

· 述 评 ·

强直性脊柱炎中医证候研究进展*

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摘要:强直性脊柱炎(ankylosing spondylitis, AS)中医证候研究主要涉及证候分型和不同证候特点两个方面。AS 的中医分型标准尚未完全统一,而证候研究仅限于中医证候学特征描述、中医证候与实验室指标间的相关性研究,不同因素间因果关系及内在机制有待明确。此外,AS 证候的演变规律研究也相对滞后,中医证候标准化、客观化研究不足。今后的研究亟需加强多学科协作,发掘 AS 证候特征,寻找有高度特异性的“疾病-证候-症状”体系标志,同时基于多种现代临床研究统计方法开展证候的动态时空性、非线性系统性研究,为中医药精准治疗 AS 提供借鉴。

关键词:强直性脊柱炎; 大 楼; 中医证候

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Research Progress of TCM Syndromes of Ankylosing Spondylitis

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Abstract:TCM syndrome research of ankylosing spondylitis (AS) mainly involves syndrome classification and different syndrome characteristics. The standard of TCM classification of AS has not been completely unified, and the study of AS syndrome is limited to the description of TCM syndrome characteristics, TCM syndrome, laboratory indicators and some omics related studies. The causal relationship and internal mechanism between different factors need to be clarified. In addition, the research on the evolution law of AS syndrome is relatively backward, and the standardization and objectification of TCM syndrome are insufficient. In the future, multidisciplinary cooperation is urgently needed to explore the characteristics of AS syndromes and find highly specific system signs of "disease-symptom-symptom". At the same time, based on various modern clinical research statistical methods, the dynamic spatio-temporal and nonlinear systematic study of syndromes is carried out, which provides reference for the accurate treatment of AS by traditional Chinese medicine.

Key words:ankylosing spondylitis; TCM syndrome; rickets; research progress

强直性脊柱炎(ankylosing spondylitis, AS)是一种难治性自身免疫性疾病,目前尚无根治方法^[1]。中医强调辨证论治、整体观念,治疗 AS 独具优势,

疗效确切,安全性较高^[2],进一步探究 AS 的中医诊疗特点,挖掘证的本质十分必要。目前,虽然 AS 的中医诊断不断完善,证型论述较为完备,但仍缺乏客观诊断标准,此亦为中医药治疗其他疾病的共性问题,一方面需要客观临床数据的支持,另一方面有待阐明作用机制。2020 年,北京召开的全国中医标准化技术委员会大力推进中医药标准化建设,完善中

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医国家标准体系^[3],这也是中医药进一步发展的需求。本文通过检索 AS 中医证候研究相关文献,总结目前发展现状,以供临床参考借鉴。

1 AS 中医病名及病因病机

强直性脊柱炎作为现代医学病名,在中医历代文献中无相关记载,根据其发病特点可归属于中医“痹证”范畴,与肾痹最为相关。《素问·痹论》中有“风寒湿三气杂至合而为痹”“肾痹者,善胀,尻以代踵,脊以代头”的记载。根据其致病特点,又有“龟背风”“竹节风”“驼背”“伛偻”“大倮”之称。国家“十一五”“十二五”重点专科优势病种明确指出,“大倮”对应的西医病名主要为强直性脊柱炎,并制定相应临床路径。“大倮”病名最初亦见于《素问·生气通天论》,其中有“阳气者,精则养神,柔则养筋。开阖不得,寒气从之,乃生大倮”的记载,揭示了 AS 的病机特点。

AS 的发病包括内因、外因两方面,焦树德教授指出,在外寒湿风邪外侵,在内肾督阳虚,“阳气不得开阖,寒气从之”而致病^[4]。张鸣鹤教授认为,AS 外因除感受风寒湿邪外,还包括跌扑损伤,内因除肾虚督空也强调了先天禀赋不足^[5],先天禀赋不足与 AS 基因易感性具有高度统一性。人之先天也是由肾所藏先天之精所主,故先天禀赋不足也是肾精不足的另一种体现。AS 患者往往伴颈、背、腰、骶部等不适症状,与督脉、足少阴肾经、足太阳膀胱经关系密切,其中,督脉也归属于肾,其经气和肾同荣损,而足少阴肾经、足太阳膀胱经互为表里关系,最后皆可归源于肾^[6]。因此,AS 的核心病机为肾督亏虚^[7],病位在肾和督脉^[8],与足少阴肾经和足太阳膀胱经相关。AS 的基本病理变化为肌腱、韧带附着点炎,热毒闭阻经络、流注肢体骨节也是其关键病机。多数患者发病时的疼痛表现为痛有定处,夜间痛更加明显,表明瘀血贯穿于整个病程。因此,娄多峰教授进一步从虚、邪、瘀 3 个方面阐述了 AS 的发生发展^[9],亦认为其基本病机为肾督亏虚,感邪后致痰瘀气滞留于脊部经脉骨骱而致痹。

2 AS 中医证候分型

2.1 名老中医对 AS 中医证候分型的认识 焦树德教授^[10]将 AS 患者分为肾虚督寒证、邪郁化热证、

痹阻肢节证、邪及肝肺证 4 个证型。朱良春教授将 AS 患者分为阳虚络瘀证与阴虚脉痹证两个主要证型。冯兴华教授将 AS 患者分为湿热痹阻证、寒湿痹阻证、肾阳亏虚证、肝肾不足证及瘀血痹阻证 5 个证型^[11]。

胡荫奇教授以正邪虚实为纲,兼顾痰瘀辨治 AS,将其分为三期:活动期正邪交争,邪胜为彰,正虚不显,湿热瘀阻为主要证候特点;稳定期正邪交争不甚,正虚不甚,以肝肾不足,寒湿痹阻证为主;疾病后期需要兼顾痰瘀阻络证^[12]。阎小萍教授秉承焦树德教授经验,以寒热虚实为纲,逐步将二期(活动期与缓解稳定期)的肾虚督寒证、邪郁化热证、湿热伤肾证、邪痹肢节证及邪及肝肺证 5 个证型归纳为肾虚督寒证与肾虚湿热证两证以执简驭繁^[13]。

王为兰教授根据 AS 的临床特点将其分为明显型和隐匿型,其中明显型见于极高疾病活动度与高疾病活动度,包括湿热内蕴、督脉阻滞证与寒热错杂、湿毒内蕴证;隐匿型见于低疾病活动度和稳定期,包括寒湿阻络证、营卫失和证与肾精亏虚证、督脉阻滞证^[8]。娄多峰教授根据 AS 患者“虚、邪、瘀”等临床表现进行辨证,将 AS 分为正虚候、邪实候与瘀(痰)血候^[9]。张鸣鹤教授则更注重 AS 活动期湿热瘀毒阻滞、肾督亏虚的特点,因此确立清热利湿补肾壮督为基本治疗大法^[14]。

2.2 国家及专业风湿病学书籍等对 AS 中医证候分型标准 1997 年出版的《中药新药临床研究指导原则》^[15]将 AS 分为风寒湿痹证、气滞血瘀证、肝肾不足证 3 个证型。2002 年出版的《中药新药临床研究指导原则》增订修改将 AS 分为湿热痹阻证、寒湿痹阻证、瘀血痹阻证、肾阳亏虚证和肝肾不足证共 5 证^[16]。2009 年再版的《实用中医风湿病学》^[17]将 AS 分为肾虚督寒证、邪郁化热证、湿热伤肾证、邪痹肢节证、邪及肝肺证及缓解稳定型共 6 证。2010 年,国家中医药管理局医政司制定的《大倮临床路径》关于 AS 中医辨证分型标准为肾虚督寒证与肾虚湿热证两证^[18]。

3 AS 中医证候特点

3.1 AS 主要证型 在一项有关 AS 证候的文献研究中,翁於欢等^[19]通过检索中国知网、维普和万方数据库中有 AS 中医证候文献 4 014 篇(经筛选纳

入89篇,发表时间为1988—2018年),包含16474例病例,涉及AS各类中医证型29种,统计得出肝肾不足证(46.64%)、湿热痹阻证(22.96%)、瘀血痹阻证(21.74%)及寒湿痹阻证(6.37%)为4个主要证型。在临床研究中,沈逸等^[20]通过对278例AS患者四诊信息进行主成分分析、聚类分析,最终发现5组证候要素与肾阴虚和阳虚兼湿热、湿热内蕴、肾虚督寒、湿热痹阻关节或兼脾虚及瘀血痹阻相关,总结出AS患者4个具有代表性的中医证候群,即肾虚督寒证、肾阴虚证、湿热痹阻证和瘀血痹阻证。邱冬妮等^[21]收集广东地区306例AS患者的中医临床四诊信息,采用主成分因子提取法提取了12个具有代表性的公因子,分别对应得出AS患者肾虚督寒证、督寒脾湿证及肾督痰瘀证3个中医临床常见证型。此外,通过收集广安门医院的192例AS病例,证型出现频率从高到低依次为瘀血痹阻证(75.8%)、肾阳亏虚证(45.9%)和湿热痹阻证(38.7%)^[22]。有学者观察广西地区医院就诊的226例AS患者,发现其主要证型为湿热痹阻证(32.30%)、邪郁化热证(19.47%)、瘀血阻络证(12.39%)、肾阴亏虚证(11.06%)、痰瘀互结证(8.41%)、寒湿痹阻证(7.96%)、肝肾不足证(6.64%)及肾阳亏虚证(1.77%)^[23]。

综上,肾虚督寒证(肝肾不足证)、湿热痹阻证及瘀血痹阻证为AS患者常见证型。活动期AS患者主要证型为湿热痹阻证、邪郁化热证及痰浊瘀阻证等^[24],非活动期患者肾阳亏虚证较多^[25]。

3.2 AS患者基本资料特征

相较于其他疾病,AS也有其自身特点。根据临床流行病学调查方法,娄玉铃等^[26]在河南风湿病AS数据库中观察379例AS患者发现,男女比例约为4.7:1,年龄(31.29±9.81)岁,有43.8%AS患者有家族史,既往14.5%AS患者有眼部炎症史,9.2%有肠炎史,2.9%有尿道炎史;肾虚督寒证患者相较于肾虚湿热证患者人群年龄大,病程长^[27]。

此外,有学者在一项临床研究中观察到,AS患者伴高尿酸组与AS患者组相比,男性所占比例大,平均发病年龄较小,体质量指数(body mass index, BMI)较大($P<0.05$),两组起病病程、确诊病程、人白细胞抗原-B27(HLA-B27)基因及亚型、红细胞沉降率、C-反应蛋白相比,差异无统计学意义($P>$

0.05)^[28]。

3.3 AS患者中医证候症状及体征特点 AS经中医辨证分型,兼具AS疾病和其证型特点。以下研究总结了AS患者湿热血瘀证及脾虚湿阻证的证候特点。周雍明等^[29]通过对AS湿热血瘀证患者进行聚类分析及Logistic分析得出其辨证要素为关节红肿热痛、肢体困重、足跟痛、驼背、苔薄黄或黄厚、脉细弦或弦滑等。杨辉等^[30]基于德尔非法,经过3轮专家调查问卷得到AS脾虚湿阻证的主症为中轴关节酸痛;脊背活动受限、凌晨痛甚伴活动后缓解,伴腰骶沉重、僵硬(必备);纳少甚或纳呆;肢体酸楚困重,神疲乏力;舌苔腻。次症为面色淡黄或萎黄;形体偏瘦;大便偏溏或黏滞或泄泻;胸、脘胀闷,食后为甚;舌质有齿痕或伴有裂纹;脉濡或滑或细。AS其他证候的症状特点有待进一步挖掘和探究。

3.4 AS患者中医证候的实验室指标、影像学等病情特点 受科学技术所限,传统中医辨证所依靠的症状体征往往特异性较小,AS中医辨证客观化研究依赖于中医证候的标志性实验室指标,以下总结了AS患者中医证候与炎症标志物及影像学特点。刘磊等^[31]发现AS患者血清超氧化物歧化酶水平与中医证候积分呈负相关($P<0.05$)。有学者研究发现,AS证属湿热型者大便肺炎克雷白杆菌的检出率高于正常对照组和瘀血型、肾虚型AS患者^[32]。韩善夸等^[33]比较肾虚督寒证、湿热痹阻证、痰瘀阻络证及肝肾亏虚筋骨失荣证AS患者,发现湿热痹阻证型患者CRP、ESR高于肝肾亏虚筋骨失荣证($P<0.05$),湿热痹阻证髋膝关节CT分级低于3个证型($P<0.05$)。在AS患者髋膝关节MRI结果中,吴娟等^[34]发现,男性AS患者肾虚湿热证多见髋膝关节骨髓水肿程度较高者,多因素Logistic回归分析显示,肾虚湿热证、HLA-B27阳性和ESR水平是男性AS患者骨髓水肿的危险因素。

总体来看,AS湿热痹阻证患者的ESR、CRP水平明显高于其他证候^[16],且入院患者热证多于寒证。热证组患者多与炎症活动有关,寒证组患者脊柱结构损伤程度较热证组重^[35]。AS患者肾虚督寒证的骨密度、疾病活动度较肾虚湿热证患者减低^[36]。此外,AS是一种长期慢性疾病,除患者身体的疼痛以外,心理状况也是患者生存质量的重要体现,应作为研究的重点。刘晓玲等^[37]发现,AS患者

中医证型与焦虑抑郁程度之间存在一定的相关性,其中,单一瘀血痹阻或兼杂瘀血痹阻的患者较湿热痹阻证、寒湿痹阻证、瘀血痹阻证、肝肾不足证及肾阳亏虚证焦虑抑郁倾向较高。

3.5 AS患者中医证候的蛋白组学、代谢组学相关特点 为进一步探索中医不同证型的微观物质基础,基因组学、转录组学、蛋白组学、代谢组学等技术逐渐被引入中医药研究中。研究表明,miRNA参与AS免疫炎症反应与异位骨化^[38]。一项有关AS湿热痹阻证的蛋白质组学研究成功鉴定出5个差异表达蛋白:胞外基质蛋白、蛋白酶类、凝血因子、细胞因子和转运蛋白^[39]。一项AS寒湿痹阻证血清蛋白质组学研究得到5个寒湿痹阻证差异蛋白:聚腺苷二磷酸核糖聚合酶1、弗林蛋白酶、血管内皮钙黏蛋白、激肽原1、血管紧张素原^[40]。关于代谢组学,一项研究结合GC-MS、LC-MS技术,从代谢组学角度评估AS患者血浆中主要的代谢变化,采用单变量和多变量分析对改变代谢物进行比较和模式识别,能够准确区分AS患者与正常对照组,表明其潜在的诊断应用价值^[41]。梁伟东等^[42]基于代谢组学技术筛选出19个代谢产物,认为肾虚督寒型AS患者病理机制或与患者能量代谢、氨基酸代谢、脂类代谢以及胃肠道菌群和免疫紊乱等代谢异常有关,可多方面影响脾、肾两脏功能轴。

4 总结与展望

综上所述,AS中医证候研究主要涉及证候分型与不同证候特点两方面。多数中医学者认为AS的核心病机为肾督亏虚,但其中医分型标准尚未完全统一。随着现代科学的发展,AS中医证候特点研究已不仅限于中医传统意义上的症状与体征,而是逐渐赋予了实验室指标、影像学等病情特点,并深入到不同证候微观物质基础,包括蛋白组学与代谢组学特征。尽管AS的中医证候研究已多方面展开,但仅限于中医证候学特征描述、中医证候与实验室指标间的相关性研究,不同因素间因果关系及内在机制研究仍处于初级阶段,证候演变规律研究也相对滞后^[43],离中医证候完全标准化、客观化尚有差距。中医药治疗AS具有多靶点、多通路及系统共同作用的特点,具有高度复杂性,需要多元学科协作参与以发掘其证候特征,从症状体征深入到生物标志物,

可将寻找有高度特异性的“疾病-证候-症状”体系标志作为今后的研究方向^[44]。同时借助多种现代临床研究统计方法,如数据挖掘、概率论等,开展证候的动态时空性、非线性系统性研究^[43],为中医药精准治疗AS提供借鉴。

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