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中枢神经系统脱髓鞘疾病与痫性发作

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摘　要

中枢神经系统脱髓鞘疾病是一种以神经功能障碍为主要表现的自身免疫性疾病，常见病种包括多发性硬化、视神经脊髓炎谱系疾病、少突胶质细胞糖蛋白IgG抗体相关疾病。这类疾病以视神经炎、脊髓炎、共济失调等为主要临床表现，部分有痫性发作。近年来，越来越多的研究表明，中枢神经脱髓鞘疾病与痫性发作有关，但其痫性发作的机制尚不明确。本文旨在对常见中枢神经脱髓鞘疾病与相关痫性发作进行综述。

关键词

中枢神经系统脱髓鞘疾病，痫性发作，少突胶质细胞糖蛋白IgG抗体相关疾病

Demyelinating Diseases of the Central Nervous System and Seizures

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Abstract

Demyelinating diseases of the central nervous system are autoimmune diseases with neurological dysfunction as the main manifestation. Common diseases include multiple sclerosis, neuromyelitis optica spectrum disorders, anti-myelin oligodendrocyte glycoprotein-IgG associated disorders. The prominent clinical symptoms include optic neuritis, myelitis and ataxia, and seizures. In re-

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cent years, more and more studies have shown that demyelinating diseases of the central nervous system are related to seizures, but the mechanism is not clear. This paper aims to review demyelinating diseases of the central nervous system and related seizures.

Keywords

Demyelinating Diseases of the Central Nervous System, Seizures, Anti-Myelin Oligodendrocyte Glycoprotein-IgG Associated Disorders

1. 引言

中枢神经系统脱髓鞘疾病是一种以神经功能障碍为主要表现，具有反复发作、复发缓解特点的自身免疫性疾病，以多发性硬化(multiple sclerosis, MS)、视神经脊髓炎谱系疾病(neuromyelitis optica spectrum disorders, NMOSD)、少突胶质细胞糖蛋白 IgG 抗体相关疾病(anti-myelin oligodendrocyte glycoprotein-IgG associated disorders, MOGAD)常见[1]。这类疾病以中枢神经系统髓鞘脱失为主要病理改变，神经元及轴突结构与功能基本完整。临床表现以视神经炎、脊髓炎、共济失调为主，多项研究表明中枢神经脱髓鞘疾病有痫性发作表现[2]-[24]，甚至部分少突胶质细胞糖蛋白 IgG 抗体相关疾病出现孤立于脱髓鞘事件的痫性发作，并将孤立性痫性发作(Isolated seizures)定义为一种独立的临床表型[23]，中枢神经系统脱髓鞘疾病痫性发作成为近年来研究热点。本文旨在对常见中枢神经脱髓鞘疾病及其痫性发作进行综述，并对其可能机制进行初步探讨。

2. 少突胶质细胞糖蛋白 IgG 抗体相关疾病与痫性发作

少突胶质细胞糖蛋白 IgG 抗体相关疾病是一种由抗体介导的中枢神经炎性脱髓鞘疾病[25] [26]，临床上较为罕见，儿童患病率较成人高，儿童患病率约 0.31/10 万(95% CI 0.17~0.5) [27]。最初认为这类疾病与经典的中枢神经系统炎性脱髓鞘疾病多发性硬化存在一定相关性[28]，随着进一步研究发现 MOG-Ab 阳性的患者的临床特征、疾病预后、病理改变具有一定共性，与经典中枢神经系统脱髓鞘疾病 MS、NMOSD 有所不同[26]，2018 年 MOG-Ab 阳性的中枢神经系统脱髓鞘疾病被定义为一种独立疾病谱，即少突胶质细胞糖蛋白 IgG 抗体相关疾病(MOGAD) [25]。

MOGAD 临床表现多样，目前尚无一种特定的临床表型可以解释 MOG-Ab 阳性患者的所有表现。其典型临床表型包括急性播散性脑脊髓炎(acute disseminated encephalomyelitis, ADEM)、视神经炎(optic neuritis, ON)、横贯行脊髓炎(transverse myelitis, TM)等，不同年龄常见表型有所不同[27]。近几年来一些非典型表型被提出，如皮质脑炎(cortical encephalitis) [13]、脑膜脑炎(meningoencephalitis) [29]、抗 NMDAR 脑炎重叠综合征(overlapping syndromes of anti-NMDAR encephalitis) [24]、孤立性痫性发作[23]等。

一项大型混合队列研究表明 MOGAD 总体预后良好[30]，部分患者可遗留视力障碍、运动障碍、感觉障碍、认知缺陷及膀胱功能障碍[7]。急性发作时，常使用大剂量糖皮质激素和/或免疫球蛋白冲击治疗，在维持治疗期间，静脉注射免疫球蛋白是儿童首选的一线治疗，而硫唑嘌呤、吗替麦考酚酯和利妥昔单抗等免疫抑制剂常作为成人的一线治疗[31]。有研究报道，发病时抗体滴度越高，首发表型为 ON，急性期单用糖皮质激素是复发危险因素[32]。部分患者在类固醇停药期间或停药后复发[33]，之前的一项研究

表明，延长类固醇减量可以减少 MOGAD 的早期复发[34]。

MOGAD 患者痫性发作发生率差异较大，几项国内外研究中，MOG-Ab 阳性患者癫痫发作的发生率约 1.4%~24.6%，儿童较成人更易发生[6] [11] [22]。发作类型主要包括全身强直阵挛发作、局灶性发作伴或不伴继发全身性发作，伴或不伴惊厥持续状态，急性发作间期脑电图表现为局灶性或全脑背景慢化，部分患者出现局灶性棘波和多棘波[12] [16]，国外的一项研究提供了 1 例患者急性发作期的脑电图，其痫性波与临床症状相符，而与 MRI 病灶无关[23]。伴痫性发作的 MOGAD 病灶常累及皮质或皮质下，一项国内的研究表明有痫性发作 MOGAD 患者深部白质和大脑脚较易受累[16]。Ramanathan 等发现 3% MOGAD 患者出现继发性癫痫[7]。

痫性发作在 ADEM、皮质脑炎或抗 NMDAR 脑炎重叠综合征等表型常见，不同表型出现痫性发作的比率不同[2] [4] [5] [7] [8] [9] [12] [13] [14] [18] [20] [21] [22]。国内外研究发现在急性播散性脑脊髓炎患者中，痫性发作比率约为 17.9%~35% [2] [22]，Rossor [12]等学者研究发现 16.2%的有痫性发作的急性播散性脑脊髓炎患者出现继发性癫痫，且有继发性癫痫患者脱髓鞘事件复发率较高(95% *CI* 2.0~48.7)，MOG-Ab 阳性的 ADEM 患者继发癫痫风险等大。2017 年日本学者[13]首次描述了在 MRI 出现单侧皮质肿胀，FLAIR 序列上呈高信号的病例，并定义为皮质脑炎。有学者系统性回顾了 35 例 MOG-Ab 阳性皮质脑炎发现，82.6%患者出现痫性发作[20]。有研究发现，11.9%的 MOGAD 患者同时或相继患有抗 NMDAR 脑炎，56.9%抗 NMDAR 脑炎重叠综合征患者在疾病进展中出现痫性发作，且复发率明显高于仅有 MOG-Ab 阳性患者[5] [8] [9]。

虽然痫性发作常发生于脑炎发作期间，但有研究报道了 MOG-Ab 阳性患者出现与脱髓鞘事件不同步的痫性发作，并定义为孤立性痫性发作，这些患者脑部 MRI 扫描均正常[23]。Foiadelli [20]等系统性回顾 8 例孤立性痫性发作患者发现，所有患者均表现为复发性病程、痫性发作时间与脱髓鞘时间相隔时间较长，发作类型均为局灶性运动性发作，50%患者痫性发作具有丛集性。

伴或不伴痫性发作的 MOGAD 在治疗原则上基本一致，其中孤立性痫性在确诊为 MOGAD 前常被误诊为癫痫，使用抗癫痫药物并不能控制其痫性发作，直至出现脱髓鞘事件并使用免疫治疗后，其痫性发作才得以控制[20]。另一项研究指出长期口服抗癫痫药物对控制癫痫发作无明显效果，而吗替麦考酚酯可显着降低 MOG-Ab 阳性脑炎急性痫性发作的发生率[3]。

3. 其他中枢神经系统脱髓鞘疾病与痫性发作

MS 是常见的中枢神经系统脱髓鞘疾病，患病率为 50~300/10 万，成人患病率率较儿童高，具有明确种族倾向[35]。MS 临床表现具有时间和空间多发性特点，症状及体征复杂多变，与病灶部位相关，常见表现包括共济失调、感觉障碍、肢体乏力、视力障碍。研究发现，MS 患者的痫性发作发生率约为 2.2%，0.9%有继发性癫痫[19]。MS 患者常有皮质病变和皮质萎缩，继发性癫痫的发生率与首次发作时有痫性发作、是否有惊厥持续状态及 MS 亚型相关[10]。没有证据表明，首次痫性发作后长期使用抗癫痫药物能控制急性痫性发作，39%的患者对抗癫痫药物耐药[19]。

NMOSD 是一种由中枢神经系统水通道蛋白-4 抗体介导的星形细胞通道病[36]，主要以视神经炎和脊髓炎为特征。NMOSD 患者痫性发作的发生率较 MOGAD 及 MS 低，约 0.4%~0.72%，超过一半的癫痫发作是单次发作和局灶性发作，脑电图表现为慢波，皮质/皮质下病变是最常见的异常，其中有 1 例继发复杂部分性癫痫[3] [17] [18]。同 MOG-Ab 阳性脑炎一样，吗替麦考酚酯可降低其急性痫性发作的发生率[3]。

4. 总结与展望

不同中枢神经系统脱髓鞘疾病痫性发作的发生率不同，其中 MOGAD 发生率最高，其中 MOG-Ab 阳性皮质脑炎发生率高达 82.6%，其次为抗 NMDAR 脑炎重叠综合征。NMOSD 痫性发作发生率最低，

且很少发展为继发性癫痫。这类患者通常表现为复发性病程，病灶常累及皮质和/或皮质下白质，而NMOSD患者皮质和/或皮质下白质病变少见，这可能是其痫性发生率低的原因。脑电图以局灶性或全面性慢波为主要表现，没有脑电图痫性波与病灶相对应的证据。免疫抑制剂吗替麦考酚酯可降低急性痫性发作的发生率，而抗癫痫药物不能。痫性发作的实质是神经元细胞异常放电，而中枢神经脱髓鞘疾病病理改变以髓鞘破坏、脱失为主，不能解释痫性发作的原因，其发病机制尚不明确。目前的研究存在样本量小、缺乏前瞻性队列研究、相关机制及病理研究等问题，研究其痫性发作的机制可能为其诊治提供进一步策略。

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