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视神经脊髓炎相关视神经炎诊治进展

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[摘 要] 视神经脊髓炎相关性视神经炎(neuromyelitis optica spectrum disorder optic neuritis，NMO-ON)是一种常见的视神经炎(optic neuritis，ON)类型。女性非白种人占优势，损伤严重，双侧受累较多，视力预后差。我国有很大部分特发性ON最终诊断为NMO-ON。在相关实验室、光学相干断层扫描(optical coherence tomography，OCT)、磁共振(magnetic resonance imaging，MRI)等技术支持下，目前对NMO-ON的认识有了很大的进步，治疗方式除了皮质类固醇外还有免疫球蛋白、血浆置换及免疫抑制剂等。但提高NMO-ON的诊疗水平还有很长的路，更好地认识NMO-ON有助于更快速的诊断、更规范的治疗、更良好的预后。我们可以联合神经科开展多中心大样本量前瞻性的临床对照研究。

[关键词] 视神经脊髓炎相关性视神经炎；视神经炎；水通道蛋白4；光学相干断层扫描；磁共振

Progress in the diagnosis and treatment of neuromyelitis optica spectrum disorder optic neuritis

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Abstract Neuromyelitis optica spectrum disorder- optic neuritis (NMO-ON) is a common type of optic neuritis (ON). This affliction is predominant in female non-Caucasians, with severe injury, more bilateral involvement, and poor visual prognosis. In China, a large proportion of idiopathic ON is ultimately diagnosed as NMO-ON. Our understanding of NMO-ON has made great progress under the technical support, such as the relevant laboratory, optical coherence tomography (OCT), magnetic resonance imaging (MRI). In addition to corticosteroids, immunoglobulin, plasmapheresis and immunosuppressive agents are also available for treatment. However, there is still a long way to improve the diagnosis and treatment level of NMO-ON. A better understanding of NMO-ON contributes to faster diagnosis, more standardized treatment, and better prognosis. We should cooperate with the neurology department to conduct a multi-center, large sample size prospective clinical control study.

Keywords neuromyelitis optica spectrum disorder optic neuritis; optic neuritis; aquaporin 4; optical coherence tomography; magnetic resonance imaging

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视神经脊髓炎相关视神经炎(neuromyelitis optica spectrum disorder optic neuritis，NMO-ON)是一种常见的脱髓鞘性视神经炎(demyelinating optic neuritis，DON)类型。NMO-ON包括经典视神脊髓炎中发生的ON和视神经脊髓炎谱系病相关ON(NMOSD-ON)，后者即水通道蛋白4(aquaporin protein 4，AQP4)抗体阳性的ON。NMO-ON与特发性视神经炎(idiopathic demyelinating optic neuritis，IDON)相比，女性非白种人占优势，复发率高，视力预后差[1]，通常很严重(平均视力≤20/400)，双侧受累较多，有报道[2]认为双侧ON的发生率高达20%。近期的研究[3]发现：我国很大部分ON最终诊断为NMO-ON。提高对NMO-ON的认识有助于眼科医生更好地诊断ON，更规范地治疗，最终获得更好的预后。鉴于2021年中国DON诊断及治疗循证指南中关于疾病诊断类推荐意见主要提及抗体相关和磁共振(magnetic resonance imaging，MRI)检查，而在19个结局指标中除了最佳矫正视力、视野参数常规检查等，光学相干断层扫描(optical coherence tomography，OCT)被视为重要结局监测指标，尤其是OCT及MRI可以在体内可视化和量化中枢神经系统损伤[4]，现重点阐述以上3种诊断工具。

1 实验室检查：生物学标志物

2015年的视神经脊髓炎谱系疾病(neuromyelitis optica spectrum disorder，NMOSD)的国际共识诊断标准中把NMOSD诊断分为AQP4抗体阳性和AQP4抗体阴性[5]。随着AQP4抗体的发现，NMO-ON现在可以作为一种特殊的疾病与其他类型的ON区别开来，因为它存在于大多数NMOSD患者中[6]。一项关于AQP4抗体检测在视神经脊髓炎患者中的特异性和敏感性的荟萃分析[7]提示以细胞、组织为基础的检测的灵敏度及特异性皆为95%。而且鉴于血清AQP4抗体阳性并非是NMOSD诊断的必需条件，除了优化血清AQP4抗体检测准确性，寻找其他生物学标志物也成为热点。

髓鞘少突胶质细胞糖蛋白(myelin oligodendrocyte glycoprotein，MOG)抗体的发现使得在AQP4抗体相关NMOSD、多发性硬化等之外能单独定义一种疾病，临床和病理证据也能帮助区分，但两者之间存在临床表型重叠[8]。有研究[9]认为MOG抗体有潜力成为NMO-ON的生物学标志物，MOG抗体血清阳性的NMOSD患者较AQP4抗体血清阳性或两种抗体均阴性的患者临床特征更明显，较容易同时累及双侧视神经，且发作次数少，恢复好[10]。Van Pelt等[11]研究发现MOG抗体血清阳性视神经炎常引起明显的视盘水肿。另有研究[12]认为MOG抗体血清阳性与AQP4抗体血清阴性患者的双眼和/或复发型ON有很强的相关性。

Tzartos等[13]在AQP4抗体血清阴性的NMOSD患者中发现了主要针对AQP1的自身抗体，由此认为AQP1-Ab抗体有可能成为AQP4抗体血清阴性患者的新的生物标志物。Tüzün等[14]研究了30例NMO患者，发现所有AQP1抗体与AQP4抗体血清抗体双阳性患者在第1次发作时均有ON，认为视神经聚集AQP1很可能启动了自身免疫反应，另外，该研究还发现血清抗体双阳性患者以及AQP4抗体血清阳性患者比双阴性患者更容易复发。

脑脊液(cerebrospinal fluid，CSF)分析可以提供重要线索，NMO-ON患者可能表现出CSF抗神经特异性抗体，这在自身免疫性胶质细胞病患者中被普遍报道[15]。急性ON患者CSF细胞常可轻度增多，然而广泛的细胞增多(>100 cells/mm^3)在MOG抗体血清阳性患者中更为常见。而在多发性硬化相关视神经炎(multiple sclerosis-optic neuritis，MS-ON)的典型病例中，细胞的增多少于50个/mm^3。CSF中嗜酸性粒细胞以及多形核细胞则提示NMOSD。MS-ON的特点是鞘内寡克隆条带和抗体的合成，在NMO-ON中并不常见，也很少持续[16]。针对脑脊液中AQP4抗体检测问题，Majed等[17]研究认为AQP4抗体主要产生于外周血，脑脊液AQP4抗体检测既不敏感也不具有成本效益。

关于潜在生物学标志物的研究还很多[18-19]，这些潜在的标志物或许能对AQP4抗体血清阳性，尤其血清阴性患者的诊断提供帮助，生物学标志物的发展也能帮助我们更深入地理解NMOSD和NMO-ON的发病机制。

2 眼底检查：OCT

OCT作为一种非侵入性成像技术，得益于其对细微的视神经和视网膜病变的识别能力，已在ON的轴突损伤的定量分析中得到了广泛应用[4,20]。在急性ON中，OCT常能初始发现视网膜周围乳

头神经纤维层增厚，进而发展为视网膜神经纤维层(retinal nerve fiber layer，RNFL)局灶性变薄和黄斑变薄[21]。而整体变薄的RNFL的缺失意味着NMO-ON患眼的轴突损伤更大[22]。Schneider等[23]报道NMO-ON的患眼比MS-ON的患眼显示出更明显的视网膜结构损伤和视觉功能损害的关联。Ratchford等[24]分析认为非多发性硬化(multiple sclerosis，MS)患者发生RNFL损失(>15 mm)后，应立即考虑NMO-ON的情况。后又出现关于MS和NMOSD非视神经炎的眼的OCT结果的报道[25]，但是在亚洲，NMO-ON与特发性ON之间的OCT研究相对较少。在NMO-ON患者一次急性ON发作后，其OCT的特性欠清晰，随着数据采集速度、分辨率和再现性的提高，OCT可以更清楚地识别视网膜的不同层以及一些细微的异常，如微囊性黄斑水肿(microcystic macular edema，MME)。有研究[26]发现在既往患有急性ON的NMOSD患者中有一定比例发生MME，以此提出可通过进一步的研究来了解这种视网膜的病理改变，确定它是否有助于研究NMO-ON后的持续性视力障碍。

OCT增强深度成像(enhanced depth imaging，EDI)扫描技术可以精确测量脉络膜厚度(choroidal thickness，CT)。所有这些进步拓宽了NMO-ON和特发性ON之间可以比较的特征，并提高了对它们之间差异的理解。有研究[27]认为NMOSD患者单次ON发作造成视神经损伤更为严重，NMO-ON组的RNFL比特发性ON组薄得多。首次发生ON的NMO-ON患眼和复发性ON的NMO-ON患眼之间的RNFL变薄没有显著差异，这表明对NMO-ON患者来说，一次发作的ON可能严重到足够摧毁大部分的RNFLT，造成严重的轴突损伤，而RNFLT下降到一定阈值后，视觉功能可能就不再能够维持了。Zhao等[28]为了解ON急性发作对视网膜和脉络膜的影响，利用谱域光学相干断层扫描(spectral domain optical coherence tomography，SD-OCT)测量了RNFLT、CT及视网膜厚度(retinal thickness，RT)，分析患有NMO-ON或特发性ON的中国患者急性发作6个月后的视神经、视网膜及CT的OCT变化，结果发现与特发性ON组相比，NMO-ON组RNFL变薄和视觉功能损害更明显，这与之前的研究[24]结果一致。

OCT血管造影术是OCT技术的一种新改良，可提供视网膜血管的高分辨率信息，并可为ON患者提供新的诊断和预后信息。OCT血管摄影显示ON后视网膜及黄斑周围血管密度减低[29]。Huang等[30]研究发现在NMOSD患者中，视乳头周围和中央凹周围血管密度的减少与有无ON病史无关，视网膜血管密度降低可先于RNFL萎缩。在有ON病史的NMOSD患者中，乳头周围血管密度与SD-OCT测量值和视觉功能系统评分有很好的相关性。因此认为视乳头周围血管密度可能是一个NMO-ON敏感的预测视力预后指标。

3 影像学检查：MRI

MRI是一种检测ON的敏感工具[4,20]。由于视神经屏障破坏导致MRI对比剂漏出而显影，因此T1加权成像(T1 weighted image，T1WI)钆增强成像呈异常增强，而脂肪抑制T2加权成像(T2 weighted image，T2WI)能除去脂肪伪影，使视神经显像更清晰[31]。双侧视神经炎在NMOSD和MOG-IgG疾病中较MS更常见，累及视交叉和视神经束的病变高度提示NMO-ON。在NMOSD和MOG-IgG疾病中，均常见到球后视神经纵向广泛病变，在MOG-IgG疾病中更为常见[32]。Chen等[33]研究发现视神经束膜强化和较短的视神经病灶多发于MOG-IgG血清阳性的ON。Akaishi等[34]针对23例抗AQP4-IgG血清阳性的NMOSD患者的研究中，在首次发病急性期对比增强光学MRI成像检查，发现急性期病灶长度可作为一项预测NMO-ON患者视力预后的重要因素。

脑和脊髓MRI病变的部位及特点也能为诊断提供一定价值。比如，在多个区域的脑和/或脊髓T2WI高信号和强化病灶可能高度提示MS[35]。而中脑导水管、穹窿和下丘脑病变可能支持NMOSD，MOG-IgG疾病更常累及脊髓下部和圆锥[29]。

4 治疗方案

单纯针对急性IDON来说，已经有研究[35-36]表明1 000 mg甲泼尼龙静脉冲击治疗能提供快速的恢复效果，尤其合并AQP-4抗体和MOG抗体阳性DON，明确诊断后及早进行静脉注射甲泼尼龙(intravenous methylprednisolone，IVMP)治疗[37-38]，肌肉注射或皮下应用促肾上腺皮质激素(adrenocorticotrophic hormone，ACTH)也被批准

用于急性ON的治疗，并提供了一种替代方案来增强皮质类固醇作用。

NMO-ON的治疗原则参考NMOSD，目前国外推荐NMOSD糖皮质激素冲击的剂量为1 000 mg/d，使用3~5 d[39]。我国指南推荐急性期静脉注射甲泼尼龙冲击(intravenous methylprednisolone pulse，IVMP) 1 000 mg/d，使用3 d，然后口服泼尼松1 mg/(kg·d)并逐渐减量，口服维持治疗至少4~6个月[40]。考虑到糖皮质激素不良反应的问题，郭思彤等[41]对NMO-ON糖皮质激素冲击疗效的回顾性分析发现，甲泼尼龙用量1 000 mg或500 mg对急性发病期的NMO-ON皆有效，且两种剂量的疗效并无差异。并且该研究认为NMO-ON发病时年龄≤50岁，NMO-ON患眼IVMP治疗有效率可以达到50%以上，而>50岁的患者，IVMP对其患眼的疗效会有一定程度降低。须要注意急性期IVMP治疗不良事件，其中最常见的为高血糖(43.5%)和感染(29.0%)[42]。在与MS-ON患者的比较中，Kleiter等[43]发现NMO-ON患者对高剂量皮质类固醇完全应答的病例要少得多，只有36%，对于IVMP治疗无反应、反应性不佳或进行性加重的 DON可以选择静脉免疫球蛋白(intravenous immunoglobulin，IVIg)治疗，用量0.4 g/(kg·d)[44-45]。有研究[46-47]显示血浆置换及免疫吸附对ON均有治疗作用。一项比较IVMP和血浆置换的回顾性研究[48]表明：血浆置换治疗可改善NMO-ON患者的视力和视野。血浆置换反应增强与男性性别、较低的基线残疾、快速启动治疗和较短的复发时间有关[49]。有研究[50]显示：对严重NMOSD，早期同时行IVMP加血浆置换治疗的临床疗效好于IVMP后序贯血浆置换治疗。但在ON患者中血浆置换的合理应用和时机尚未定义，有研究[51]发现ON发作和进行血浆置换之间的短时间间隔(≤5 d)与完全好转的可能性增加有关，因此，疑似NMOSD的急性ON患者可以在确认AQP4抗体阳性之前开始进行血浆置换，使用免疫吸附的治疗性单采术是替代血浆置换的一种方法，且Koziolek等[52]发现其对皮质激素难治性ON疗效显著。

鉴于高复发率的风险，国际共识建议进行免疫抑制治疗[53]。可选药物有硫唑嘌呤[45]、吗替麦考酚酯(mycophenolate mofetil，MMF)和利妥昔单抗(rituximab，RTX)等[44,54-55]。多项研究[6,56-57]显示：上述药物均能有效降低儿童NMOSD的疾病活动程度。对于硫唑嘌呤单药治疗复发的NMO-ON，联合IVIG或联合口服小剂量糖皮质激素有助于降低年复发率[45]，对于给予硫唑嘌呤或MMF有效治疗剂量治疗6个月以上，期间出现2次及以上复发，或1次及以上严重复发的患者，建议更换免疫抑制剂，可考虑采用eculizumab、satralizumab、inebilizumab等药物[20,58]。不过须要注意的是，一些已批准的MS的免疫调节疗法可能加重NMOSD疾病的活动[45]，这同时也表明鉴别MS-ON和NMO-ON的重要性。

5 总结

目前对NMO-ON的认识在相关的实验室、眼底、影像学等技术支持下有了很大进步，对IDON患者行AQP4等相关抗体检测，并以OCT、MRI等辅助检查作为鉴别依据，提高诊断水平，依据情况制订详尽系统的治疗及预防策略，减少复发风险、降低致残率等方面，但提高NMO-ON的诊疗水平还有很长的路，要规范我国的NMO-ON的诊断及治疗，可以联合神经科开展多中心大样本量前瞻性的临床对照研究。

开放获取声明

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