

丙型肝炎病毒感染相关睡眠障碍的研究进展

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Advances in research of sleep disturbance in patients with hepatitis C virus infection

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Abstract

According to the WHO statistics, approximately 171 million people are infected by hepatitis C virus (HCV) worldwide. Chronic HCV infection is associated with physical and mental symptoms including fatigue, sleep disturbance, and depression that adversely affect quality of life. But sleep disturbance has received little attention in the literature, with the exception of sleep changes noted in patients with cirrhosis and end-stage liver disease. More studies focusing on the role of chronic hepatitis C (CHC) infection in the development of sleep disorders are needed. Increased knowledge about the mechanisms behind the pathogenesis of sleep disturbance in patients with CHC will help us develop appropriate treatments.

Key Words: Hepatitis C virus; Chronic hepatitis C;

Sleep disorders

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摘要

据WHO的统计, 全球约有1.71亿人罹患丙型肝炎病毒(hepatitis C virus, HCV)的感染^[1]。伴随HCV的感染, 患者常常会出现疲劳、睡眠障碍、抑郁等身心异常的状态。既往有文献报道丙肝患者存在睡眠的问题, 但往往淹没在众多肝纤维化及终末期肝病相关的睡眠障碍文献中, 鲜有人关注与HCV感染直接相关的睡眠障碍^[2]。近年来, 有少量的文献致力于慢性丙型肝炎睡眠障碍的探讨, 让人惊讶的是睡眠问题在慢性丙肝患者中存在着很大程度的普遍性, 有证据提示其可能独立于干扰素的治疗。对HCV感染相关睡眠障碍的研究可能会为慢性丙型肝炎的发生、发展及转归提供新的研究思路, 也有利于提高患者生活质量, 优化现有的治疗方案。

关键词: 丙型肝炎病毒; 慢性丙型肝炎; 睡眠障碍

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0 引言

在慢性丙型肝炎(chronic hepatitis C, CHC)患者的诸多症状中, 倦怠是最明显的^[3]。事实上, 对CHC的研究显示超过97%的患者存在疲倦^[4,5], 同时可伴有社交能力、身体机能的减退以及明显的抑郁^[6]。疲倦和抑郁在丙肝患者的诸多症状中被得到重视, 但作为一项与疲倦密切相关的症状-睡眠障碍, 却很少受到关注^[7]。睡眠障碍分为原发性和继发性, 最新的定义将睡眠障碍分为8个主要类别: 失眠、睡眠相关性的呼吸障碍、中枢性嗜睡、周期性睡眠节律失调、异态睡眠、睡眠相关的动作失调、与睡眠障碍

■背景资料

在中国, 慢性丙型肝炎与艾滋病、慢性乙型肝炎等慢性传染性疾病成为了重大的公共卫生问题, 但现有的治疗方法较为单一, 且疗效并不显著。而在临床上很多慢性丙肝患者存在睡眠障碍, 这引发了我们思考丙肝发病机制的新思路。

■同行评议者

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■ 研究前沿

近年来从事相关研究主要集中在临床观察,而从机制探讨的较少。但HCV感染常伴随HIV感染或经干扰素治疗后,会出现一定的睡眠问题,这为相关研究增加了一定的困难。

相关性的综合征及其他睡眠障碍^[8]。常见的有异态睡眠(主要包括夜惊、夜游及快速动眼期的动作失调)、失眠、睡眠相关性的呼吸障碍及睡眠相关的动作失调(主要表现为不宁腿综合征)等。本文旨在探讨CHC患者存在的睡眠障碍问题,包括经或不经干扰素 α (interferon α , IFN α)治疗,以及这一症状产生的潜在机制。

1 未行抗病毒治疗相关的睡眠障碍

慢性丙型肝炎患者的疲劳症状相当常见,其中一个重要的原因在于睡眠障碍。有研究认为对于未进行治疗的CHC患者中,大约有60%存在睡眠问题^[14]。丙肝患者常由于静脉注射染病,药物的毒副作用或戒断综合征等进而对睡眠产生影响。情绪失调、抑郁症也常出现在CHC患者中,这些因素均可导致睡眠障碍的产生^[9]。

Carlson等^[10]研究了80例HCV感染患者的睡眠问题。受试者完成了匹兹堡睡眠质量指数(Pittsburgh Sleep Quality Index, PSQI^[11])和疲惫严重积分(Fatigue Severity Scale, FSS^[12]),并收集相关的精神病学和肝病阶段的信息。PSQI结果中,大约63%的患者存在失眠,而有56人(70%)达到显著疲倦的标准。研究结果显示,PSQI与FSS之间存在显著联系。进一步地分析揭示睡眠障碍与有无精神疾病没有明显相关性。睡眠质量的下降与肝病在进展中所处的阶段无关,提示了睡眠障碍不仅仅是终末期肝病的独有表现。

Clifford等^[13]对264名感染人类获得性免疫缺陷病毒(human immunodeficiency virus, HIV)的患者的睡眠障碍问题进行了研究,其中30名患者合并感染了HCV。在排除了由于抑郁、焦虑及认知功能障碍所导致的睡眠障碍后,他们采用了PSQI检测过去1 mo内的睡眠质量。观察量表提供了包括:睡眠质量、睡眠潜伏时间、睡眠持续时间、习惯性睡眠效率、睡眠惊扰次数、使用安眠药物和白天的不适等相关指标。相较于单纯HIV感染的患者,HCV和HIV合并感染的患者存在的睡眠问题更为严重,主要表现为睡眠质量存在显著差异。此外,本研究结果亦显示:与单纯HIV感染患者比较,合并感染的患者更容易出现抑郁、身体反应速度及记忆力下降等临床表现。

Lang等^[14]在对188例未进行治疗的CHC患者的研究发现,约有65%的患者存在睡眠问题,睡眠问题是患者的十大最明显症状之一。与抑郁、身体疲倦、精神倦怠及健忘等症状不同,

睡眠问题在不同性别中的发生率没有差异。此外,在对丙肝患者采用跨度为0-10的视觉模拟量表检查(越高的分值表示在过去3 mo中的症状越为严重)。结果显示接受检查的患者中,睡眠问题的分值达到了8,是出现的21个症状中分值最高的一项。

CHC发展至终末期肝病也会产生睡眠障碍^[15]。巴西的一项研究观察了42名肝硬化患者与24名正常人的睡眠多导图,结果显示肝硬化患者睡眠效率下降,快速动眼期(REM)睡眠增加^[16]。而一项主要针对丙肝后肝硬化患者的研究中,入组患者在排除肝性脑病后,其中50%患者自我陈述存在睡眠问题,35%的患者睡眠动作电位图检测提示存在睡眠障碍,较健康对照组高出4.5%^[17,18]。

2 与抗病毒治疗相关的睡眠障碍

CHC患者接受干扰素治疗会增加睡眠障碍发生的风险^[19]。大规模的临床试验显示,常规干扰素治疗出现睡眠障碍的比率基本保持在22%-24%^[20,21]。有将近25%-33%的患者在应用干扰素后会出现抑郁,伴有睡眠障碍,并且常常合并其他情绪障碍^[22,23],因此干扰素导致的睡眠障碍的出现比率难以与干扰素导致的抑郁伴随的睡眠障碍相区分^[24]。有证据显示,包括睡眠障碍在内的植物神经功能紊乱是CHC患者干扰素治疗后出现抑郁的早期症状或罹患的危险因素^[25,26]。一项对71例CHC患者进行的48 wk干扰素治疗的前瞻性研究显示,睡眠障碍与抑郁及自杀倾向有显著的相关^[27,28]。在进一步对其中46例^[29]干扰素治疗组的患者运用PSQI后显示,失眠可能是干扰素治疗后抑郁的前驱症状,而在治疗前改善睡眠障碍有助于减少由于干扰素所引发抑郁的潜在风险。

其他一些对病情早期睡眠障碍的研究主要侧重于与干扰素治疗相关的抑郁症间的关系。研究者们运用PSQI对睡眠质量进行检测,采用临床访视诊断抑郁症。结果显示,在干扰素治疗中,睡眠质量与抑郁相关,但是抑郁并不一定和睡眠质量的程度有关^[30]。然而,CHC患者中有一种特殊基因型的患者睡眠问题相对不严重,而恰恰这种基因型的患者也较少出现抑郁症,这个结果揭示了在CHC患者中睡眠质量与抑郁症的潜在联系^[31]。

Malaguarnera等^[32]观察96例行干扰素治疗的CHC患者,发现与重组IFN α -2a相比,接受重

组IFN α -2b的患者出现晚间失眠与持续性失眠的比率更高。这可能与IFN α -2b在体内快速吸收有关。此外,有学者认为聚乙二醇 α 干扰素在治疗CHC时可出现不宁腿综合征,而这一症状可在治疗结束后消失^[33]。

近年来许多学者对于干扰素治疗后产生的睡眠障碍的潜在机制进行了研究。这些研究主要集中在一些细胞因子及5-羟色胺(5-HT)代谢方面。目前越来越多的研究提示IL-6、IL-1、TNF参与对睡眠调控的影响^[34,35]。IL-6介导了与睡眠相关的细胞因子IL-1、TNF。有观察显示IL-6水平升高可以导致以白天嗜睡为表现的睡眠障碍,进一步揭示细胞因子水平的改变与睡眠障碍显著相关^[36,37]。IL-1能诱导睡眠,有初步证据显示IFN- α 可导致IL-1的分泌。这些细胞因子的异常或许可以解释IFN- α 导致的嗜睡^[38,39]。

IFN- α 导致的睡眠调节异常与5-羟色胺的代谢相关^[40,41]。IFN- α 增加了一种色氨酸分解代谢: 吲哚胺-2, 3-双加氧酶(IDO)的活性,还增加了犬尿氨酸的水平,并能导致5-HT及色氨酸水平的减少^[42]。正常情况下,在抑郁状态中色氨酸的急性衰竭导致了睡眠障碍,这样的睡眠障碍尤其表现为睡眠及快速动眼潜伏期的减少,增加REM的比例^[43],并且睡眠障碍的反复出现与情绪异常并无相关,他与低色氨酸及低5-HT水平有关^[44,45]。Wichers等^[46]详尽地描述了对IDO-IFN α 的假说,认为IFN α 导致的神经症状来源于增加IDO活性后产生的神经毒性,并检测到了喹啉酸(犬尿氨酸代谢中的一种神经毒性物质)水平的增加。此外,犬尿氨酸和色氨酸的水平在经过IFN α 治疗后可回到治疗前水平^[47]。实验结果显示IDO的激活在无抑郁而接受IFN α 治疗的CHC患者中与睡眠障碍的发生有密切关系。此外,目前尚有些研究认为IFN α 还可以导致发作性睡眠,其机制可能跟人类白细胞抗原DR2(HLA-DR2)相关^[48]。

3 结论

HCV感染相关的睡眠障碍,在临床上经常发生,较大地影响了患者的生活质量。虽然此症状出现频率不低,但临床关注程度并不高。截至目前,为数较少的文献均提示了HCV的感染与患者的睡眠障碍存在一定的联系。此外,除睡眠及精神症状外,近年来与HCV感染相关的周围及中枢神经症状的临床病例也时有报道^[49,50],从侧面提示了HCV产生失眠、抑郁等相关精神症状可能

存在的致病机制。然而,纵观现有的文献,首先有些研究缺少精神心理方面的测试,导致终末期肝病后的精神异常与干扰素治疗后的精神症状区分不明显。其次,研究病例样本偏少亦使得结果的代表性不够强。令人欣慰的是,对HCV感染相关睡眠障碍的研究为我们对丙型肝炎的进一步研究启示了新的思路和视角,对睡眠质量的诊断与治疗做进一步的深入探讨亦有利于在临床治疗中优化现有的治疗方案,提高患者生活质量。

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■创新盘点

通过总结近年来对慢性丙肝患者相关睡眠障碍的文献,探讨潜在机制并有利于在临床治疗中优化现有的治疗方案,提高患者生活质量。

■名词解释

睡眠障碍: 睡眠量不正常以及睡眠中出现异常行为的表现, 也是睡眠和觉醒正常节律性交替紊乱的表现。美国睡眠医学科学院最新的定义包括一下8类: 失眠、睡眠相关性的呼吸障碍、中枢性嗜睡、周期性睡眠节律失调、异态睡眠、睡眠相关的动作失调、与睡眠障碍相关性的综合征及其他睡眠障碍。

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■同行评价

本文从新的研究视角来探讨慢性丙型肝炎及其与睡眠障碍的关系,为丙型肝炎的诊治及发病机制的研究提供了新的思路。

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• 消息 •

《世界华人消化杂志》外文字符标准

本刊讯 本刊论文出现的外文字符应注意大小写、正斜体与上下角标。静脉注射iv, 肌肉注射im, 腹腔注射ip, 皮下注射sc, 脑室注射icv, 动脉注射ia, 口服po, 灌胃ig。s(秒)不能写成S, kg不能写成Kg, mL不能写成ML, lcpm(应写为1/min)÷E%(仪器效率)÷60=Bq, pH不能写PH或P^H, *H pylori*不能写成HP, T_{1/2}不能写成tl/2或T_{1/2}¹, V_{max}不能V_{max}, μ不写为英文u。需排斜体的外文字, 用斜体表示。如生物学中拉丁学名的属名与种名, 包括亚属、亚种、变种。如幽门螺杆菌(*Helicobacter pylori*, *H. pylori*), *Ilex pubescens* Hook, et Arn. var. *glaber* Chang(命名者勿划横线); 常数K; 一些统计学符号(如样本数n, 均数mean, 标准差SD, F检验, t检验和概率P, 相关系数r); 化学名中标明取代位的元素、旋光性和构型符号(如N, O, P, S, d, l)如n-(normal, 正), N-(nitrogen, 氮), o-(ortho, 邻), O-(oxygen, 氧, 习惯不译), d-(dextro, 右旋), p-(para, 对), 例如n-butyl acetate(醋酸正丁酯), N-methylacetanilide(N-甲基乙酰苯胺), o-cresol(邻甲酚), 3-O-methyl-adrenaline(3-O-甲基肾上腺素), d-amphetamine(右旋苯丙胺), l-dopa(左旋多巴), p-aminosalicylic acid(对氨基水杨酸)。拉丁字及缩写in vitro, in vivo, in situ; Ibid, et al, po, vs; 用外文字母代表的物理量, 如m(质量), V(体积), F(力), p(压力), W(功), v(速度), Q(热量), E(电场强度), S(面积), t(时间), z(酶活性, kat), t(摄氏温度, °C), D(吸收剂量, Gy), A(放射性活度, Bq), ρ(密度, 体积质量, g/L), c(浓度, mol/L), φ(体积分数, mL/L), w(质量分数, mg/g), b(质量摩尔浓度, mol/g), l(长度), b(宽度), h(高度), d(厚度), R(半径), D(直径), T_{max}, C_{max}, V_d, T_{1/2} CI等。基因符号通常用小写斜体, 如ras, c-myc; 基因产物用大写正体, 如P16蛋白。