·癫痫及发作性疾病·

自身免疫相关性癫痫临床研究进展

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【摘要】 癫痫病因复杂，免疫因素已成为癫痫的独立病因。随着对“自身免疫性癫痫”概念和发病机制的深入研究，提出“继发于自身免疫性脑炎的急性症状性发作”和“自身免疫相关性癫痫”两个概念。本文介绍“自身免疫相关性癫痫”概念进展，阐述抗神经元细胞内或细胞表面抗原抗体通过不同途径介导癫痫发作的作用机制，总结常见的以癫痫发作为主要表现的自身免疫性脑炎，以提高临床对自身免疫相关性癫痫的认识及诊断术语的规范。

【关键词】 脑炎；　自身免疫疾病；　癫痫；　自身抗体；　神经元；　综述

Progress of clinical research on autoimmune-associated epilepsy

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【**Abstract**】 Etiology of epilepsy is complex. Immune has been defined as one of the etiological groups of epilepsy. Autoimmune epilepsy attracts experts worldwide to investigate and new conceptual definitions has been proposed. Based on the pathophysiology, autoimmune epilepsy includes two entities, which are acute symptomatic seizures secondary to autoimmune encephalitis (AE) and autoimmune-associated epilepsy (AAE). We interpret the new concepts, the characteristics of extracellular and intracellular neuronal antibodies which contribute to the pathogenesis of epilepsy, and AE manifested by seizures in this review. We hope that the article helps researchers and clinicians have a better understanding of AAE and use standard terms in practical situations, thus improving diagnosis and treatment of epilepsy.

【**Key words**】 Encephalitis; Autoimmune diseases; Epilepsy; Autoantibodies; Neurons; Review
This study was supported by Financial Support of National Key Research and Development Program of China (No. 2022YFC2503800).
Conflicts of interest: none declared

癫痫是一种由多种病因引起的慢性脑部疾病。近年研究显示，系统性自身免疫性疾病患者合并癫痫的风险显著增加，主要包括抗磷脂抗体综合征（APS）、系统性红斑狼疮（SLE）、重症肌无力（MG）等[1]，提示免疫机制可能在癫痫发生发展中发挥重要作用。随着多个靶向神经元细胞内或者细胞表面抗原的特异性自身抗体的相继发现，自身免疫性脑炎（AE）成为临床常见疾病，部分患者急性期常表现为持续性、难治性癫痫发作，免疫治疗有明确疗效[2]。此类自身免疫性脑炎继发癫痫发作称为继发于自身免疫性脑炎的急性症状性发作（actue symptomatic seizures secondary to AE），脑炎治愈后出现的反复癫痫发作则称为自身免疫相关性癫痫（AAE）[3]。本文阐述“自身免疫相关性癫痫”概念进展，以推动临床诊断术语的规范，总结常见的癫痫相关抗神经元抗体和自身免疫性脑炎类型，并对未来药物研发和治疗进行展望。

一、“自身免疫相关性癫痫”概念进展

Levite在第3届国际自身免疫大会（ICA）首次提出了“自身免疫性癫痫”的概念，指一系列免疫细胞

doi：10.3969/j.issn.1672-6731.2023.02.004
基金项目：国家重点研发计划重点专项（项目编号：2022YFC2503800）
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或自身抗体介导的癫痫[4]。这一概念突出免疫机制发挥主要作用的癫痫，但尚未明确特定自身抗体，因其指代范围较大，故临床应用存在一定争论。2017年，国际抗癫痫联盟（ILAE）将免疫因素列为癫痫的独立病因，建议将“自身免疫性癫痫”定义为自身免疫性疾病过程中出现的癫痫发作[5]。然而临床实践中，自身免疫性脑炎急性期常因应用免疫抑制剂使癫痫发作改善，不符合其反复性、刻板性、可重复性本质，且癫痫发作并非自身免疫性脑炎的唯一临床表现，患者常合并认知功能和记忆障碍、人格和精神行为改变、自主神经功能紊乱，提示癫痫发作可能仅为自身免疫性脑炎的临床表征之一。自身免疫性脑炎急性期仅单独应用抗癫痫发作药物（ASM）无法完全控制发作[6]，大部分患者联合应用免疫抑制剂和抗癫痫发作药物后可完全控制发作甚至停用抗癫痫发作药物。因此，准确定义传统的“自身免疫性癫痫”这一具有争议性的概念，有助于临床医师尽早予以免疫治疗、制定抗癫痫发作药物方案。2020年7月，国际抗癫痫联盟自身免疫和炎症工作组在*Acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune-associated epilepsy: conceptual definitions*[3]一文中提出“继发于自身免疫性脑炎的急性症状性发作”和“自身免疫相关性癫痫”两个新概念，二者在临床表现、治疗方案和预后方面均不同，新概念的提出有助于临床医师进行更好的治疗决策。部分自身免疫性脑炎患者急性期后可继续进展至癫痫[7]，未来有望通过自身免疫性脑炎发病机制和生物学标志物的探索，进一步完善继发于自身免疫性脑炎的急性症状性发作的细化分类。

1. 继发于自身免疫性脑炎的急性症状性发作　自身免疫性脑炎急性期背景下的初始或反复发作定义为急性症状性发作，有时可持续数周甚至数月方缓解，是自身免疫性脑炎的主要症状之一。大多数患者经免疫治疗后，自身免疫性脑炎各种临床症状均改善的同时，癫痫发作显著减少或消失。自身免疫性脑炎最常累及边缘系统，尤其是颞叶内侧和岛叶，故局灶性癫痫（FE）是其最常见类型，发作频率显著高于其他原因引起的局灶性癫痫，每天均有发作或一天数次发作，甚至首发即发生难治性癫痫持续状态（RSE）。此类患者癫痫发作时通常无意识改变，且发作后意识障碍相对少见[8]。一项继发于自身免疫性脑炎的急性症状性发作与海马硬化（HS）致癫痫的对比分析显示，前者发作时间更短，仅持续数秒，后者发作持续1～3分钟；前者双侧强直-阵挛发作更常见，且更倾向夜间发作[8]。

2. 自身免疫相关性癫痫　与继发于自身免疫性脑炎的急性症状性发作不同，部分患者急性期后出现慢性、反复性、非诱发性发作，且无合并明显炎症反应的证据，符合传统“癫痫”的定义，称为自身免疫相关性癫痫。继发于自身免疫性脑炎的急性症状性发作早期对免疫治疗有效，而自身免疫相关性癫痫对免疫抑制剂和抗癫痫发作药物的效果不明显[9]。“自身免疫相关性癫痫”的术语强调免疫机制并非癫痫的唯一病因，继发性异常神经回路形成可能在癫痫发生发展中发挥重要作用，如抗富亮氨酸胶质瘤失活基因1（LGI1）抗体相关脑炎的海马萎缩、Rasmussen脑炎（RE）的多灶性皮质神经元脱失伴神经胶质增生等损害均可能是导致慢性癫痫的原因[10-11]。一旦诊断自身免疫相关性癫痫，应立即开始规范的抗癫痫治疗，而不局限于免疫治疗，对于难治性癫痫患者，可手术切除明确的癫痫灶[12]。

3. 两个概念的争议　“急性症状性发作”的原定义局限于脑卒中或颅脑创伤等脑损伤后7天内，明确为脑损伤后立即出现的癫痫发作[13]。自身免疫性脑炎继发癫痫发作的发病时间不确定，免疫治疗后癫痫发作可遗留数周甚至数月，故国际抗癫痫联盟提出的新概念无法对“急性期”予以明确界定，仅要求癫痫发作发生于自身免疫性脑炎“活动期”，如实验室检出高滴度抗神经元抗体、脑脊液炎性标志物，或者有脑组织炎症反应活跃的临床证据。明确定义自身免疫相关性癫痫，应持续随访自身免疫性脑炎至少1年[14]；而对于脑脊液自身抗体阴性、病因无法明确的新发难治性癫痫持续状态、随访1年仍无法明确诊断自身免疫相关性癫痫的患者，其随访诊断尚无参考标准，有待临床试验进一步探究。此外，自身免疫性脑炎的复发率为15%～35%，并取决于自身抗体类型[15-17]，其复发通常伴随癫痫发作的复发，此类患者癫痫发作总时间远远超出“急性症状性发作”的时间范围，因此尚待更全面的临床研究对自身免疫性脑炎急性期进行明确分层。

二、抗神经元抗体与癫痫

血清或脑脊液检出抗神经元抗体不仅是自身免疫相关性癫痫的重要诊断指标，且可预测急性症状性发作能否进展为癫痫，有助于制定治疗方案。抗神经元抗体包括抗神经元细胞内抗原抗体和抗

神经元细胞表面抗原抗体。不同研究中癫痫患者抗神经元抗体阳性率差异较大(15%～25%)[18-20],也有未检出抗神经元抗体的报道[21-22]。最常见的抗体是抗谷氨酸脱羧酶65(GAD65)抗体(3.94%),其次为抗甘氨酸受体(GlyR,2.36%)、N-甲基-D-天冬氨酸受体(NMDAR,2.15%)、接触蛋白相关蛋白-2(CASPR2,1.37%)、LGI1(1.37%)抗体[23]。

1.抗神经元细胞内抗原抗体 抗神经元细胞内抗原抗体主要包括抗谷氨酸脱羧酶(GAD)抗体,抗Hu、Ma1和Ma2抗体,多见于副肿瘤边缘性脑炎(PLE),与潜在恶性肿瘤相关,临床常表现为边缘系统癫痫发作[24]。针对特定抗原的细胞毒性T细胞(CTL)在副肿瘤综合征(PNS)的致病机制中发挥重要作用,可导致神经元死亡,而自身抗体更多是免疫反应产物,并不具有直接致病作用[25-26]。此类患者免疫治疗效果较差,预后不良,有持续性癫痫发作的倾向,更易进展为自身免疫相关性癫痫[27-28]。尽管尚无证据表明抗GAD65抗体和副肿瘤综合征抗体对自身免疫相关性癫痫有直接的致病作用,但脑组织活检或癫痫外科手术病理学检查常有炎症反应证据[29],推测可能是T淋巴细胞介导的炎症反应使脑结构改变,形成异常神经回路,导致自发性癫痫发作。

2.抗神经元细胞表面抗原抗体 抗神经元细胞表面抗原抗体包括抗α-氨基-3-羟基-5-甲基-4-异噁唑丙酸受体(AMPAR)、γ-氨基丁酸受体(GABAR)、NMDAR、LGI1和CASPR2抗体等[30-31]。此类抗体的致病机制与B淋巴细胞介导的免疫反应有关,通过影响兴奋性或抑制性神经递质合成及其作用而致病,部分可伴发肿瘤[34-35]。目前认为,抗神经元细胞表面抗原抗体特别是抗LGI1和NMDAR抗体引起的自身免疫性脑炎,免疫治疗效果较好,相关癫痫发作亦可缓解[35]。

三、与癫痫发作密切相关的自身免疫性脑炎

1.抗LGI1抗体相关脑炎 抗LGI1抗体相关脑炎好发于中老年,发病年龄40～80岁、中位发病年龄65岁,男性多于女性(66%对34%),呈急性或亚急性发病[36-37]。临床最常见表现是伴知觉保留的局灶性发作,此外还包括热气上涌感、自主神经性发作如发作性竖毛、躯体感觉性发作如局部麻木感和针刺感[38-39],大约50%患者可出现特征性发作——面-臂肌张力障碍发作(FBDS)[40]。面-臂肌张力障碍发作时间较短,仅持续数秒,每天数次发作,通常表现为上肢肌肉和同侧面颈部肌肉同时收缩,有时可累及下肢;单次发作仅累及一侧肢体,但对侧肢体很快出现相同发作。与其他原因引起的局灶性发作相比,抗LGI1抗体相关脑炎发作类型多样,且早于其他脑炎症状的出现,发作频率高、持续时间短、发作后意识障碍相对少见[41]。阵发性短暂性头晕虽不常见,但抗LGI1抗体相关脑炎的特征性表现,呈眩晕样发作[42],同时可能出现近记忆力下降、精神行为异常和肌张力障碍等。头部MRI多表现为单侧或双侧颞叶内侧异常信号,部分可见基底节区异常信号。此外,海马萎缩虽为抗LGI1抗体相关脑炎的常见后遗症,但纵向研究显示,海马损伤并不足以导致癫痫发作,提示免疫机制在抗LGI1抗体相关脑炎导致的癫痫发作中发挥重要作用[37,43-44]。此类患者的实验室检查无特异性,脑脊液缺乏提示炎症反应的表现,如白细胞计数增多、蛋白定量或IgG指数升高[45-46]。

2.抗NMDAR脑炎 抗NMDAR脑炎好发于儿童和年轻女性,发病机制为抗NMDAR抗体阻断NMDAR与EphrinB2受体之间的相互作用,导致细胞表面NMDAR内化[47]。约80%的抗NMDAR脑炎患者可出现癫痫发作,如单纯运动性发作、复杂部分性发作或伴知觉障碍的局灶性发作,甚至同一例患者可出现多种发作类型[48]。临床还表现为自主神经功能紊乱,以高热、流涎、心律失常常见,患者早期即出现明显的精神症状是最突出的临床表征,从情景记忆丧失到焦虑、失眠、紧张、人格改变、强迫性摄食等[49-50]。运动障碍也是常见临床特征,约50%癫痫发作患者可出现运动障碍[51],主要表现为口舌面肢体运动障碍、手足徐动症、肌张力障碍和动眼神经危象等,应注意与口部自动症相鉴别[52]。自身免疫性脑炎发病前可能有病毒感染的前驱症状,单纯疱疹病毒性脑炎(HSE)可继发抗NMDAR脑炎,既往存在恶性肿瘤病史提示副肿瘤性自身免疫性脑炎[53]。大多数(70%)抗NMDAR脑炎患者影像学无异常[54],但可见典型的颞叶内侧FLAIR成像高信号[55]以及急性期枕叶皮质低代谢[56]的相关报道。Schmitt等[57]和Gillinder等[58]提出,抗NMDAR脑炎患者脑电图随疾病进展可出现广泛性节律性δ活动,并最终在30%的患者中形成特异性改变,即极度δ刷,表现为持续性节律性1～3 Hz活动上叠加1～2秒的β或γ活动[59],提示预后不良。某些情况下,抗NMDAR抗体仅存在于脑脊液而非血清中,故

脑脊液抗体检测在抗NMDAR脑炎的诊断中更重要。多数患者急性期脑脊液可见单核细胞计数增多,蛋白定量轻至中度升高[60]。

3. 抗GAD65抗体相关脑炎 尽管抗GAD65抗体的致病性仍存争议,但可确定的是抗GAD65抗体阳性在自身免疫相关性癫痫中最常见。抗GAD65抗体相关脑炎常引起慢性颞叶癫痫[61-63],伴不同程度认知功能障碍和精神异常,具有难治性特点,预后较差。约40%的抗GAD65抗体相关脑炎患者合并系统性自身免疫性疾病,尤其是1型糖尿病和桥本甲状腺炎。癫痫发作频率较其他脑炎引起的癫痫发作更频繁,同时也存在局灶性发作或伴知觉改变的意识障碍[64]。出现局灶性运动发作时表现为异常运动,如口舌面肢体运动障碍和肌张力障碍。

4. Rasmussen脑炎 Rasmussen脑炎是一种好发于儿童的慢性炎症,中位发病年龄为6岁[65],常累及一侧大脑半球导致慢性难治性癫痫,伴进行性神经系统功能障碍。Rasmussen脑炎致病机制由T淋巴细胞介导,即使至疾病晚期仍有少量T淋巴细胞介导的炎症反应[66];此外,针对NMDAR GluN2亚单位、AMPAR GluA3亚单位的抗神经元抗体也与疾病进展有关[67-68]。脑脊液可检出IgG、$CD4^+$T细胞、肿瘤坏死因子-α(TNF-α)和颗粒酶B(GZMB),表明免疫机制参与Rasmussen脑炎的发生,但Rasmussen脑炎对免疫治疗的反应并不一致,甚至疾病活动期的免疫治疗效果也不尽相同,静脉注射免疫球蛋白(IVIg)仅可使病情缓解,多种抗癫痫发作药物联用效果欠佳[69]。目前对于Rasmussen脑炎伴高癫痫发作负担的患儿,常需手术控制发作,大脑半球切除术和大脑半球离断术是最有效的方法,可使60%~85%的患儿癫痫发作明显改善[70]。

综上所述,免疫因素是癫痫的独立病因,明确该病因可预测免疫治疗获益患者。自身免疫性脑炎急性期出现急性症状性发作,应尽早开始免疫治疗,并辅以抗癫痫发作药物;一旦出现免疫介导的结构性脑损伤、持续活跃的异常神经回路,即应考虑自身免疫相关性癫痫,并予以规范的抗癫痫治疗;对于难治性癫痫、新发难治性癫痫持续状态,应及时进行免疫学病因评估。尚待进行更多的抗神经元抗体致病机制研究,进而开展疾病修饰治疗,更好地控制癫痫发作、预防癫痫灶形成。明确基于致病机制的新型生物学标志物,有助于早期诊断、及时治疗,最终改善患者预后。

利益冲突 无

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(收稿日期:2023-02-17)
(本文编辑:彭一帆)