综 述

影响中轴型脊柱关节炎影像学进展的相关因素及机制分析*

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关键词 中轴型脊柱关节炎;影像学;影响因素;疾病进展
中图分类号 R593.21 文献标识码 A DOI 10.11768/nkjwzzzz20200215

中轴型脊柱关节炎(axial spondyloarthritis,axSpA)是一种主要累及中轴骨的慢性炎性疾病,以炎性腰背痛、附着点炎、晨僵为主要临床表现,包括强直性脊柱炎(ankylosing spondylitis,AS)和放射学阴性脊柱关节病(non-radiographic axial spondyloarthritis,nr-axSpA)[1,2]。随着疾病进展,受累关节可逐渐发生结构损害、新骨形成、关节融合而致关节活动受限、功能减退,从而影响患者生活质量[3]。影像学检查是显示axSpA结构损害及判断预后的重要手段,通过影像学的变化监测患者病情变化,进行早期有效干预而阻止其关节结构损害及影像学进展。影响中轴型脊柱关节炎患者影像学进展的因素繁多,包括生活习惯、工作性质、疾病活动度、基线时影像学表现、药物治疗等。本文阐述影响axSpA患者影像学进展的相关因素及其机制。

临床相关因素

生活方式和工作类型 生活方式和工作类型对axSpA患者病情进展有着重要影响。一项对比体力劳动和非体力劳动axSpA患者影像学进展的研究发现[4],2组患者在2年内的改良Stoke强直性脊柱炎脊柱评分(modified stoke ankylosing spondylitis spine score,mSASSS)变化值为1.2:0.2,体力工作者疾病活动度更高,影像学进展相对更快。此外,在脊柱关节炎小鼠模型中,匹配2组小鼠体重,对照组小鼠正常活动,实验组小鼠的臀部被悬挂起来,减少臀部、脊柱所受机械压力。与正常活动小鼠比较,实验组小鼠关节炎性反应更轻,影像学进展相对缓慢[5]。以上研究提示关节处所受机械压力增加,会加重相应关节的炎性反应及结构损害。

肥胖与axSpA患者的疾病活动度、影像学进展相关。一项长达5年的前瞻性研究显示,肥胖是axSpA患者影像学进展的独立危险因素[6]。同时,有研究证实肥胖患者较非肥胖患者药物治疗反应及预后均较差[7,8]。此外,吸烟患者炎性腰背痛、关节活动受限及结构损害较严重,对药物的治疗反应差。因此,吸烟是高疾病活动度、影像学加速进展、关节活动度降低的重要危险因素[4,6,9~15]。建议axSpA患者戒烟、控制体重并适度运动,避免过度劳累、注意休息,通过改善生活方式控制疾病进展,有助于延缓其结构损害及影像学进展。

疾病活动度 多项临床研究结果提示,疾病活动度、C反应蛋白(CRP)水平是影像学进展的高危风险因素[16~19]。Ramiro等[18]报道axSpA患者疾病活动度与影像学进展线性相关,与非活动性疾病的患者比较,高疾病活动度的患者每2年的mSASSS评分平均增加2.31分。同时,女性患者高疾病活动度对影像学改变的影响更加显著。Poddubnyy等[17]随访了178名axSpA患者,其结果显示患者的强直性脊柱炎疾病活动性得分(ankylosing spondylitis disease activity score,ASD-AS)评分与患者2年后的影像学进展明显相关,患者的疾病活动度越高,其影像学进展更快速。因此,在疾病治疗中,应积极控制疾病炎性反应,减缓后期结构损害,控制影像学进展速度。

基线时影像学表现 影像学检查是评估axSpA患者结构损害的重要手段,基线时影像学表现不同的患者其后影像学进展速度及预后也存在差异。多个临床研究提示,磁共振成像(MRI)显示有骨髓水肿[9,20-22]、骨侵蚀[23]、脂肪变性[24~28]的axSpA患者影像学进展明显,易形成新骨。Maksymowych等[25]对AS患者进行2年的随访,并将患者分为2组,一

*基金项目:国家自然科学基金(No:81771754);同济医院临床研究领航项目(No:2019CR26)
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组患者MRI仅显示有骨髓水肿,即急性炎症;另一组患者MRI表现为骨髓水肿合并结构损害,如骨侵蚀或脂肪沉积、新骨形成。结果显示,有结构破坏的患者影像学进展风险较仅有急性炎症患者的风险明显增加,提示阻止axSpA患者的影像学进展可能存在一个时间窗,在结构损害发生之前,炎性损害可逆,控制炎性损害可阻止其影像学进展。同时有研究显示,骨侵蚀减轻及炎性损害与2年后发生新的脂肪沉积及回填独立相关,且骨侵蚀减轻和脂肪沉积增加是新骨形成的独立危险因素,从而证实了炎性损害、骨侵蚀的修复导致组织化生-脂肪变性,从而促进新骨形成、关节强直这一假说[26]。

此外,有韧带骨赘形成的AS患者影像学进展更快[9,20,27],可能是新骨形成信号通路一旦被触发,其后快速进展,类似于自身正反馈调节,导致恶性循环。同时,骨质疏松、骨量降低的axSpA患者更易形成韧带骨赘[29]。因此,基线时骨髓水肿、骨侵蚀、脂肪变性、韧带骨赘形成、骨量降低均是axSpA患者影像学进展的风险因素,存在上述影像学表现的axSpA患者应密切关注疾病进展情况,积极治疗以延缓患者关节的结构损害。

外周关节表现 axSpA以累及中轴骨为特征,但部分患者可伴有外周关节受累。外周关节受累对影像学进展的影响一直存在争议[30,31],Kim等[31]报道髋关节受累的患者疾病进展速度较快,提示预后不良;而肩关节受累的患者,影像学进展速度较缓慢,预后相对较好。以上研究提示外周关节受累对疾病严重程度、进展及预后有一定影响,但是否会因为不同外周关节受累而导致不同的结局,仍无明确证据,其中具体机制尚不明确,需要更多大样本、长期随访进行深入研究 。

药物治疗 axSpA治疗首选非甾体类抗炎药(non-steroidal anti-inflammatory drugs, NSAIDs),对两种及两种以上NSAIDs药物反应不佳患者,可选用肿瘤坏死因子阻滞剂(tumor necrosis factor inhibitor,TNFi)治疗[32]。关于使用足量TNFi 2年以上是否能延缓axSpA患者影像学进展,其研究结果存在不一致性[32~35]。针对病程不超过10年的AS患者,TNFi治疗通过有效的控制炎性反应,明显延缓AS患者的影像学进展[33]。在新近诊断的axSpA患者中,长期使用依那西普治疗的患者较未使用依那西普治疗的患者影像学进展缓慢[36],且早期使用TNFi治疗的axSpA患者影像学进展较慢[19]。这些研究说明,早期、长期使用TNFi治疗能很好地控制炎症并延缓影像学进展。但有研究表明,TNFi治疗axSpA并不能延缓患者的影像学进展[35],因此,TNFi治疗是否能延缓axSpA患者的影像学进展仍存在争议,但大家一致认为,尽早使用TNFi治疗将有益于axSpA患者。

有临床研究显示,长期使用标准剂量的NSAIDs治疗可以延缓其影像学进展[37,38]。但Sieper等[39]认为,AS患者使用标准剂量的双氯芬酸治疗或按需使用双氯芬酸治疗,治疗2年后2组患者之间影像学进展比较,差异无统计学意义。因此,需进一步加大样本量,采用多中心研究观察NSAIDs对axSpA患者影像学进展的影响。

近年来有研究提示IL-17A抑制剂治疗AS有效。AS患者在基线、第2、4周按10mg/kg注射负荷剂量的苏金单抗,其后每8周注射150mg或每4周注射75mg,持续使用苏金单抗或NSAIDs治疗2年,使用苏金单抗的AS患者中无影像学进展的比率更高,且其平均mSASSS评分变化值更小,但2组之间差异并无统计学意义[40]。其扩展研究结果显示,使用苏金单抗治疗长达4年的AS患者,有79%的患者无影像学进展[41]。该结果提示IL-17A抑制剂治疗可能是延缓axSpA结构损害、阻止其影像学快速进展的新方法,但仍需更多大样本、多中心研究以进一步证实其有效性及安全性。目前尚无研究表明任何一种药物能明确阻止axSpA患者结构损害及影像学进展,但仍建议尽早使用药物治疗,对于改善疾病预后有一定作用。

影响影像学进展的相关机制

axSpA是一种附着点疾病,附着点处可同时或先后出现炎性损害、骨侵蚀、新骨形成。附着点处的炎症损害及骨侵蚀主要发生在疾病早期阶段,而新骨形成主要发生在疾病晚期阶段,新骨形成也是导致其后影像学进展、关节功能丧失的主要原因之一[3,42]。软骨下骨形成主要涉及两条主要的信号通路——骨形态发生蛋白(bone morphogenetic protein,BMP)信号通路和Wnt信号通路。

BMP信号通路 在骨形成的早期,主要由BMP控制,BMP是一种细胞因子及生长因子,属于TGF-β大家族,在调节成骨细胞分化和功能成熟、新骨形成中发挥着重要作用。有一研究将健康供体和AS患者的骨髓间充质干细胞进行培养,发现AS患者的骨髓间充质干细胞成骨分化能力优于健康供体,并存在异常成骨分化,前者分泌更多的BMP-2,但

Noggin(BMP 抑制剂)分泌较少,当 Noggin 浓度增加或 BMP-2 表达被抑制时,AS 患者骨髓间充质干细胞的异常成骨分化得以纠正[43]。这项研究表明 BMP-2 和 Noggin 分泌之间的失衡会诱导 AS 间充质干细胞的异常成骨分化,揭示了 AS 中病理性成骨的机制[43]。此外,有研究证明 BMP-2、BMP-6 与 axSpA 患者的放射学损害程度显著相关[44、45]。以上研究均提示 BMP 信号通路参与 axSpA 患者的新骨形成、影像学进展过程,该通路的抑制剂可能是抑制 axSpA 患者影像学进展、改善预后的重要分子。

Wnt 信号通路 Wnt 信号通路及其抑制剂,如 Dickkopf-1 (DKK-1),是调节 axSpA 新骨形成的重要因素。有研究发现,AS 患者血清中 Wnt-3a 的水平显著升高,且是 AS 患者的 Bath 强直性脊柱炎衡量指数(Bath ankylosing spondylitis metroloty index, BASMI)、mSASSS 分值的独立危险因素[46]。在双侧骶髂关节炎的 TNF 转基因小鼠中,分别用载体、抗 TNF 抗体、抗 DKK-1 抗体处理小鼠,结果显示 TNFi 能有效减轻炎症、骨侵蚀并减少破骨细胞数量,且不导致关节强直。DKK-1 阻滞剂对骶髂关节炎症无效,但能明显减少骨侵蚀及破骨细胞数量,同时增加 X 胶原蛋白的表达、肥大软骨细胞的形成,促进骶髂关节强直。这一结果提示 Wnt 信号通路是 axSpA 新骨形成的重要信号通路[47]。此外,与 DKK-1 活性降低的患者相比,DKK-1 活性增加的 AS 患者韧带骨赘形成较少,提示高活性的 DKK-1 能抑制新骨形成[48]。在蛋白多糖诱导的脊柱关节炎小鼠中,DKK-1 和骨硬化蛋白的 mRNA 水平均低于对照组小鼠[49]。以上结果均显示,Wnt 信号通路是 axSpA 患者新骨形成的重要信号通路,该信号通路的抑制剂是抑制新骨形成、延缓影像学进展的重要调控因子。

炎性因子 炎性因子是骨代谢过程中的重要因子,其中 IL-23/IL-17 信号轴是 axSpA 关节炎症的重要信号通路,也可能参与新骨形成过程。AS 患者的关节面和血清中表达 IL-23 和 IL-17 的细胞比骨关节炎、健康人群水平高[50~52]。Sherlock 等[53]在一项体内研究显示,过度表达的 IL-23 将导致附着点炎症,同时也可导致附着点处新骨形成。以上这些研究均提示 IL-23/IL-17 信号轴不仅在 axSpA 的炎性损害中发挥着重要作用,也是新骨形成的重要信号通路。Chen 等[54]报道,在 AS 患者中,TNF-α 和 IL-1β 都能增强外周血单个核细胞(peripheral blood mononuclear cell,PBMC)BMP-2、-4、-7 的表达,PBMC 的 BMP-2、-4、-7 表达水平升高与患者 mSASSS 评分正相关,脊柱完全强直的患者 PBMC 的 BMP-2、-7 基因表达更加明显。以上研究均表明多个炎性因子与 axSpA 患者的新骨形成、影像学进展明显相关,这一结果与疾病高活动度促进 axSpA 患者影像学进展的结果相一致。因此,axSpA 患者需积极治疗,积极控制疾病炎性反应对改善预后有重要影响。

结 语

AxSpA 是一种慢性、系统免疫性疾病,具有一定的致残性,阻止其结构损害、影像学进展是改善预后的关键。良好的生活习惯、药物治疗、不同的临床表现对其结构破坏、影像学进展均有重要影响。AxSpA 患者应在改变不良生活方式的基础上早期、长期积极治疗,从而有效的控制疾病活动度、延缓其影像学进展。影像学显示有骨侵蚀、脂肪沉积、新骨形成的患者应更加积极治疗,密切监测其影像学改变。同时,多个细胞因子及信号通路参与 axSpA 患者新骨形成的过程,是潜在的药物治疗靶点。在未来研究中,将这些细胞因子及信号通路作为作用靶点,有望研发出阻止 axSpA 结构破坏的有效治疗药物。

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(2019-06-26 收稿 2019-12-26 修回)

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(2019-11-20 收稿 2020-02-07 修回)