao University, Qingdao Shandong
[3]Department of Urology, The Affiliated Hospital of Qingdao University, Qingdao Shandong

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Abstract

Autoimmune encephalitis is a rare neuroinflammatory disease, and since the first report of N-

*通讯作者 Email: yangshaonan@qdu.edu.cn

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Methyl-D-Aspartate (NMDA) antibody encephalitis in 2005, a remarkable number of novel pathogenic antibodies have been described. Autoimmune encephalitis can be categorized into different types based on the specific antibodies involved. Anti-Leucine-Rich Glioma-Inactivated 1 (LGI1) antibody-associated encephalitis is a subtype of autoimmune encephalitis characterized by acute or subacute cognitive impairment, faciobrachial dystonic seizures, seizures, psychiatric disturbances, and hyponatremia. In this case report, we present a case of anti-LGI1 antibody-associated encephalitis coexisting with Hashimoto's thyroiditis. Due to the diverse clinical and radiological presentations of autoimmune encephalitis, diagnosis can be challenging. In this article, we discuss the distinctive features of this subtype of autoimmune encephalitis and its comorbidities. Raising awareness among neurologists about this type of autoimmune encephalitis is crucial for early diagnosis, treatment, and prognosis.

Keywords

Autoimmune Encephalitis, Hashimoto's Thyroiditis, LGI1, Immunotherapy

1. 引言

自身免疫性脑炎是一组异质性的炎症性自身免疫介导的疾病，可影响脑实质，也可能累及脑膜和脊髓[1]。根据靶抗原在中枢神经系统的细胞定位共分为三组抗体，即抗细胞内树突神经元抗原的抗体、抗神经元突触抗原的抗体及细胞表面抗原抗体[2] [3]，其特征是针对参与突触信号传导和可塑性的神经元蛋白的自身抗体[4]。该疾病通常急性或者亚急性起病，在六周内迅速发展[5]。临床特征包括行为改变、精神症状、癫痫、记忆和认知障碍、异常运动、自主神经失调和意识水平下降等[6]。大多数脑炎的原因是感染性的，但自身免疫性脑炎的主要发病原因是癌症(副肿瘤性) [7]、感染(副感染性) [8]，也可能是隐源性的[2]。多数患者神经系统症状先于癌症的诊断[9]。因此，根据不同类型的脑炎，排查肿瘤相关疾病尤为重要[7]。接下来我们报道了一例抗 LGI1 抗体相关脑炎的患者。

2. 个案报道

患者，男，70 岁，既往高血压、脑梗死、冠心病及骨质疏松病史，此次因记忆力下降 1 个月，加重 3 天于急诊就诊。患者 1 个月前无明显诱因出现记忆力下降，伴幻嗅、伴头晕、恶心，伴右上肢及右侧面部放电感，每次持续性数秒钟；3 天前上述症状加重，立即于急诊就诊。急诊查体：体温：36.3℃，脉搏 57 次/分，呼吸 17 次/分，血压 168/95 mmHg，心肺腹未见明显异常。专科查体：神志清楚，反应稍迟钝，言语流利，双眼球各方向活动自如，无眼震，双侧瞳孔等大等圆，直径约 3.0 mm，对光反射灵敏，双侧额纹、鼻唇沟对称，伸舌居中，四肢肌力 5 级，肌张力正常，四肢腱反射(++)，感觉、共济查体未见明显异常，双侧病理征(−)，颈软，脑膜刺激征(−)。急查血常规、电解质、肝功、肾功、血糖及心肌酶未见明显异常。颅脑 MR 提示自身免疫性脑炎可能性大(图 1)。于急诊行简易智能状态检查量表及蒙特利尔认知评价量表分别为 14/30，20/30 (患者文化程度：文盲)。为进一步明确诊断，收入病房行进一步检查。

完善相关辅助检测，入院后立即行腰椎穿刺术，脑脊液压力 200 mmHg，脑脊液常规白细胞总数 11 × 10^6/L (正常值 0~8 × 10^6/L)，脑脊液生化、脑脊液内免疫球蛋白、脑脊液细菌三项(细菌、抗酸杆菌及隐

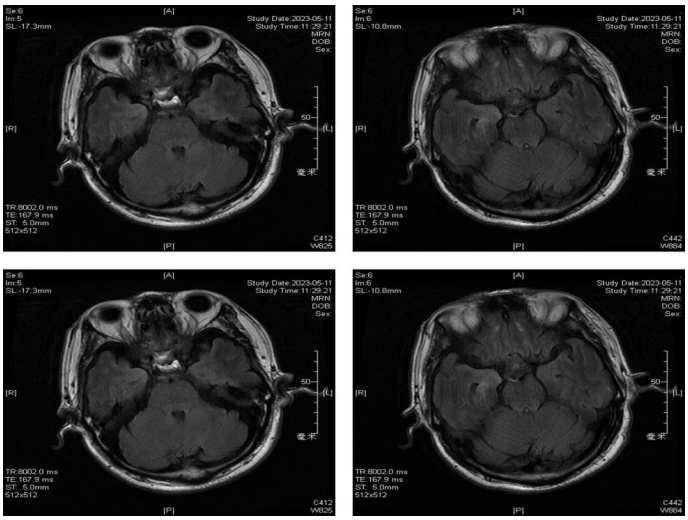

Figure 1. MRI indicates abnormal signals in the right hippocampus and medial temporal lobe, suggesting a high possibility of mesial temporal lobe epilepsy
图 1. 颅脑 MR 提示右侧海马、颞叶内侧异常信号，自免脑可能性大

球菌)、血免疫球蛋白、血糖均未见明显异常，血液及脑脊液中抗富亮氨酸胶质瘤失活蛋白 1 (LGI 1)抗体 IgG 阳性(1:10)；血凝常规结果提示 D-二聚体 590 ng/ml；甲状腺球蛋白 0.11 ng/ml，抗甲状腺球蛋白抗体 > 4000 IU/ml，甲状腺过氧化物酶抗体 > 600 IU/ml；免疫学相关指标抗核抗体(胞浆颗粒) 1:100，抗 Ro-52 抗体(++)；男性肿瘤标志物、传染四项、尿常规、粪便常规均未见明显异常；胸部 CT 提示慢性炎症可能性大(图 2)；心脏及颈部血管超声未见明显异常；颅脑增强 MR 提示右侧海马、颞叶内侧异常信号强化不明显，不除外自身免疫性脑炎(图 3)；甲状腺超声提示弥漫性病变；脑电图检查未见明显异常(图 4)。目前诊断为抗富亮氨酸胶质瘤失活蛋白 1 (LGI 1)脑炎、桥本甲状腺炎。由于患者既往骨质疏松病史，患者家属拒绝激素治疗，我们给予了丙种球蛋白，治疗后第 3 天患者诉记忆力明显好转，同时幻嗅及右上肢及面部放电感消失。我们再次对患者进行简易智能状态检查量表及蒙特利尔认知评价量表分别为 21/30，25/30。出院前复查颅脑核磁(图 5)提示自身免疫性脑炎较前好转。

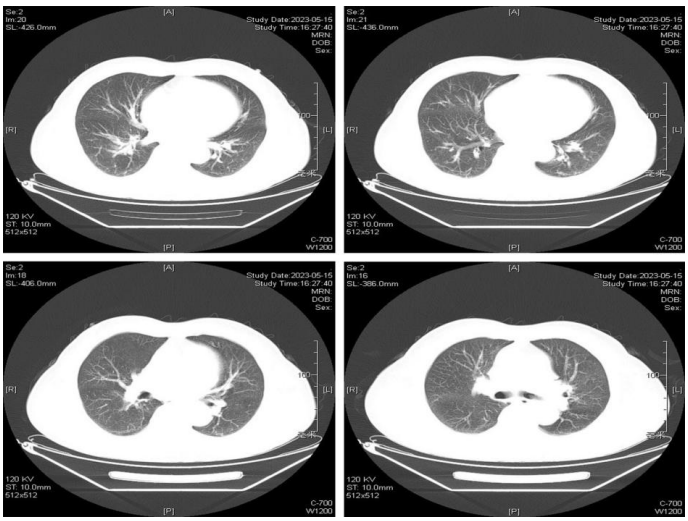

Figure 2. Chest CT suggests a high likelihood of chronic inflammation
图 2. 胸部 CT 提示慢性炎症可能性大

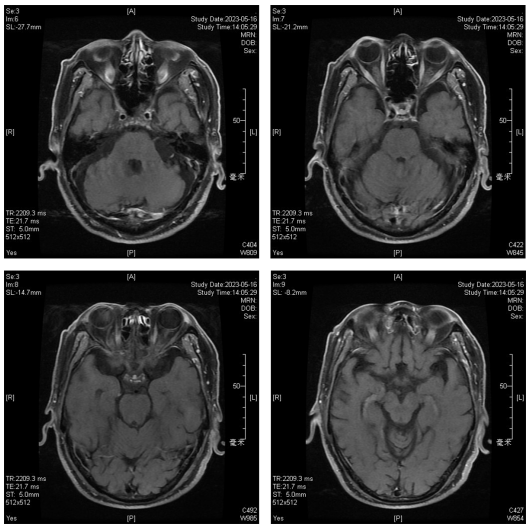

Figure 3. Enhanced brain MRI indicates that the enhancement of abnormal signals in the right hippocampus and medial temporal lobe is not clearly visible
图 3. 颅脑增强 MR 提示右侧海马、颞叶内侧异常信号强化不明显

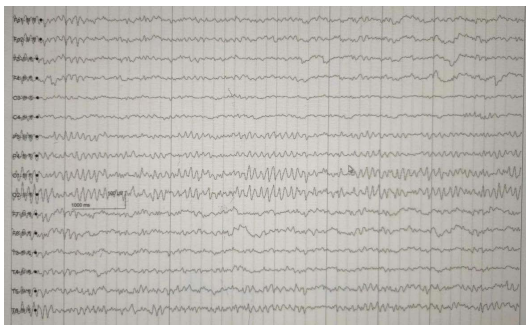

Figure 4. The electroencephalogram does not show any significant abnormalities
图 4. 脑电图未见明显异常

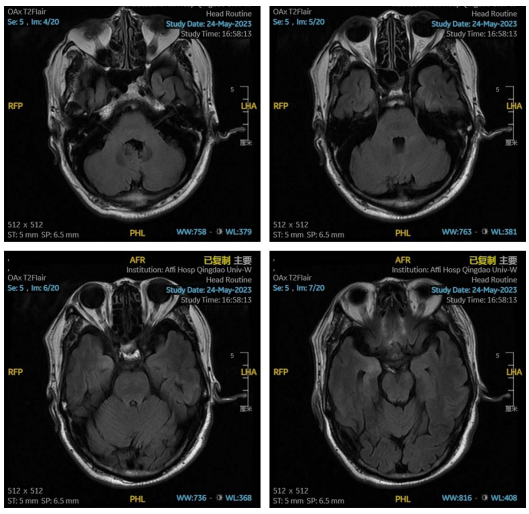

Figure 5. Brain MRI shows improvement compared to the previous one
图 5. 颅脑核磁较前好转

3. 讨论

LGI1 抗体相关性脑炎是一种罕见的自身免疫性边缘性脑炎[10]，该病平均发病年龄在 63 岁左右[11]，其发病率约为 0.83/1 亿[12]。LGI1 是电压门控钾通道分子复合物的组成部分，可以破坏突触功能并诱发神经元的高兴奋性；此外，它们的滴度与疾病的严重程度有关[13]。该病主要累及内侧颞叶、杏仁核、海马、扣带皮层和岛叶[14]，这些结构在人的情绪、记忆、癫痫发作等方面至关重要。LGI 1 抗体相关脑炎临床表现多样，根据现有的个案报道，临床表现主要包括记忆力下降(90%) [15]、癫痫发作(发病率 65%~82%) [16]、精神症状(18%) [17]、面肌张力障碍[12]、低钠血症(发病率 65%~75%) [18]及睡眠障碍(14%) [19] [20]。其中，面－臂肌张力障碍发作是典型的临床表现，影响 34%~68%的患者，与 LGI 1 抗体脑炎具有独特关联[21]。面－臂肌张力障碍发作是一种局灶性癫痫的表现，这些癫痫发作是 1~2 秒肌张力异常收缩，影响单侧面部和手臂(或腿) [22]。该患者出现右侧面部及上肢放电感，但脑电图并未提示异常，其主要原因在于患者在使用免疫球蛋白后进行脑电检测，此时患者症状已完全好转。因此，我们并未使用抗癫痫药物。除面－臂肌张力障碍发作外，记忆障碍也是一种常见的表现形式[23]，尤以短时记忆障碍为主。其主要原因是由于抗原抗体反应导致海马体发生炎症变化，最终导致海马萎缩或硬化，认知功能迅速下降[15]。多项研究证明 LGI-1 抗体相关性脑炎患者后期复发率较高[24] [25]，尤其以认知障碍为主[14]。在认知功能障碍发生之前进行早期诊断，在没有脑炎标准的情况下识别该疾病，以及可能更积极的前期免疫治疗是改善结局的重要步骤[26] [27]。

自身免疫性边缘性脑炎是一种快速进展性痴呆。因此，与其他可以导致记忆障碍的疾病进行鉴别尤为重要[18]。由于该患者还存在甲状腺过氧化物酶抗体>600 IU/ml，是否存在桥本脑病是我们鉴别诊断的重点。甲状腺过氧化物酶抗体和甲状腺球蛋白抗体升高是桥本甲状腺炎的诊断标准[28]。桥本甲状腺炎是一种常见的自身免疫性疾病[29]。其最常见的临床表现是甲状腺肿大，伴有或不伴有甲状腺功能减退。这主要是甲状腺过氧化物酶(TPO)抗体和甲状腺球蛋白抗体对甲状腺的攻击作用[28]。当这两种抗体异常升高时，可以诱发桥本脑病的发生[30]。但由于桥本脑病发病率低、临床表现多样、发病机制不明，目前还没有公认和完善的诊断标准[31] [32]，这对我们临床诊断造成极大的困难。从桥本脑病的诊断标准来说，血清和脑脊液中缺乏明确的神经元抗体、出现神经系统症状、存在高滴度抗 TPO 抗体、类固醇治疗后症状好转，我们可以诊断其为桥本脑病[31]。但通过文献阅读[33] [34] [35]我们发现桥本脑病也可能合并其他自身免疫性脑炎抗体的存在，这主要是桥本脑病诱发的继发性免疫反应所致。该病例中的患者血清及脑脊液存在 LGI 1 抗体，结合以上两点，我们优先诊断该患者为自身免疫性脑炎，但我们并不能排除桥本脑病的存在。随着我们检验手段的提升以及更多自身免疫性脑炎抗体的出现，桥本脑病与自身免疫性脑炎共存的概率可能会增加。在既往没有自身免疫性抗体检测技术的情况下，相当一部分的桥本脑病患者可能合并自身免疫性脑炎，但并未进行相关抗体检测。同时多项研究表明[35] [36] [37]桥本脑病与其他系统性和/或器官特异性自身免疫性疾病共病，如狼疮、干燥综合征、萎缩性胃炎/恶性贫血和重症肌无力。该患者甲状腺过氧化物酶抗体及抗甲状腺球蛋白抗体极高，也是造成上述免疫学指标异常的原因。

LGI1 相关性脑炎与肿瘤的相关性较低，但当存在时，胸腺瘤最常见[38] [39]。因此，我们仅进行了胸部 CT 及男性肿瘤标志物的筛查。该患者胸部 CT 及男性肿瘤标志物未见异常。文献报道约 2/3 的患者在确诊肿瘤前出现神经系统症状[40]。因此，我们也告知患者 1~3 个月定期复查相关指标。

在疾病急性期，大多数患者可检测到单侧或双侧颞叶内侧 T2/FLAIR 高信号[41]。该患者也出现了右侧海马及颞叶 T2/FLAIR 高信号，且在增强 MR 下强化不明显，由此排除了脑肿瘤相关病变。由于存在颞叶受累，该患者可出现幻嗅这一异常症状。目前 ASL 及 PET-CT 已经被用于自身免疫性脑炎患者检查脑内灌注/代谢异常[18] [41] [42]。由于预约周期较长，考虑到患者已使用免疫球蛋白且患者临床症状完

全好转，我们取消了该项检查。LGI 1 抗体介导的自身免疫性脑炎治疗的关键治疗方案是免疫治疗。一线治疗药物包括单药或联合高剂量皮质类固醇、静脉注射免疫球蛋白或血浆置换。二线治疗包括环磷酰胺和/或利妥昔单抗[43] [44] [45]。目前研究表皮质醇激素比丙种球蛋白治疗更有效[46]。由于患者存在骨质疏松，因此，我们给予丙种球蛋白治疗。

4. 结论

综上所述，虽然 LGI-1 抗体相关性脑炎较为罕见，但当患者出现急性或亚急性记忆障碍、幻嗅和面肌张力异常发作等临床表现，同时磁共振扫描发现单侧或双侧颞叶、海马等边缘系统为高信号时，应高度怀疑此病。及时完善颅脑核磁和腰椎穿刺术有助于疾病诊断。较早应用激素或免疫球蛋白对患者预后具有重要意义。该患者的甲状腺相关抗体异常升高是该患者自身免疫性脑炎的一个诱发因素，后期我们会继续关注甲状腺相关抗体异常升高且伴有自身免疫性抗体阳性的患者，为提高患者预后做好坚实的基础。

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