·理论研究·

从脑神失养探讨膝骨关节炎患者中枢敏化发生机制*

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摘要:膝骨关节炎(Knee Osteoarthritis,KOA)发病与肾虚髓减密切相关。肾虚髓减导致 KOA 发病时,又会使脑髓失充,从而导致脑神失养。所以,肾虚髓减是 KOA 患者发病及脑神失养的根本病因病机。KOA 好发于中老年人群,在其发展进程中,肾虚髓减更甚,则脑神失养,脑主神明功能异常,继而发生中枢敏化(Central sensitization,CS)。CS 是 KOA 疼痛发展和维持重要机制之一,CS 诱发的痛觉异常、情绪障碍、认知障碍以及睡眠障碍等,实际是脑神失养后,中医学“脑”对于人体精神活动、意识思维的异常调控。通过改善脑神失养,抑制 CS 可缓解 KOA 患者异常疼痛、痛觉过敏,改善认知障碍、焦虑、抑郁等其他伴随症状。骨痹是 KOA 主要表现形式,脑神失养所导致的 CS 是 KOA 发展过程的延伸,这为中医药通过抑制 CS 干预 KOA,从而改善膝关节疼痛和功能障碍提供了一定的理论基础,有利于从整体观认识 CS 的发病机制,继而辨证识别 CS 的潜在靶点,为抑制 CS 改善 KOA 患者膝关节疼痛和功能障碍提供新的思路与策略。

关键词:膝骨关节炎;脑神失养;脑;中枢敏化;肾虚髓减
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Study on the Mechanism of Central Sensitization in Patients with Knee Osteoarthritis Based on Dysfunction of the Brain Spirit

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Abstract:The occurrence of knee osteoarthritis (KOA) is closely related to kidney deficiency and marrow decrease. When kidney deficiency and marrow decrease leads to the onset of KOA,it will cause the lack of cerebral nourishment,leading to the dysfunction of the brain spirit. So kidney deficiency and marrow decrease is the fundamental etiology and pathogenesis for the occurrence of KOA and dysfunction of the brain spirit. KOA tends to occur in middle-aged and elderly people. In the course of its development,the kidney deficiency and marrow decrease are more severe,which leads to the dysfunction of the brain spirit,and then Central sensitization (CS) occurs. CS is one of the important mechanisms for the development and maintenance of pain in KOA. The pain abnormalities,emotional disorders,cognitive disorders,and sleep disorders induced by CS are actually the abnormal regulation of human mental activity and conscious thinking by the brain in TCM after dysfunction of the brain spirit. Improving dysfunction of the brain spirit,and inhibiting CS can allevi-

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ate abnormal pain and hyperalgesia in KOA patients, and improve other accompanying symptoms such as cognitive impairment, anxiety, and depression, etc. Bone stiffness is the main manifestation of KOA, and CS caused by dysfunction of the brain spirit is an extension of the development process of KOA. This provides a theoretical basis for TCM to intervene KOA by inhibiting CS, thereby improving knee joint pain and dysfunction. It is conducive to understanding the pathogenesis of CS from a holistic perspective, identifying potential targets of CS through syndrome differentiation, and providing new ideas and strategies for inhibiting CS to improve knee joint pain and dysfunction in KOA patients.

Keywords: knee osteoarthritis (KOA); dysfunction of the brain spirit; brain; central sensitization; kidney deficiency and marrow decrease

骨性关节炎(osteoarthritis, OA)是最常见的老年慢性关节疾病,全球患病总人数超过 2.5 亿[1]。OA 在手、膝、髋等关节好发,以膝关节最为常见[2-4]。膝骨关节炎(knee osteoarthritis, KOA)作为全球致残的主要原因[5-6],是导致 80% 以上老年人长期疼痛的主要原因[7]。目前,疼痛被列为“人类第 5 大生命指征”,已经受到充分重视[8]。55 岁以上人群中约 10% 患有 KOA,其中,约 25% 的患者因疼痛致严重残疾[9]。全球 KOA 总患病率约为 2.63 亿人,是造成疾病负担主要因素之一[10]。在许多发达国家,随着人口老龄化及肥胖人口增多,与 KOA 相关的医疗负担日益加重。例如,2013 年澳大利亚因 KOA 导致的膝关节置换手术就花费 9.05 亿澳元,预计到 2030 年这一数字将上升到 13.8 亿澳元[11]。因此,如何有效缓解 KOA 患者疼痛和功能障碍,并提高其生活质量已成为临床急需解决的重要难题。

中枢敏化(central sensitization, CS)以异常疼痛、痛觉过敏为主要特点,还会引起认知障碍、焦虑、抑郁等其他伴随症状[12-16]。CS 是引起 KOA 患者疼痛超敏的主要原因,是其痛觉过敏的主要病理基础。2012 年,国际疼痛研究协会(international association for the study of pain, IASP)将中枢敏化定义为中枢神经系统中的伤害性感觉神经元对正常或者阈下初级传入信息的反应性增加。在终末期 KOA 患者中,CS 发生率高达 20% ~40%[17]。KOA 属于中医学“骨痹”范畴,肾虚髓减,筋骨失养,风寒湿等邪乘虚而入留驻关节,阻滞筋脉,发为骨痹。《中藏经》记载:“骨痹者,乃嗜欲不节,伤于肾也,肾气内消……而精气日衰,精气日衰则邪气妄入。”同时,肾虚髓减会导致髓海失充,脑神失养,进而引起脑主神明功能异常。因此,骨痹是 KOA 主要表现形式,脑神失养所导致的 CS 是 KOA 发展过程的延伸。本文从脑神失养探讨 KOA 患者 CS 发病机制,旨在为中医药防治 CS,改善 KOA 患者膝关节疼痛和功能障碍,提供一定理论依据。

1 中枢敏化与 KOA

CS 由 Woolf 等[18]正式提出,指的是中枢神经系统对疼痛的一种超敏状态,与慢性疼痛的发生和维持有关。同时,其还进一步明确了 CS 对疼痛诊疗的重要作用,并指出其主要特征是异常性疼痛、痛觉过敏[19]。CS 通常由持续关节组织损伤和炎症所导致的外周持续性伤害刺激引起,可持续存在。在一项 113 例 KOA 患者队列研究中,定量感觉测试(quantitative sensory testing, QST)被用于检测 CS,多因素分析显示,在缺乏影像学证据的中度至重度 OA 病理性改变的亚组患者中,疼痛敏感性显著升高[20]。明确 KOA 患者是否存在 CS,可以帮助评估患者疼痛个体差异、预后、共病。CS 患者可能疼痛更严重,传统止痛药对其效果较差[21];CS 是外周持续性伤害刺激的结果,同时也是 OA 疼痛维持的一种机制[22-23];CS 发生后,即使没有新的外周持续性伤害刺激输入,也仍然持续存在[22]。

CS 反映了调节疼痛感知的中枢神经元特性的变化,这些特征与传统观念相矛盾,传统观念认为,OA 疼痛只是急性和伤害性,主要与炎症和机械因素有关,如软骨损伤[24-28]。当 CS 发生时,中枢神经系统神经元兴奋性增高,降低疼痛阈值,并在关节组织损伤和炎症所导致的外周持续性伤害刺激消失或减弱后继续维持疼痛。CS 发生和脊髓背角及大脑皮层和皮层下区域密切相关[22,29]。基于神经功能影像学的研究已证实,人脑中广泛参与疼痛整合加工的皮层和皮层下区,如中脑导水管周围灰质、前额叶皮层、丘脑等,其兴奋性增高是 CS 发生的重要病理基础[29]。CS 会降低 KOA 患者总体生活质量,降低关节功能,增加心理共病(如焦虑、抑郁等)[30]。OA 患者 CS 的存在预示着一些不良的临床结果,包括止痛药物疗效差、生活质量降低和功能性残疾等[31],如 KOA 患者术前 CS 的存在是全膝关节置换术后残留疼痛的重要危险因素[32]。

2 脑神失养与 KOA

KOA 是以关节软骨变性、磨损、骨质增生为特征的慢性骨关节病[33-36]，属于中医学“骨痹”范畴，其发病与肾虚髓减密切相关[37-40]。同时，肾虚髓减导致 KOA 发病时，又会使脑髓失充，从而导致脑神失养。所以，肾虚髓减是 KOA 患者发病及脑神失养的根本病因病机。有关骨痹的论述最早见于《黄帝内经》，《素问·长刺节论》记载：“病在骨，骨重不可举，骨髓酸痛，寒气至，名曰骨痹。”《素问·奇病论》记载：“肾藏精，精充骨而生髓。”肾藏精，精可生髓，脑为髓之海，骨内亦有髓，髓海充足，遂分于骨内。人到中年，肾精渐虚，则骨髓化源不足，骨弱髓空，筋脉肌肉失养不能束骨而利关节，风寒湿等邪乘虚而入留驻关节，阻滞筋脉，最终导致 KOA。《证治准绳》曰：“痹病有风、有湿、有寒、有热……皆标也，肾虚其本也”。

肾虚髓减导致 KOA 发病，日久则会使脑神失养。《素问·奇病论》记载：“肾藏精，精充骨而生髓，髓聚而为脑，髓满而脑髓充，精脱而脑髓消。”故肾藏精充养骨，然后才会通过“髓聚”而充养脑。《医旨绪余·上卷》记载：“盖脑者，髓之海，肾窍贯脊通脑。”明确说明肾借助脊髓与脑相通，脑藏元神，肾精充盈，才会通过“髓聚”使神有所养。《素问病机气宜保命集》记载：“肾为作强之官，得所养，则骨髓之气荣而不枯。”《类证治裁》记载：“脑为元神之府，精髓之海，实记忆所凭也”。肾虚髓减更甚，则会导致脑神失养，使患者出现一系列感觉、运动等精神活动异常。

3 从脑神失养探讨中枢敏化

KOA 好发于中老年人群，在其发展过程中，肾虚髓减更甚，则脑神失养，脑主神明功能异常，继而发生 CS。CS 诱发的痛觉异常、情绪障碍、认知障碍以及睡眠障碍等，实际是脑神失养后精神活动、意识思维的异常表现。CS 中枢神经机制的进一步明确，有利于为 KOA 患者脑神失养提供证据支持。

人体感觉、运动、思维和记忆等精神活动的正常，均是脑主神明生理功能的体现，《素问·脉要精微论》记载：“头者，精明之府”，《类证治裁》记载：“脑为元神之府，精髓之海，实记忆所凭也”。在脑主神明作用下，人体所有生理活动才能正常进行，因此脑对人体认知、情感等高级神经活动统领是脑主神明的具体体现[41]，《医学原始》记载：“人之一身，五脏藏于内，为生长之具、五官居于身上，为知觉之具，耳、目、口、鼻聚于首，最显最高，便于接物。耳、目、口、鼻之所导人，最近于脑，必以脑先受其象而觉之，而寄之，而存之也。”脑神失司，便会出现一系列精神意识、思维活动异常[42]。CS 诱发的痛觉异常、情绪障碍、认知障碍以及睡眠障碍等，实际是脑神失养后，中医学“脑”对于人体精神活动、意识思维的异常调控。

4 改善脑神失养病理状态可抑制中枢敏化治疗 KOA

越来越多的研究表明，通过对慢性疼痛患者意识、思维等的调整，可以有效缓解疼痛，有利于疏导心理压力和提高生活质量，这说明通过改善脑神失养的状态治疗 KOA 在临床是有一定的应用潜力。如正念疗法作为一种心理治疗方法，在国际上被广泛运用，其主要是通过改变患者对疼痛刺激的感知，以提高药物治疗效果或减少药物干预量，进而有效减轻慢性疼痛[43]。KOA 患者出现 CS 后，主要临床特征是异常疼痛、痛觉过敏，同时伴有认知、精神等异常，改善脑神失养状态和应用正念疗法，两者都是作用于脑神，旨在恢复脑主神明正常功能。

《黄帝内经》记载：“肾主骨，生髓，通于脑”。表明肾精是脑与骨生理功能正常的基本物质。杨清叟《外科集验方·服药通变方第一》提出“肾实则骨有生气”，《素问·奇病论》云：“肾藏精，精充骨而生髓，髓聚而为脑，髓满而脑髓充，精脱而脑髓消。”因此，肾虚髓减是导致脑神失养及 CS 的病理基础。随着现代医学对 CS 的深入研究，已证实 KOA 会引起大脑结构和功能的异常[44]。因而，通过改善脑神失养，抑制 CS 可缓解 KOA 患者异常疼痛、痛觉过敏，改善认知障碍、焦虑、抑郁等其他伴随症状。

5 小结

疼痛是 KOA 患者主要临床不适症状，也是患者就诊的重要因素，其所引起的长期疼痛会严重影响患者日常生活、身心功能，减少社会和家庭劳动力，增加医疗负担以及患精神类疾病（如焦虑、抑郁等）的风险，降低 KOA 患者生活质量。CS 在 KOA 患者中的高发病率，会加剧 KOA 诊疗的难治性、高负担以及阿片类药物过度依赖危险。CS 状态对 KOA 疼痛治疗的不良影响正在逐渐引起临床医生重视，目前，已有相关量表识别伴有 CS 的 KOA 患者。

目前，基于临床行为评价及神经功能影像学的 CS 研究，为进一步阐释 KOA 患者脑神失养中医学理论提供了科学证据支持。因此，对于 KOA 患者脑

神失养中医学理论的深入研究,有利于从整体观认识 CS 的发病机制,继而辨证识别 CS 的潜在靶点,为抑制 CS,改善 KOA 患者膝关节疼痛和功能障碍,提供新的思路与策略。

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