短篇论著

以神经系统损伤为首发症状的2例原发性干燥综合征报道

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［摘要］**目的·**总结以神经系统损伤为首发症状的2例原发性干燥综合征（primary Sjögren′s syndrome，pSS）患者的临床特点并复习相关文献。**方法·**对以神经系统受累为首发症状的2例pSS患者的临床表现、实验室检查结果、影像学检查结果、唇腺活检结果、治疗效果等进行总结和分析。**结果·**病例1，女性，自50岁起出现进行性行走不稳伴下肢远端感觉障碍，表现为痉挛步态、感觉性共济失调、传导束性感觉障碍和二便障碍；58岁起无法独立行走。实验室检查提示抗核抗体阳性（1∶1 000着丝点型），抗干燥综合征抗原A（SSA）/Ro-52抗体、抗SSA/Ro-60抗体、抗着丝点抗体阳性；唇腺活检可见唾液腺组织、导管间及小叶内淋巴细胞浸润灶2个/4 mm^2（淋巴细胞>50个）。头颅磁共振成像可见“蛇眼征”；肌电图显示右侧腓神经运动纤维轴索损伤。在院期间予以大剂量糖皮质激素冲击、联合免疫抑制剂治疗后明显好转。3个月后可推助行器行走，日常生活基本自理。病例2，女性，自81岁起出现颈部不自主右斜，既往有轻度口干、眼干、伴膝关节疼痛1年。实验室检查提示抗SSA/Ro-52抗体、抗SSA/Ro-60抗体阳性，血红蛋白86 g/L；唇腺活检可见小唾液腺组织部分腺泡萎缩，间质内见淋巴细胞、浆细胞浸润灶2个/4 mm^2（淋巴细胞>50个）。周围神经电生理检查结果提示右侧正中神经传导速度减慢。经免疫抑制剂、解痉、肌松药物治疗后症状较前好转。**结论·**以复杂型痉挛性截瘫样表现、颈部肌张力障碍为首发症状的病例拓展了pSS的临床表型谱；临床上应注意鉴别继发于pSS的神经系统损伤与其他原发神经系统疾病；对于具有无明显原因的神经系统损伤症状的患者，应当筛查相关自身免疫抗体。

［关键词］原发性干燥综合征；神经系统受累；痉挛性截瘫；痉挛性斜颈

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Two cases of primary Sjögren′s syndrome with neurological impairment as initial symptom

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[Abstract] Objective·To study the clinical features of two primary Sjögren′s syndrome (pSS) patients with neurological symptoms as initial manifestations and review the related literature. **Methods·**The clinical data, response to treatment as well as prognosis of 2 cases were analyzed and followed up. **Results·**Case 1, female, initially presented progressive gait instability and distal sensory impairment at the age of 50. Clinical manifestations included spastic gait, sensory ataxia, conduction fascicular sensory impairment, as well as urination and defecation dysfunction. At the age of 58, this patient was unable to walk independently. The laboratory findings revealed a positive result for anti-nuclear antibody with a titer of 1∶1 000, anti-Sjögren′s syndrome A (SSA)/Ro-52, anti-SSA/Ro-60, and anti-centromere antibodies. Labial salivary gland biopsy showed lymphocytes and plasma cells infiltration into the glandular tissues, interstitium, and lobules, with 2 foci/4 mm^2 (lymphocytes >50). The cranial magnetic resonance imaging exhibited bilateral symmetric hyperintensity in the brainstem, characterized by the "snake-eye sign". Electromyography examination revealed axonal impairment of the right peroneal nerve. The patient was treated with high-dose corticosteroid therapy in combination with

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immunosuppressants. She experienced remarkable improvement. After three months, she was able to walk with aids and take care of herself in daily life. Case 2, female, presented spasmodic torticollis since the age of 81 with unknown reason. She had a history of mild mucosal dryness of mouth and eyes, and painful knee for one year. Laboratory findings revealed positive results for anti-SSA/Ro-52 and anti-SSA/Ro-60 antibodies, as well as hemoglobin of 86 g/L. Labial salivary gland biopsy demonstrated partial atrophy of the acini and the presence of 2 foci/4 mm^2 of lymphocytes and plasma cells infiltration into the stroma (lymphocytes>50). Electromyography examination showed reduced conduction velocity in the right median nerve. She got a significant relief after the treatment of immunosuppressants, antispasmodics, and muscle relaxants. **Conclusion**·Patients presenting initial symptoms such as complex forms of spastic paraplegia and cervical dystonia expand the clinical spectrum of pSS. In clinical practice, it is important to distinguish neurological involvement secondary to pSS from other primary neurological disorders. For patients with neurological impairments but without apparent etiology, it is crucial to screen relevant series of autoimmune antibodies.

[Key words] primary Sjögren′s syndrome (pSS); neurological involvement; spastic paraplegia; spasmodic torticollis

原发性干燥综合征（primary Sjögren′s syndrome，pSS）是一种以淋巴细胞浸润外分泌腺体为核心病理特征的慢性炎症性自身免疫疾病[1]。pSS常见于中年妇女，男性、老年和儿童也偶有报道[2-3]。不同地区的患病率差异较大，总体患病率约43.03/10万，女性是男性的10.72倍[4-7]。pSS临床主要表现为口干、眼干、腮腺肿大、疲劳和关节疼痛等[8]。30%~40%的患者还存在腺外并发症，如发热、盗汗、良性淋巴结病、淋巴瘤、间质性肾炎、肾小球肾炎、紫癜、间质性肺病、慢性支气管炎、周围神经损伤和横贯性脊髓炎等[8]。

1982年，ALEXANDER等[9]首次报道了伴有神经系统损伤的pSS病例。BAKCHINE等[10]首次在尸检中发现pSS患者脑内有大量淋巴细胞浸润。在神经系统并发症中，周围神经损伤最常见，尤以多发性感觉神经病变显著，表现为肢体远端麻木、疼痛等[11-12]。中枢神经系统受累相对罕见，且具有一定的临床异质性，包括认知功能障碍、无菌性脑膜炎、头痛、脊髓炎、视神经炎、偏瘫、多发性硬化样表现和精神症状等[13]。此外，约30%的患者兼有中枢和周围神经系统症状[14-15]。本研究中，我们报道2例分别以复杂型痉挛性截瘫、痉挛性斜颈为首发症状的pSS病例，总结和对比其临床特点、实验室检查结果、电生理结果、影像学表现和唇腺活检结果，强调筛查相关自身免疫抗体的重要性，旨在加深临床医师对以神经系统受累为突出表现的pSS的认识，以提高该病诊断准确率。

1 对象与方法

1.1 研究对象

回顾性分析安徽医科大学附属宿州医院和上海交通大学医学院附属第六人民医院神经内科分别于2023年2月和7月收治的以神经系统损伤为首发症状的2例pSS患者临床资料。2例患者诊断均符合2016年美国风湿病学会（American Rheumatism Association，ARA）和欧洲抗风湿病联盟（European League Against Rheumatism，EULAR）制定的pSS诊断标准[16]。根据评分准则，唇腺活检灶性指数2个灶/4 mm^2为3分，血清抗干燥综合征抗原A抗体（anti-Sjögren′s syndrome A antibody，anti-SSA antibody）阳性为3分；2例患者均为6分，确诊pSS。

1.2 研究方法

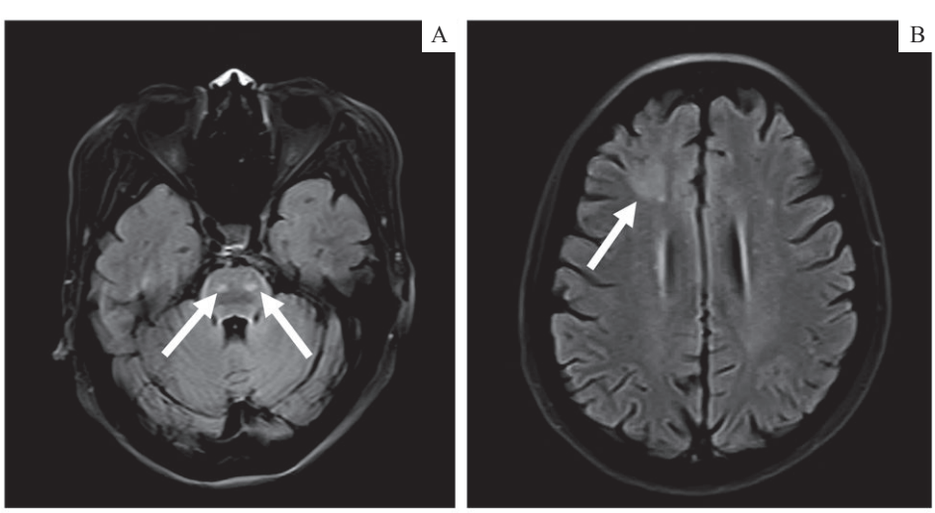
收集患者的临床资料，包括性别、年龄、家族史、临床症状、既往史、体格检查结果、实验室检查结果（肝肾功能、血糖、电解质、红细胞沉降率、C反应蛋白、补体、甲状腺功能、尿及粪便常规等）、人类免疫缺陷病毒（human immunodeficiency virus，HIV）抗体、梅毒螺旋体抗体、肝炎病毒抗体、肿瘤标志物、自身抗体（抗“O”抗体、抗类风湿关节炎抗体、抗核抗体谱、抗中性粒细胞胞浆抗体、抗磷脂综合征抗体、抗类风湿关节炎抗体、副肿瘤抗体、中枢脱髓鞘抗体）、免疫固定电泳、脑脊液检查（脑脊液常规、生化检查、副肿瘤及中枢脱髓鞘抗体）、头颅磁共振成像（magnetic resonance imaging，MRI）、脊髓MRI、腮腺B超、全身淋巴结B超、肌电图、脑电图以及唇腺活检组织学检查。

2 结果

2.1 病例1临床资料

女性，59岁，2023年2月6日因“进行性行走不稳伴双下肢麻木9年”就诊。患者自2014年开始出现行走不稳伴有双足麻木；2018年双下肢沉重感较前

加重，行走有踩棉感，易摔跤，双下肢痛温觉减退；2022年1月病情逐渐进展，无法独立行走，并伴有双上肢无力，语速慢，饮水呛咳、吞咽困难，大便失禁，排尿困难；2022年6月起开始卧床，出行依赖轮椅。外院曾考虑“复杂型痉挛性截瘫可能”“脊髓根动脉栓塞可能”等诊断，先后予以巴氯芬、银杏叶提取物注射液、右旋糖酐、甲钴胺等治疗无效。既往有口干、眼干症状1年余，无糖尿病、高血压、HIV感染、结节病、肝炎等病史或肿瘤放疗史，无家族史。大体检查：全身浅表淋巴结未扪及肿大，全身未见皮疹，未见龋齿，无口腔黏膜溃疡、腮腺肿大；皮肤色泽正常，无汗液分泌异常。神经系统查体：神志清，言语含糊，语速慢，面部表情和瞬目减少；上肢肌张力正常，远端肌力Ⅳ级，近端肌力Ⅴ级，腱反射正常；下肢肌张力增高，双下肢肌力Ⅲ级，双侧膝反射活跃（+++），踝反射亢进（++++），踝阵挛阳性，巴宾斯基征（+）；第六胸神经（T6）平面以下双侧针刺觉、深感觉减退；指鼻试验欠稳准，跟-膝-胫试验结果不佳，“一字步”不能完成，龙贝格征检查睁眼和闭眼均摇晃。自身抗体检查：抗核抗体阳性（1∶1 000着丝点型），抗SSA/Ro-52抗体、抗SSA/Ro-60抗体、抗着丝点抗体阳性，余自身抗体阴性。脑脊液检查：白细胞8×10^{6}个/L，蛋白0.34 g/L，血清学副肿瘤抗体及中枢脱髓鞘抗体阴性。外周血免疫固定电泳、血常规、叶酸、维生素B12、同型半胱氨酸、甲状腺功能、肿瘤标志物、肝肾功能、电解质、尿常规、粪便常规指标均在正常范围。卧立位血压测试结果阴性。肌电图提示右侧腓神经运动纤维轴索损伤。脑电图结果正常。腮腺B超：双侧颌下腺、腮腺未见肿块，双侧颌下未见肿大淋巴结。头颅MRI（T2-Flair）可见“蛇眼征”，即脑干双侧皮质脊髓束走行区对称性高信号（图1A），以及右前额叶斑片状高信号（图1B），未见强化。脊髓MRI未见明显异常信号。唇腺活检：唾液腺组织、导管间及小叶内淋巴细胞浸润灶2个/4 mm^2（淋巴细胞>50个）。住院期间予以注射用甲泼尼龙琥珀酸钠500 mg冲击治疗5 d，自觉下肢力量较前好转，随后激素逐渐减量，出院改为口服。出院后予以泼尼松每日1次、每次30 mg，硫酸羟氯喹每日2次、每次0.2 g，氨甲蝶呤每周1次、每次10 mg，辅以护胃、补钙、补钾等对症支持治疗。治疗3个月后，患者可推助行器行走，日常生活基本可以自理。



Note: A. "Snake-eye sign" in the brainstem on the T2 Flair-weighted image, which presents symmetrical hyperintensity in the corticospinal tract regions. B. Patchy hyperintensity in the right prefrontal lobe on the T2 Flair-weighted image.

图1　病例1头颅MRI检查

Fig 1　Brain MRI of case 1

2.2　病例2临床资料

女性，81岁，2023年7月28日因“颈部不自主向右偏斜3个月”就诊。患者在3个月前无明显诱因下出现头颈向右侧偏斜，站立和行走时加重。既往存在轻度口干、眼干症状，伴有膝关节疼痛1年。患者无糖尿病、高血压、HIV感染、结节病、肝炎等病史或肿瘤放疗史，无家族史。大体检查：全身浅表淋巴结未扪及肿大，全身未见皮疹，未见龋齿、口腔黏膜溃疡、腮腺肿大，皮肤色泽正常，无汗液分泌异常。神经系统查体：神志清，构音清晰，颈部右侧偏斜，

颈部肌张力明显增高，四肢肌张力、腱反射正常，双上肢肌力正常，下肢肌力Ⅳ级，双侧巴宾斯基征（+），指鼻试验、跟-膝-胫试验结果尚可。实验室检查：抗SSA/Ro-52抗体阳性，抗SSA/Ro-60抗体阳性，余自身抗体阴性；血清IgG 9.54 g/L，血清IgA 11.80 g/L，血清IgM 0.37 g/L，血清κ轻链4.97 g/L，血清λ轻链1.04 g/L，κ/λ比值4.78；免疫固定电泳示IgA单克隆增高，κ型轻链；红细胞2.66×10^{12}个/L，血红蛋白86 g/L，红细胞比容26.8%，平均红细胞体积100.8 fL；临床生化检查包括叶酸、维生素B12、同型半胱氨酸、甲状腺功能、肿瘤标志物、肝肾功能、电解质、脑脊液检查、尿粪常规检查均在正常范围；血清副肿瘤及中枢神经系统脱髓鞘抗体阴性。全身淋巴结B超未见明显肿块及肿大淋巴结。腮腺B超，双侧颌下腺、腮腺未见肿块，双侧颌下未见肿大的淋巴结。肌电图检查提示右侧正中神经传导速度轻度下降。脑电图正常。头颅及脊髓MRI未见异常。唇腺活检可见小唾液腺组织部分腺泡萎缩，间质内有淋巴细胞、浆细胞浸润灶2个/4 mm^2（淋巴细胞>50个）。住院期间予以硫酸羟氯喹片每日2次、每次0.2 g，琥珀酸亚铁每日3次、每次0.1 g，巴氯芬片每日1次、每次2.5 mg，氯硝西泮片每日1次、每次1 mg，盐酸硫必利片每日2次、每次0.05 g等治疗。治疗2周后，患者头颈部向右偏斜有部分缓解，头后仰位时胸锁乳突肌张力增高。

3 讨论

pSS是一种主要影响外分泌腺的慢性自身免疫性疾病，其主要特征是干燥症状，病程中常伴有多系统受累。腺外系统受累对于本病的长期预后起到决定性作用[17-18]。神经系统受累是本病腺外最常见的表现之一，8.5%~70%的患者合并神经系统症状，通常是在pSS被诊断前2年，或是在确诊后的6~8年出现[12,19]。2%~25%的患者合并神经系统损伤，其中12%~15%伴有视神经炎，约1.5%伴有小脑共济失调[20]，10%~20%有多发性硬化样表现[12,15,21]。本研究中，我们报道了2例相对罕见的以神经系统受累为首发症状的pSS患者，一例表现为脑干双侧皮质脊髓束脱髓鞘，另一例以颈部肌张力增高为突出表现。2例患者的干燥症状并未明显影响日常生活和工作，未曾因此就诊过。总结和对比上述2例的临床特点，有助于进一步了解该疾病的罕见临床表型谱。

病例1头颅MRI可见脑干典型“蛇眼征”，即皮质脊髓束走行区双侧对称性高信号，脑脊液检查基本正常，结合抗核抗体阳性（1∶1 000着丝点型），抗SSA/Ro-52抗体、抗SSA/Ro-60抗体、抗着丝点抗体阳性，唇腺活检病理可见2个淋巴细胞灶，最终确诊pSS[16]。“蛇眼征”又叫“鹰眼征”，是一种独特的影像学征象，由脊髓缺氧缺血导致，灰质前角区域对缺氧较为敏感，故多表现为脊髓MRI横断面T2序列上双侧脊髓灰质前角对称性高信号，以颈、胸髓节段受累多见，亦有报道累及脑干[22-24]。这种影像学表现可见于颈椎结构性改变（脊髓型颈椎病、后纵韧带骨化等）、血管异常（脊髓前动脉闭塞、椎动脉狭窄等）、运动神经元病（肌萎缩侧索硬化症、青少年上肢远端肌萎缩等）、自身免疫性疾病（贝赫切特综合征、血管炎等）、感染（脊髓灰质炎、HIV性脊髓炎等）、急性脊髓减压病、毒品滥用、钴中毒等[24-28]。值得一提的是，pSS表现为突出的痉挛性截瘫样症状者，仅有个案报道[29-30]，经及时治疗，预后通常较好[29]。此外，其他系统性自身免疫性疾病也可以痉挛性截瘫作为首发症状。例如PENG等[31]报道了以痉挛性截瘫为唯一临床特点的系统性红斑狼疮患者，该患者抗双链DNA抗体、抗史密斯（anti-Smith，anti-Sm）抗体和抗核糖体蛋白（anti-ribonuclear protein，anti-RNP）抗体阳性；头颅MRI也存在脑干双侧对称异常高信号，侧脑室旁、小脑可见点状高信号。MANTERO等[32]报道了1例在确诊pSS后5年出现颈部肌张力障碍、眼睑痉挛的病例。pSS所合并的常见肌张力障碍表现包括口面部肌张力障碍、单侧肢体肌张力障碍、阵发性肌张力障碍、肢体其他不自主运动[33-36]。此外，血液系统是pSS常见的受累靶点之一，约占40%[37]。西班牙一项400例pSS患者的多中心队列研究[38]发现，20%合并贫血，16%存在白细胞减少症，13%存在血小板减少症。约有1/5患者最终死于淋巴瘤，其中紫癜和血清低水平补体C4是不良预后的危险因素[39]。此外，ZHANG等[40]发现本病的性别差异较大，女性患者更易表现为口干、眼干、关节痛、龋齿、贫血、低中性粒细胞，而男性患者更易患间质性肺疾病、淋巴瘤以及腮腺肿大。

pSS导致神经系统损伤的机制尚不明确，目前认为是一个多因素互相作用的过程，环境因素、遗传易感性、细胞免疫以及体液免疫均与疾病发生有

关[41-42]。T淋巴细胞和树突状细胞扮演了重要角色，其通过分泌细胞因子导致血管炎；淋巴细胞可浸润背根神经节，并通过特异性自身抗体直接损伤神经系统[12,14,43-44]。以神经系统损伤为首发甚至是唯一表现的病例，极易被误诊为其他疾病，包括共济失调、痉挛性截瘫、肌张力障碍以及运动神经元病等。临床实践中，如考虑自身免疫相关因素，则应仔细询问有无黏膜干燥、关节疼痛、龋齿、疲劳等症状，同时结合体格检查、自身抗体及影像学等辅助检查结果进行甄别。在排除其他病因后，pSS的早期确诊和针对性治疗对于改善患者预后有重要意义。随着更多罕见表型的病例被相继报道，其相关机制值得进一步研究和探索，这也将为诊断、鉴别诊断、不同表型临床规范化诊治策略的制定提供参考。

利益冲突声明/Conflict of Interests

所有作者声明不存在利益冲突。

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伦理批准和知情同意/Ethics Approval and Patient Consent

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作者贡献/Authors' Contributions

姚莉参与数据收集、数据分析和论文写作。田沃土、曹立负责研究设计、数据整理、数据解释和论文修改。所有作者均阅读并同意了最终稿件的提交。

YAO Li contributed to data collection and analysis and drafted the manuscript. TIAN Wotu and CAO Li contributed to the study design, data acquisition, interpretation of data, and manuscript revision. All the authors have read the last version of paper and consented for submission.

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