·临床研究·

原发性干燥综合征合并视神经脊髓炎谱系疾病临床分析及文献复习

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【摘要】 **目的** 探讨原发性干燥综合征合并视神经脊髓炎谱系疾病的临床表现、实验室检查和MRI特点，以及治疗和预后。**方法** 回顾分析4例诊断明确的原发性干燥综合征合并视神经脊髓炎谱系疾病患者的临床资料，分析其发病特点。**结果** 临床症状与体征主要表现为原发性干燥综合征合并复发性纵向延伸性脊髓炎或球后视神经炎，实验室检查血清抗干燥综合征抗原A抗体(4例)、抗干燥综合征抗原B抗体(3例)、视神经脊髓炎特异性抗水通道蛋白4(AQP4)抗体(3例)阳性。头部MRI病灶主要分布于双侧基底节和大脑脚皮质脊髓束走行区、双侧额叶、右侧皮质脊髓束区、双侧侧脑室旁和脑干；脊髓MRI病灶以累及颈胸髓为主，≥3个椎体节段(3例)或累及延髓(2例)。急性期以大剂量糖皮质激素冲击和序贯口服泼尼松，并辅助免疫抑制药治疗为主。**结论** 原发性干燥综合征和视神经脊髓炎均为自身免疫性疾病，二者关系密切。对于视神经脊髓炎和(或)视神经脊髓炎谱系疾病患者建议行血清自身抗体和抗AQP4抗体检测，抗AQP4抗体阳性者复发率高，预后不良。建议辅助应用免疫抑制药，以减少复发。

【关键词】 干燥综合征； 视神经脊髓炎； 水孔蛋白质类； 磁共振成像

Primary Sjögren´s syndrome patients with neuromyelitis optica spectrum disorders: clinical analysis of 4 cases and review of the literature

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【**Abstract**】 **Objective** To explore the clinical manifestations, laboratory examination, MRI characteristics, treatment and prognosis of primary Sjögren´s syndrome (PSS) with neuromyelitis optica spectrum disorders (NMOSDs). **Methods** The clinical manifestations, laboratory examination, MRI characteristics, treatment and prognosis of 4 patients diagnosed as PSS with NMOSDs were retrospectively analyzed. **Results** There were 2 PSS patients with neuromyelitis optica (NMO), 1 PSS patient combined with recurrent myelitis associated with longitudinally extensive spinal cord lesions (RLESLs), and 1 PSS patient with retrobulbar optic neuritis. Laboratory examination showed serum Sjögren´s syndrome antigen A (SSA) antibody positive in 4 cases, Sjögren´s syndrom antigen B (SSB) antibody positive in 3 cases and serum specific aquaporin 4 (AQP4) antibody positive in 3 patients with NMO. Abnormal features in cranial MRI mainly distributed in bilateral basal ganglia, cerebral peduncle corticospinal tract, beside lateral ventricles, and brainstem. Spinal MRI showed the lesions were mainly at cervical or thoracic spinal cord (≥ 3 vertebral segments) and also involved medullary bulb (2 cases). In acute stage, glucocorticoid and prednisone combined with immunosuppressive drugs were used. **Conclusion** PSS and NMO are autoimmune diseases, and the two diseases are closely linked. Patients with NMO and (or) NMOSDs were suggested to detect serum auto-antibody and AQP4 antibody. In patients with serum AQP4 antibody positive, the recurrence rate is high and prognosis is poor. Immunosuppressive therapy is recommended to reduce recurrence.

【**Key words**】 Sjogren´s syndrome; Neuromyelitis optica; Aquaporins; Magnetic resonance imaging

doi:10.3969/j.issn.1672-6731.2013.05.016

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原发性干燥综合征(PSS)是一种累及外分泌腺的慢性炎症性自身免疫性疾病,主要侵犯泪腺和唾液腺,发病隐匿,进展缓慢,少数病例可进展迅速,易合并其他系统损害,如消化系统、呼吸系统、神经系统等。神经系统损害主要表现为周围神经病变、癫痫、脑血管病、脊髓炎等[1-3]。视神经脊髓炎(NMO)是主要累及视神经和脊髓的中枢神经系统炎性脱髓鞘疾病,自2004年发现其特异性抗水通道蛋白4(AQP4)抗体以来[4],更加支持将视神经脊髓炎与多发性硬化(MS)区分开来。因为临床上复发性视神经炎(RON)和复发性纵向延伸性脊髓炎(RLESLs)易进展为视神经脊髓炎,故目前将其与视神经脊髓炎一并称为视神经脊髓炎谱系疾病(NMOSDs)[5-6]。Wandinger等[7]的研究表明,原发性干燥综合征常合并视神经损害。流行病学调查发现,自身免疫性疾病如原发性干燥综合征、系统性红斑狼疮(SE)、甲状腺炎合并视神经脊髓炎的发生率为10%~40%,且抗AQP4抗体在发病机制中起重要作用。上海交通大学附属第六人民医院神经内科自2010年1月–2012年6月共诊断与治疗4例原发性干燥综合征合并视神经脊髓炎谱系疾病患者,结合文献复习对其临床特点进行分析。

表1 原发性干燥综合征诊断标准

Table 1. Revised international classification criteria for primary Sjögren´s syndrome

Diagnostic criteria
Ⅰ. Ocular symptoms: a positive response to at least one of the following questions
ⅰ. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
ⅱ. Do you have a recurrent sensation of sand or gravel in the eyes?
ⅲ. Do you use tear substitutes more than 3 times a day?
Ⅱ. Oral symptoms: a positive response to at least one of the following questions
ⅰ. Have you had a daily feeling of dry mouth for more than 3 months?
ⅱ. Have you had recurrently or persistently swollen salivary glands as an adult?
ⅲ. Do you frequently drink liquids to aid in swallowing dry food?
Ⅲ. Ocular signs: that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests
ⅰ. Schirmer´s Ⅰ test, performed without anaesthesia (< 5 mm in 5 min)
ⅱ. Rose bengal score or other ocular dye score (> 4 according to van Bijsterveld´s scoring system)
Ⅳ. Histopathology: in minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score > 1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm^2 of glandular tissue
Ⅴ. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests
ⅰ. Unstimulated whole salivary flow (< 1.50 ml in 15 min)
ⅱ. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts
ⅲ. Salivary scintigraphy showing delayed uptake, reduced concentration and (or) delayed excretion of tracer
Ⅵ. Autoantibodies: presence in the serum of the following autoantibodies Antibodies to Ro (SSA) or La (SSB) antigens, or both

SSA, Sjögren´s syndrome antigen A, 干燥综合征抗原A; SSB, Sjögren´s syndrome antigen B, 干燥综合征抗原B

临床资料

一、诊断标准

1. 原发性干燥综合征 在无任何潜在疾病情况下,符合以下两项标准中任意一项即可明确诊断:(1)符合表1中至少4项标准,但必须包含第Ⅳ项(组织学检查)和(或)第Ⅵ项(自身抗体)。(2)符合表1中第Ⅲ~Ⅵ项客观标准中的任意3项,同时排除头颈部放射治疗史、丙型肝炎病毒感染史、抗乙酰胆碱药物(如阿托品、莨菪碱、溴丙胺太林、颠茄等)服用史,以及获得性免疫缺陷综合征(AIDS)、淋巴瘤、结节病、移植物抗宿主病(GVH)[8]。

2. 视神经脊髓炎谱系疾病 (1)符合2006年Wingerchuk等[9]修订的视神经脊髓炎诊断标准:必要条件为视神经炎、急性脊髓炎;支持条件为脊髓MRI病灶≥3个椎体节段,头部MRI不符合多发性硬化诊断标准,血清NMO-IgG阳性。具备全部必要条件和支持条件中任意两项,即可明确诊断为视神经脊髓炎。(2)视神经脊髓炎限定形式(limited forms of neuromyelitis optica)[10]:原发性单次发作或复发性纵向延伸性脊髓炎(脊髓MRI病灶≥3个椎体节段);复发性或双侧同时发生视神经炎;亚洲视神经脊髓型多发性硬化(AOSMS);伴系统性自身免疫性疾病的视神经炎或纵向延伸性脊髓炎;伴视神经脊髓炎特征性脑部病灶(下丘脑、胼胝体、脑室旁或脑干)的视神经炎或脊髓炎。

二、一般资料

按上述诊断标准,本组4例患者均符合2002年修订的干燥综合征国际分类标准[8],其中2例符合2006年Wingerchuk等[9]提出的视神经脊髓炎诊断标准,1例为原发性干燥综合征合并复发性纵向延

伸性脊髓炎，1例为原发性干燥综合征合并球后视神经炎。均为女性，年龄30～55岁，平均39.25岁；病程2～21个月，平均11.50个月。

1. 临床症状与体征　本组患者呈单相病程2例、复发病程2例。其中3例发病前出现消化系统症状；1例首次发病前有腹泻史，发病初期表现为急性脊髓炎症状，其眼干及口干主诉并不十分明显，经实验室检查提示血清自身抗体阳性，进一步询问病史方才明确眼干及口干症状；病程中因上呼吸道感染或劳累后四肢无力症状反复发作，发病9个月后出现视神经炎症状，方才明确诊断为原发性干燥综合征合并视神经脊髓炎。本组1例患者病程中反复流产及下肢深静脉血栓形成，结合曾经实验室检查血清抗心磷脂抗体（ACA）阳性，考虑为抗心磷脂抗体综合征；患者引产后反复呕吐，不能进食，随后出现视力减退、干眼、眼球活动障碍，同时合并四肢深浅感觉减退、紧箍感、Lhermitte征阳性，结合实验室和MRI检查明确诊断为原发性干燥综合征重叠抗心磷脂抗体综合征合并视神经脊髓炎。1例患者主要表现为发热伴恶心、呕吐，逐渐出现四肢无力，外院诊断为“急性脑脊髓膜炎”，予糖皮质激素（甲基氢化泼尼松500 mg，静脉滴注）等药物治疗后病情好转，但遗留双侧下肢乏力；发病6个月后出现帕金森样症状，四肢肌张力显著增高，头部和双侧上肢静止性震颤，明确诊断为原发性干燥综合征合并复发性纵向延伸性脊髓炎。1例患者明确诊断为原发性干燥综合征后6个月才出现双眼视力减退。

2. 实验室检查　（1）血清学检查：4例患者血清抗干燥综合征抗原A（SSA）抗体均阳性，其中3例抗干燥综合征抗原B（SSB）抗体亦呈阳性。3例血清抗AQP4抗体呈阳性反应。（2）脑脊液检查：3例患者接受腰椎穿刺脑脊液检查，一般性状及物理检查无异常。化合物检测1例蛋白定量为800 mg/L（150～450 mg/L），葡萄糖和氯化物于正常值范围。免疫学检测1例IgG指数为1.04（<0.70）；血-脑脊液屏障正常；寡克隆区带（OB）阳性。（3）基础泪液分泌试验（Schimmer试验）：4例均呈阳性反应，提示双眼泪液分泌减少。

3. 影像学检查　（1）MRI检查：3例患者脊髓MRI检查显示，脊髓异常信号长度≥3个椎体节段（图1，2），2例病变累及延髓（图1a，2）。3例患者头部MRI检查显示异常信号，主要分布于双侧基底节和大脑脚皮质脊髓束走行区、双侧额叶、右侧皮质脊髓束区、双侧侧脑室旁、脑干（图3，4）。（2）腮腺ECT检查：3例患者ECT检查均提示双侧腮腺摄取与排泄功能重度下降，1例双侧腮腺摄取与排泄功能正常。

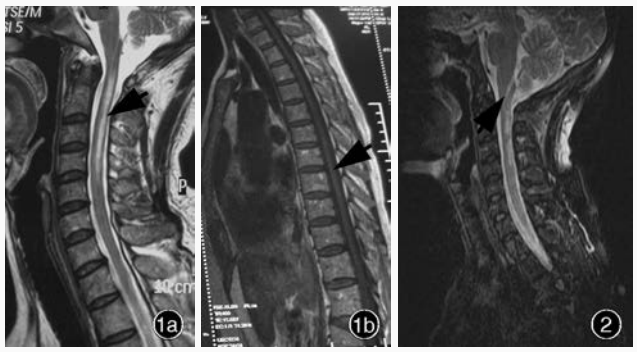

图1　例1患者，女性，36岁。临床诊断为原发性干燥综合征合并视神经脊髓炎。脊髓MRI检查所见　1a　颈髓矢状位T_2WI序列呈高信号，延髓呈线样高信号（箭头所示）　1b　胸髓矢状位T_2WI序列呈高信号（箭头所示）　**图2**　例2患者，女性，30岁。临床诊断为原发性干燥综合征重叠抗心磷脂抗体综合征合并视神经脊髓炎。颈髓矢状位T_2WI序列呈高信号，延髓可见“线样征”（箭头所示）

Figure 1　Case 1 (36 - year - old female)　Clinical diagnosis: primary Sjögren´s syndrome combined with neuromyelitis optica. Sagittal T_2WI of cervical spinal cord MRI showed hyperintensity signal and medulla oblongata abnormal line signal (arrow indicates, Panel 1a). Sagittal T_2WI of thoracic spinal cord MRI showed hyperintensity signal (arrow indicates, Panel 1b). **Figure 2**　Case 2 (30 - year - old female)　Clinical diagnosis: primary Sjögren´s syndrome eclipsing anticardiolipin antibody syndrome combined with neuromyelitis optica. Sagittal T_2WI of cervical spinal cord MRI showed hyperintensity signal and line-like signal in medulla oblongata (arrow indicates).

4. 视觉诱发电位检查　1例首次发病时视觉诱发电位（VEP）检查未见异常，第3次发病时出现左眼视力减退，复查视觉诱发电位显示右眼正常，左眼未引出P100波；1例左眼P100波波幅降低；1例双眼P100波潜伏期延长，波幅降低；1例无异常。

5. 组织病理学检查　4例患者均于局部麻醉下行唇腺组织活检，病理结果显示为小唾液腺组织，间质内多灶性淋巴细胞浸润伴腺泡萎缩（图5），单个灶的淋巴细胞计数>50个。

讨　论

视神经脊髓炎是主要累及视神经和脊髓的中枢神经系统炎症性脱髓鞘疾病。1894年Devic提出“视神经脊髓炎”的概念，认为其为一种急性发病、视神经炎和脊髓炎同时发生或在较短时间内相继

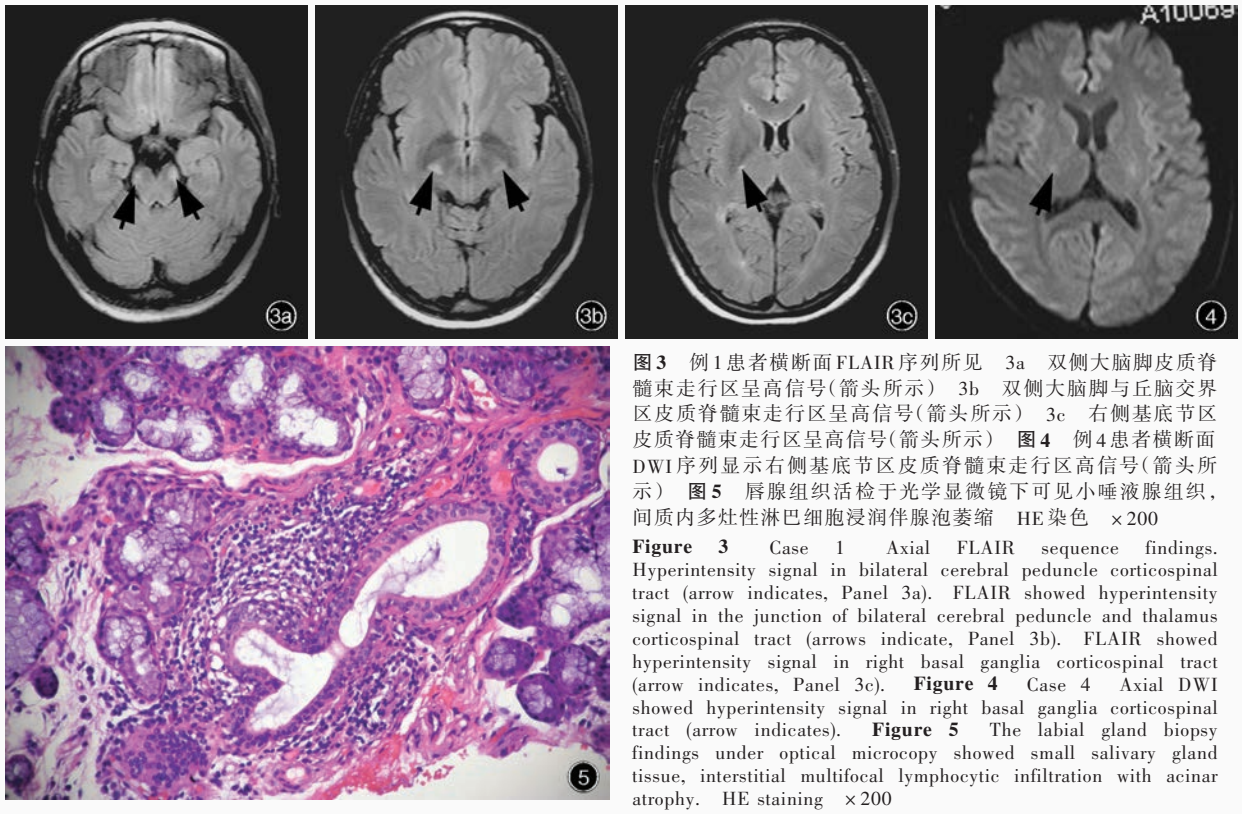

图3 例1患者横断面FLAIR序列所见 3a 双侧大脑脚皮质脊髓束走行区呈高信号(箭头所示) 3b 双侧大脑脚与丘脑交界区皮质脊髓束走行区呈高信号(箭头所示) 3c 右侧基底节区皮质脊髓束走行区呈高信号(箭头所示) **图4** 例4患者横断面DWI序列显示右侧基底节区皮质脊髓束走行区高信号(箭头所示) **图5** 唇腺组织活检于光学显微镜下可见小唾液腺组织,间质内多灶性淋巴细胞浸润伴腺泡萎缩 HE染色 ×200

Figure 3 Case 1 Axial FLAIR sequence findings. Hyperintensity signal in bilateral cerebral peduncle corticospinal tract (arrow indicates, Panel 3a). FLAIR showed hyperintensity signal in the junction of bilateral cerebral peduncle and thalamus corticospinal tract (arrows indicate, Panel 3b). FLAIR showed hyperintensity signal in right basal ganglia corticospinal tract (arrow indicates, Panel 3c). **Figure 4** Case 4 Axial DWI showed hyperintensity signal in right basal ganglia corticospinal tract (arrow indicates). **Figure 5** The labial gland biopsy findings under optical microcopy showed small salivary gland tissue, interstitial multifocal lymphocytic infiltration with acinar atrophy. HE staining ×200

发生的炎症性脱髓鞘疾病。此后陆续有研究发现,视神经脊髓炎在东西方种族分布、免疫机制、病理改变、临床表现、影像学改变、治疗和预后等方面均有别于多发性硬化[11]。视神经脊髓炎谱系疾病好发于女性,本组4例患者均为中年女性,平均发病年龄为39.25岁,根据文献报道,男女视神经脊髓炎发病率之比约为1∶6.60[12],中位发病年龄为39岁。关于视神经脊髓炎谱系疾病合并原发性干燥综合征的报道较多[13-14]。视神经脊髓炎以非白种人多见,我国则以视神经脊髓炎谱系疾病更为多发。

视神经脊髓炎是由B细胞介导的以体液免疫为主的自身免疫性炎症性脱髓鞘疾病。约50%的视神经脊髓炎患者血清中可检出抗核抗体(ANA)、抗双链DNA抗体(dsDNA)、抗可提取性核抗原(ENA)抗体等一种或一种以上自身抗体。系统性红斑狼疮(SLE)、抗心磷脂抗体综合征和原发性干燥综合征等自身免疫性疾病累及视神经和脊髓时可出现类似视神经脊髓炎的症状[15]。本组4例患者血清抗SSA抗体均为阳性,其中3例抗SSB抗体亦阳性。抗SSA抗体与多种自身免疫性疾病相关,最常见于干燥综合征;抗SSB抗体阳性对诊断干燥综合征更具特异性,且抗SSB抗体阳性常可同时伴抗SSA抗体阳性[16]。

AQP4是中枢神经系统主要水通道蛋白,主要分布在血-脑脊液屏障血管周围、室管膜星形胶质细胞足突和血-脑脊液屏障神经胶质界膜,参与钾离子缓冲,在跨膜水分子转运及维持血-脑脊液屏障和中枢神经系统内环境稳定方面发挥重要作用[17]。Saini等[18]采用逆转录-聚合酶链反应(RT-PCR)对视神经脊髓炎患者进行观察,发现视神经和脊髓AQP4总mRNA表达明显高于脑干、大脑皮质和小脑,此与视神经脊髓炎病变受累部位相符[17-19]。进一步研究表明,视神经脊髓炎患者中枢神经系统受累部位与抗AQP4抗体高表达区域相一致,证实抗AQP4抗体与视神经脊髓炎的病理改变密切相关。Hinson等[20]采用免疫荧光共聚焦显微镜技术进行临床研究显示,视神经脊髓炎患者血清抗AQP4抗体与脊髓、视神经郎飞节周围的星形胶质细胞突触前膜的AQP4相结合,启动免疫应答反应、介导星形胶质细胞损伤、血-脑脊液屏障破坏、炎性细胞浸润、少突胶质细胞损伤和脱髓鞘改变。本组有3例患者血清或脑脊液抗AQP4抗体均呈阳性反应,提示视

神经脊髓炎谱系疾病患者血清抗AQP4抗体阳性率高。不仅视神经脊髓炎高表达AQP4，复发性纵向延伸性脊髓炎和复发性视神经炎患者血清或脑脊液AQP4亦有较高的阳性检出率；且血清抗AQP4抗体阳性患者更易复发，转为视神经脊髓炎的风险更高，因此，目前倾向于将其与视神经脊髓炎一并归为视神经脊髓炎谱系疾病[4-6]。目前尚无确切的证据阐明视神经脊髓炎谱系疾病与原发性干燥综合征之间的联系。近年研究发现，唾液腺组织中存在AQP5，而AQP4则存在于中枢神经系统[21]。水通道蛋白具有结构同源性，AQP5与AQP4约有50%的蛋白质序列共享。因此，表位扩散可能作为一种假设来解释自身免疫性疾病可同时累及不同器官系统，而原发性干燥综合征是否可与视神经脊髓炎和（或）视神经脊髓炎谱系疾病共存于同一患者，尚有待进一步研究证实。视神经脊髓炎患者脑脊液检测无明显特异性，本组有1例脑脊液蛋白定量轻度升高，1例寡克隆区带阳性。

视神经脊髓炎脊髓MRI影像以累及颈胸髓多见，病灶常超过3个椎体节段，呈长条状或斑片状，急性期可伴部分病灶强化。本组3例患者脊髓MRI异常信号超过3个椎体节段，2例累及延髓。近年研究发现，视神经脊髓炎患者可出现脑部病灶[22]，2006年Wingerchuk等[9]重新修订了视神经脊髓炎的诊断标准，允许出现不符合多发性硬化特点的脑部病灶。本组有3例患者头部MRI检查显示双侧基底节区、大脑脚皮质脊髓束走行区、双侧额叶、右侧皮质脊髓束区、双侧侧脑室旁和脑干等部位受累。视神经脊髓炎患者不仅可以出现脑内病灶，而且随着病程的进展病灶数目亦呈增多趋势，且其分布具有一定特征性，幕上病灶以近皮质、皮质下、深部脑白质和侧脑室旁多见；幕下病灶则以中脑导水管-第四脑室-延髓中央管周围多见[21,23-25]。视觉诱发电位是视网膜接受视觉刺激后在视皮质发生的电反应，反应神经节细胞至视觉中枢的神经传导情况，可提示是否发生神经传导阻滞，若其中任意一个环节出现问题均可出现异常，故其检测敏感性较高，但因其定位诊断和特异性较差，且易受患者年龄、视力及理解力等因素的影响，故仅可用于视神经是否受累的早期筛查。

视神经脊髓炎的治疗包括以促进病情缓解的急性期治疗，以预防和减少疾病复发的缓解期治疗和以改善患者症状的对症治疗三方面。关于视神经脊髓炎谱系疾病的治疗目前尚无可参考的指南，因其转为视神经脊髓炎的风险较高，因此建议参考视神经脊髓炎的治疗原则。视神经脊髓炎急性期主张以大剂量糖皮质激素冲击治疗，对于反应较差者可改用血浆置换疗法或联合丙种球蛋白治疗；缓解期建议应用免疫抑制药预防和减少复发，泼尼松、硫唑嘌呤、环孢素A和麦考酚吗乙酯（MMF）可以缓解病情，并能减少复发[26-28]。近年来，有文献报道，利妥昔单抗对上述治疗不敏感的视神经脊髓炎患者治疗有效[29-30]。对于上述治疗无效或已用最大剂量而病情仍反复者，干细胞移植可以作为最后的选择[31]。本组4例患者均于急性期予以甲泼尼龙静脉滴注冲击治疗及随后序贯口服泼尼松治疗，同时辅助白芍总苷调节机体免疫功能，其中反复复发者联合丙种球蛋白静脉滴注，均症状改善；缓解期坚持应用小剂量泼尼松和免疫抑制药，随访显示均病情稳定。对症治疗主要为加巴喷丁改善痛性痉挛，B族维生素营养神经，帕罗西汀抗焦虑和抑郁，巴氯芬改善肌张力等，并进行肢体康复锻炼等。

本研究仅纳入4例患者，尚有待扩大病例数，而且MRI检查并未显示增强效应，因此未获得病灶是否强化的确切证据。原发性干燥综合征和视神经脊髓炎均为自身免疫性疾病，二者关系密切，这两种疾病之间是属于共病还是并发症，尚存争议[14]。原发性干燥综合征的临床表现可以较为隐匿，甚至可于其他中枢神经系统疾病的随访中发现。因此，对于视神经脊髓炎和（或）视神经脊髓炎谱系疾病患者建议检测抗核抗体、抗SSA抗体、抗SSB抗体、抗心磷脂抗体等自身抗体，以提高诊断的准确性。建议有条件者早期进行血清抗AQP4抗体检测，其阳性者复发率高，预后不良，治疗方面建议加用免疫抑制药，以减少复发。

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（收稿日期：2013-03-22）