

提高对不宁腿综合征规范诊断与治疗的认知

王玉平

【关键词】 不宁腿综合征； 规范； 综述

【Key words】 Restless legs syndrome; Benchmarking; Review

Improve the understandings of standardized diagnosis and treatment of restless legs syndrome

WANG Yu-ping

Department of Neurology, Xuanwu Hospital, Capital Medical University; Beijing Key Laboratory of Neuromodulation, Beijing 100053, China (Email: wangyuping01@sina.cn)

不宁腿综合征(RLS)亦称 Willis-Ekbom 病(WED),是临床常见的神经系统运动感觉性疾病。流行病学调查显示,不同国家和地区成人不宁腿综合征患病率不同,欧美国家患病率明显高于亚洲国家,其中欧美国家成人患病率为 5.0%~14.3%^[1-2]、亚洲国家为 0.1%~1.9%^[3-4]。不宁腿综合征可发生于任何年龄阶段,且随着年龄的增长、患病率逐年增加,女性患病率高于男性。由于不宁腿综合征的诊断主要依靠临床症状,缺乏特异性,加之短期内不会造成明显损害,因此目前对该病的诊断率较低,治疗方法不甚规范。

一、临床症状

不宁腿综合征临床主要表现为夜间睡眠中或安静状态下双下肢出现极度不适感(如撕裂感、蠕动感、烧灼感、搔痒感甚至疼痛),尤以小腿显著,偶累及大腿和上肢,通常呈对称性,从而使患者不停地活动下肢或下床行走,一旦恢复休息状态时再次出现上述不适感。其临床症状具有特征性昼夜变化规律,腿部不适感多出现在傍晚或夜间,发作高峰为午夜与凌晨之间,白天症状相对轻微。80%患者伴周期性腿动(PLM),即睡眠中或清醒时出现肢体不自主运动,表现为单侧或双侧下肢反复出现的周期性刻板样不自主运动,形式多样,典型症状为脚趾节律性背伸和踝部背屈,偶可见髋关节和膝关节屈曲,类似 Babinski 征^[5]。不宁腿综合征严重干扰

睡眠,导致入睡困难、夜间觉醒次数增加,进而出现疲劳、记忆力减退、情绪低落、血压波动,影响生活质量。

二、病因分类

不宁腿综合征根据病因可以分为原发性和继发性两种类型。原发性不宁腿综合征通常有家族史,现有研究支持该病呈常染色体显性遗传^[6],主要可疑致病基因定位于染色体 12q、14q 和 9q。我国以散发性不宁腿综合征患者多见。继发性不宁腿综合征与某些生理或病理状态有关,多种危险因素均可能增加不宁腿综合征的风险,其中,妊娠是目前研究最多的危险因素,激素表达变化是妊娠期女性不宁腿综合征的主要原因^[7]。铁缺乏与不宁腿综合征患病率升高显著相关,常出现血清铁蛋白水平降低,研究显示,血清铁蛋白 < 45 或 50 $\mu\text{g/L}$ 时,不宁腿综合征患病率显著增加^[8]。肾功能障碍是继发性不宁腿综合征的另一常见危险因素,常伴铁缺乏、血红蛋白降低和钙磷代谢紊乱,研究显示,肾移植术后不宁腿综合征症状可能缓解甚至消失^[9]。

三、发病机制

不宁腿综合征的发病机制尚不明确,目前观点包括:(1)中枢神经系统多巴胺能神经递质及其受体表达下调。(2)中枢神经系统铁缺乏。(3)大脑皮质运动感觉整合网络功能失调^[10]。(4)中枢神经系统下行抑制通路功能失调致脊髓神经元过度兴奋。

四、诊断标准

不宁腿综合征的诊断主要依靠详细的临床病史,目前尚无特异性实验室指标,常用辅助检查方法包括多导睡眠图(PSG)监测和暗示性制动试验

doi:10.3969/j.issn.1672-6731.2017.09.001

作者单位:100053 北京,首都医科大学宣武医院神经内科 北京市神经调控重点实验室,Email:wangyuping01@sina.cn

(SIT)。Ekblom^[11]于1960年率先提出较为详细的诊断建议,此后经历多次修订^[12],至2014年国际不宁腿综合征研究组(IRLSSG)制定不宁腿综合征诊断标准^[12],同年美国睡眠医学会(AASM)公布睡眠障碍国际分类第3版(ICSD-3)^[9],二者关于不宁腿综合征的诊断标准基本一致,须同时符合以下3项标准:(1)有想活动腿的强烈欲望,常伴腿部不适感或腿部不适感所致,同时满足以下条件,①症状在休息或不活动时出现或加重,如卧位或坐位。②活动后症状部分或完全缓解,如行走或伸展腿部。③症状仅出现在傍晚或夜间,或者即使出现在白天,症状较夜间轻微。(2)上述症状排除药物或行为习惯所致,如腿部痉挛、姿势不恰当、肌肉疼痛、静脉曲张、腿部水肿、关节炎或习惯性腿部抖动等。(3)上述症状导致忧虑、抑郁、睡眠障碍,以及生理、心理、社会交往、职业、受教育、行为及其他重要领域功能障碍。该诊断标准还对不宁腿综合征的诊断予以补充说明:不适感可出现于上肢或身体其他部位;病程早期具有腿部不适感经药物治疗减轻和夜间症状加重等特点,至疾病晚期上述特点不明显。

五、治疗

1. 治疗目标 不宁腿综合征是可治性疾病,但不能根治。对于有明确病因的继发性不宁腿综合征患者应尽可能消除病因。治疗目标是减轻或消除不宁腿综合征症状,包括减少夜间腿动次数、减轻腿动幅度、缩短夜间清醒时间、改善日间功能、提高睡眠质量和生活质量。治疗方法的选择取决于多种因素,如疾病严重程度、年龄、共病情况和患者偏好。治疗方法包括非药物治疗和药物治疗,药物治疗效果较好,针对不同临床情况的不宁腿综合征患者,药物的选择不尽一致。

2. 非药物治疗 对于症状较轻的患者,非药物治疗可以缓解症状;对于症状较重的患者,也可以考虑非药物治疗,以减少药物需求。非药物治疗包括腿部按摩、热水浴、腿部使用加热垫或冰袋、良好睡眠习惯和夜间使用振动垫等^[13-16]。

3. 药物治疗 (1)治疗前评价:治疗前首先明确是否存在铁缺乏,应测定血清铁蛋白^[17-18]。若血清铁蛋白 $<75\ \mu\text{g/L}$,建议补充铁剂^[19],治疗3~4个月后复查血清铁蛋白,此后每3~6个月复查1次,直至血清铁蛋白 $>75\ \mu\text{g/L}$ 且铁饱和度 $>20\%$ 。应注意观察铁剂治疗效果,如果治疗效果较好,认为不宁腿综合征与铁缺乏有关,应积极寻找铁缺乏原因、

纠正铁缺乏;如果治疗效果欠佳,可能与铁缺乏无关,但仍应保持血清铁蛋白于正常值范围,再予进一步治疗。在未测定血清铁蛋白前,不建议仅凭经验补充铁剂,可能出现不良反应。其次应避免加重不宁腿综合征症状的因素,包括睡眠剥夺(SD)、不良睡眠习惯和使用某些药物或物品,其中,抗抑郁药、神经阻滞剂、多巴胺能受体阻断剂类止吐药(如甲氧氯普胺)或镇静催眠类抗组胺药可以诱发或加重不宁腿综合征^[20];咖啡因、尼古丁和酒精可以加重不宁腿综合征症状^[21]。(2)药物选择:根据临床症状严重程度,将不宁腿综合征分为间歇性症状、持续性症状,病情加重和(或)恶化。目前主要应用多巴胺能药、 α -2- δ 钙通道配体、苯二氮䓬类药物和阿片类药物^[22-25]。①间歇性症状。对于轻度或部分间歇性症状患者,可以首先考虑非药物治疗。对于无需每日治疗的间歇性症状患者,建议优先间断性应用多巴胺能受体激动剂^[24,26],也可以间断性应用左旋多巴,大部分患者可以较好耐受左旋多巴短期治疗(<6 个月)。苯二氮䓬类药物可用于症状较轻的患者,特别青年患者,氯硝西泮最为常用^[13,27]。此类药物通常用于仅需间断性治疗的患者,或作为难治性不宁腿综合征的辅助药物。研究显示,氯硝西泮 $0.50\sim 2.00\ \text{mg/d}$ 即对不宁腿综合征有效^[28-29]。②持续性症状。对于非药物治疗和补充铁剂后仍频繁发作的中至重度患者,建议选择一线治疗药物,包括多巴胺能受体激动剂和 α -2- δ 钙通道配体^[23-25,30]。长期应用多巴胺能药的不宁腿综合征患者应注意病情加重和(或)恶化,予可有效控制症状的最小剂量且通常仅于傍晚服药。同时应定期(每6~12个月)复查并监测不良反应和并发症^[31]。多巴胺能受体激动剂的并发症风险较低,持续服药的不良反应少于左旋多巴。目前,非麦角类多巴胺能受体激动剂普拉克索、罗匹尼罗和罗替戈汀已经成为经美国食品药品监督管理局(FDA)批准的治疗不宁腿综合征的首选药物^[24,26]。普拉克索和罗匹尼罗通常于服药后90~120分钟起效,故应在不宁腿综合征症状开始前2小时服药^[26],不良反应轻微,仅为短暂性恶心、头晕和疲劳,通常于10~14天内缓解。罕见不良反应包括鼻塞、便秘、失眠和腿部水肿,均可于停药后消失。存在特定共病(如疼痛、焦虑、失眠、冲动控制障碍或多巴胺能受体激动剂相关成瘾)的患者,可以考虑 α -2- δ 钙通道配体进行初始治疗^[19,32]。 α -2- δ 钙通道配体包括加巴喷丁和普瑞巴林,用于每日发作的

不宁腿综合征患者,美国食品与药品管理局已批准加巴喷丁恩那卡比用于这一适应症^[26,33-35]。 α -2- δ 钙通道配体常见不良反应包括疲劳、嗜睡、头晕、头痛、行走不稳^[26,35-36]。③病情加重和(或)恶化。治疗过程中出现以下情况应考虑病情加重和(或)恶化的可能,予适当多巴胺能药后症状仍持续加重;增加药物剂量后症状仍持续加重;下午和(或)傍晚出现症状的时间提前;症状扩展至先前未受累部位;日间休息状态下,潜伏期缩短^[37]。病情加重和(或)恶化是长期应用多巴胺能药的主要并发症。因此,为避免病情加重和(或)恶化,多巴胺能药剂量应该尽可能小,不宜超过不宁腿综合征的推荐剂量(远小于帕金森病剂量)。如果患者发作频率较少,可考虑间断性治疗。一旦出现病情加重和(或)恶化应至睡眠专科就诊。根据2012和2016年不宁腿综合征治疗指南^[24,38-39],为避免病情加重和(或)恶化, α -2- δ 钙通道配体(主要包括加巴喷丁和普瑞巴林)可以考虑作为不宁腿综合征的首选药物,这是由于此类药物治疗不宁腿综合征有效且病情加重和(或)恶化风险较低。

不宁腿综合征患者常以失眠为主诉就诊,具有特征性临床症状,是可治性疾病。及时、正确治疗可以很大程度缓解患者生理和心理症状。提高对不宁腿综合征的认识以及规范治疗原则是临床医师的工作和任务。

参 考 文 献

- [1] Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, Ferini-Strambi L. Restless legs syndrome prevalence and impact: REST general population study. *Arch Intern Med*, 2005, 165:1286-1292.
- [2] Bjorvatn B, Leissner L, Ulfberg J, Gyiring J, Karlsborg M, Regeur L, Skeidsvoll H, Nordhus IH, Pallesen S. Prevalence, severity and risk factors of restless legs syndrome in the general adult population in two Scandinavian countries. *Sleep Med*, 2005, 6:307-312.
- [3] Tan EK, Seah A, See SJ, Lim E, Wong MC, Koh KK. Restless legs syndrome in an Asian population: a study in Singapore. *Mov Disord*, 2001, 16:577-579.
- [4] Chen NH, Chuang LP, Yang CT, Kushida CA, Hsu SC, Wang PC, Lin SW, Chou YT, Chen RS, Li HY, Lai SC. The prevalence of restless legs syndrome in Taiwanese adults. *Psychiatry Clin Neurosci*, 2010, 64:170-178.
- [5] Wang YJ, Wang YP. Progress in the research of restless legs syndrome. *Zhongguo Xian Dai Shen Jing Ji Bing Za Zhi*, 2008, 8:183-187. [王轶瑾, 王玉平. 不宁腿综合征临床研究进展. *中国现代神经疾病杂志*, 2008, 8:183-187.]
- [6] Högl B, Poewe W. Restless legs syndrome. *Curr Opin Neurol*, 2005, 18:405-410.
- [7] Dzaja A, Wehrle R, Lancel M, Pollmächer T. Elevated estradiol plasma levels in women with restless legs during pregnancy. *Sleep*, 2009, 32:169-174.
- [8] Frauscher B, Gschliesser V, Brandauer E, El-Demerdash E, Kaneider M, Rucker L, Poewe W, Högl B. The severity range of restless legs syndrome (RLS) and augmentation in a prospective patient cohort: association with ferritin levels. *Sleep Med*, 2009, 10:611-615.
- [9] American Academy of Sleep Medicine. International classification of sleep disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine, 2014: 282-291.
- [10] Rizzo V, Aricò I, Liotta G, Ricciardi L, Mastroeni C, Morgante F, Allegra R, Conurso R, Giralda P, Silvestri R, Quartarone A. Impairment of sensory-motor integration in patients affected by RLS. *J Neurol*, 2010, 257:1979-1985.
- [11] Ekbom KA. Restless legs syndrome. *Neurology*, 1960, 10:868-873.
- [12] Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman JW, Zucconi M, Ferri R, Trenkwalder C, Lee HB; International Restless Legs Syndrome Study Group. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria. Updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria: history, rationale, description, and significance. *Sleep Med*, 2014, 15:860-873.
- [13] Schenck CH, Mahowald MW. Long-term, nightly benzodiazepine treatment of injurious parasomnias and other disorders of disrupted nocturnal sleep in 170 adults. *Am J Med*, 1996, 100:333-337.
- [14] Garcia-Borreguero D, Grunstein R, Sridhar G, Dreykluft T, Montagna P, Dom R, Lainey E, Moorat A, Roberts J. A 52-week open-label study of the long-term safety of ropinirole in patients with restless legs syndrome. *Sleep Med*, 2007, 8:742-752.
- [15] Mitchell UH. Nondrug-related aspect of treating Ekbom disease, formerly known as restless legs syndrome. *Neuropsychiatr Dis Treat*, 2011, 7:251-257.
- [16] Lettieri CJ, Eliasson AH. Pneumatic compression devices are an effective therapy for restless legs syndrome: a prospective, randomized, double-blinded, sham-controlled trial. *Chest*, 2009, 135:74-80.
- [17] Högl B, Garcia-Borreguero D, Kohnen R, Ferini-Strambi L, Hadjigeorgiou G, Hornyak M, de Weerd A, Happe S, Stiasny-Kolster K, Gschliesser V, Egatz R, Frauscher B, Benes H, Trenkwalder C, Hening WA, Allen RP. Progressive development of augmentation during long-term treatment with levodopa in restless legs syndrome: results of a prospective multi-center study. *J Neurol*, 2010, 257:230-237.
- [18] Garcia-Borreguero D, Högl B, Ferini-Strambi L, Winkelman J, Hill-Zabala C, Asgharian A, Allen R. Systematic evaluation of augmentation during treatment with ropinirole in restless legs syndrome (Willis-Ekbom disease): results from a prospective, multicenter study over 66 weeks. *Mov Disord*, 2012, 27:277-283.
- [19] Silber MH, Becker PM, Earley C, Garcia-Borreguero D, Ondo WG; Medical Advisory Board of the Willis-Ekbom Disease Foundation. Willis-Ekbom Disease Foundation revised consensus statement on the management of restless legs syndrome. *Mayo Clin Proc*, 2013, 88:977-986.
- [20] Hoque R, Chesson AL Jr. Pharmacologically induced/exacerbated restless legs syndrome, periodic limb movements of sleep, and REM behavior disorder/REM sleep without atonia: literature review, qualitative scoring, and comparative analysis. *J Clin Sleep Med*, 2010, 6:79-83.
- [21] Shen Y, Mao CJ, Liu CF. Secondary restless legs syndrome. *Zhongguo Xian Dai Shen Jing Ji Bing Za Zhi*, 2013, 13:392-397.

- [沈赞, 毛成洁, 刘春风. 继发性不宁腿综合征. 中国现代神经疾病杂志, 2013, 13:392-397.]
- [22] Trotti LM, Bhadriraju S, Becker LA. Iron for restless legs syndrome. *Cochrane Database Syst Rev*, 2012, (5):CD007834.
- [23] Scholz H, Trenkwalder C, Kohnen R, Riemann D, Kriston L, Hornyak M. Dopamine agonists for restless legs syndrome. *Cochrane Database Syst Rev*, 2011, (3):CD006009.
- [24] Aurora RN, Kristo DA, Bista SR, Rowley JA, Zak RS, Casey KR, Lamm CI, Tracy SL, Rosenberg RS; American Academy of Sleep Medicine. The treatment of restless legs syndrome and periodic limb movement disorder in adults: an update for 2012. Practice parameters with an evidence-based systematic review and meta-analyses: an American Academy of Sleep Medicine Clinical Practice Guideline. *Sleep*, 2012, 35:1039-1062.
- [25] Wilt TJ, MacDonald R, Ouellette J, Khawaja IS, Rutks I, Butler M, Fink HA. Pharmacologic therapy for primary restless legs syndrome: a systematic review and meta-analysis. *JAMA Intern Med*, 2013, 173:496-505.
- [26] Silber MH, Ehrenberg BL, Allen RP, Buchfuhrer MJ, Earley CJ, Hening WA, Rye DB; Medical Advisory Board of the Restless Legs Syndrome Foundation. An algorithm for the management of restless legs syndrome. *Mayo Clin Proc*, 2004, 79:916-922.
- [27] Montplaisir J, Godbout R, Boghen D, DeChamplain J, Young SN, Lapierre G. Familial restless legs with periodic movements in sleep: electrophysiologic, biochemical, and pharmacologic study. *Neurology*, 1985, 35:130-134.
- [28] Montagna P, Sassoli de Bianchi L, Zucconi M, Cirignotta F, Lugaresi E. Clonazepam and vibration in restless legs syndrome. *Acta Neurol Scand*, 1984, 69:428-430.
- [29] Read DJ, Feest TG, Nassim MA. Clonazepam: effective treatment for restless legs syndrome in uraemia. *Br Med J (Clin Res Ed)*, 1981, 283:885-886.
- [30] Trenkwalder C, Hening WA, Montagna P, Oertel WH, Allen RP, Walters AS, Costa J, Stiasny-Kolster K, Sampaio C. Treatment of restless legs syndrome: an evidence-based review and implications for clinical practice. *Mov Disord*, 2008, 23:2267-2302.
- [31] Nofzinger EA, Fasiczka A, Berman S, Thase ME. Bupropion SR reduces periodic limb movements associated with arousals from sleep in depressed patients with periodic limb movement disorder. *J Clin Psychiatry*, 2000, 61:858-862.
- [32] Garcia-Borreguero D, Kohnen R, Silber MH, Winkelmann JW, Earley CJ, Högl B, Manconi M, Montplaisir J, Inoue Y, Allen RP. The long-term treatment of restless legs syndrome/Willis-Ekbom disease. Evidence-based guidelines and clinical consensus best practice guidance: a report from the International Restless Legs Syndrome Study Group. *Sleep Med*, 2013, 14:675-684.
- [33] Kushida CA, Becker PM, Ellenbogen AL, Canafax DM, Barrett RW; XP052 Study Group. Randomized, double-blind, placebo-controlled study of XP13512/GSK1838262 in patients with RLS. *Neurology*, 2009, 72:439-446.
- [34] Kushida CA, Walters AS, Becker P, Thein SG, Perkins AT, Roth T, Canafax D, Barrett RW; XP021 Study Group. A randomized, double-blind, placebo-controlled, crossover study of XP13512/GSK1838262 in the treatment of patients with primary restless legs syndrome. *Sleep*, 2009, 32:159-168.
- [35] Garcia-Borreguero D, Larrosa O, Williams AM, Albares J, Pascual M, Palacios JC, Fernandez C. Treatment of restless legs syndrome with pregabalin: a double-blind, placebo-controlled study. *Neurology*, 2010, 74:1897-1904.
- [36] Allen RP, Chen C, Garcia-Borreguero D, Polo O, DuBrava S, Miceli J, Knapp L, Winkelmann JW. Comparison of pregabalin with pramipexole for restless legs syndrome. *N Engl J Med*, 2014, 370:621-631.
- [37] Garcia-Borreguero D, Stillman P, Benes H, Buschmann H, Chaudhuri KR, Gonzalez Rodriguez VM, Högl B, Kohnen R, Monti GC, Stiasny-Kolster K, Trenkwalder C, Williams AM, Zucconi M. Algorithms for the diagnosis and treatment of restless legs syndrome in primary care. *BMC Neurol*, 2011, 11:28.
- [38] Garcia-Borreguero D, Ferini-Strambi L, Kohnen R, O'Keefe S, Trenkwalder C, Högl B, Benes H, Jennum P, Partinen M, Fer D, Montagna P, Bassetti CL, Iranzo A, Sonka K, Williams AM; European Federation of Neurological Societies; European Neurological Society; European Sleep Research Society. European guidelines on management of restless legs syndrome: report of a joint task force by the European Federation of Neurological Societies, the European Neurological Society and the European Sleep Research Society. *Eur J Neurol*, 2012, 19:1385-1396.
- [39] Garcia-Borreguero D, Silber MH, Winkelmann JW, Högl B, Bainbridge J, Buchfuhrer M, Hadjigeorgiou G, Inoue Y, Manconi M, Oertel W, Ondo W, Winkelmann J, Allen RP. Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. *Sleep Med*, 2016, 21:1-11.

(收稿日期:2017-07-27)

· 小词典 ·

中英文对照名词词汇(一)

γ-氨基丁酸 γ-aminobutyric acid(GABA)
 暗示性制动试验 Suggested Immobilization Test(SIT)
 白天过度嗜睡 excessive daytime sleepiness(EDS)
 白细胞共同抗原 leukocyte common antigen(LCA)
 半高全宽 full width half maximum(FWHM)
 不宁腿综合征 restless legs syndrome(RLS)
 长谷川痴呆量表 Hasegawa Dementia Scale(HDS)
 超敏C-反应蛋白
 high-sensitivity C-reactive protein(hs-CRP)

痴呆简易筛查量表
 Brief Screening Scale for Dementia(BSSD)
 持续气道正压通气
 continuous positive airway pressure(CPAP)
 重复经颅磁刺激
 repetitive transcranial magnetic stimulation(rTMS)
 重复时间 repetition time(TR)
 重组组织型纤溶酶原激活物
 recombinant tissue-type plasminogen activator(rt-PA)
 促甲状腺激素 thyroid stimulating hormone(TSH)