

• 理论研究 •

“水寒木郁”病机在帕金森病抑郁发病中的作用*

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摘要:“水寒木郁”即指肾阳虚水寒,肝木失温,肝郁不发而为病。此病机观源于《黄帝内经》,并被后世医家发展应用于各系统疾病中。我们通过前期研究发现“水寒木郁”亦为帕金森病抑郁(PDD)发病的重要机制,其中阳虚水寒为发病之根本,肝木郁滞为发病之肇始。许多临床研究从温阳解郁的角度治疗 PDD 效果良好,我们以此病机为据拟定温阳解郁方(制附子、巴戟天、柴胡等)进行研究,有效率达 70%。药理学研究亦表明,一些有温肾或疏肝作用的中药能通过多个途径治疗 PDD,这些研究结果反向证实了 PDD “水寒木郁”病机的正确性。从历史溯源、理论探索、相关研究依据等方面阐述该病机在 PDD 发病中的作用,以期对 PDD 的病机研究及临床治疗提供新的思路和借鉴。

关键词: 帕金森病; 帕金森病抑郁; 水寒木郁; 病机

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Pathogenesis of “water cold resulting in inhibition of the wood” in Parkinson’s disease with depression*

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Abstract “Water cold resulting in inhibition of the wood” refers to that kidney yang deficiency and cold coagulation in the kidney may lead to failure of the kidney to warm the liver and liver qi stagnation. This pathogenesis originated from the *Huangdi Neijing* (*Huangdi’s Internal Classic*), and has been developed and applied to diseases of various systems by later physicians. Based on literature research, it is observed that this pathogenesis could possibly be applied in interpreting the mechanism of Parkinson’s disease with depression (PDD) from TCM perspective. For PDD, yang deficiency and cold coagulation of the kidney is the root of the attack, and liver qi stagnation appears in the initial stage. According to various clinical studies, the therapeutic method of warming the kidney yang to relieve liver qi stagnation is effective in treating PDD. Based on such findings, we have developed a formula (composed of *Zhifuzi* (prepared aconite root, *Radix Aconiti Lateralis Praeparata*), *Bajitian* (morinda root, *Radix Morindae Officinalis*), *Chaihu* (*bupleurum*, *Radix Bupleuri*)) with corresponding effects, which proves to be 70% effective. Pharmacological studies also show that certain traditional Chinese medicinals with the effect of warming the kidney or relieving the liver qi stagnation can show some effect in the treatment of PDD. These research results support the exploration of the pathogenesis of PDD from the perspective of “water cold resulting in inhibition of the wood”. This article has explored such a pathogenesis in PDD based on literature reviews of classical TCM literature, relevant theories and modern studies, in order to provide new ideas and references for the pathogenesis research and clinical treatment of PDD.

Keywords: Parkinson’s disease; Parkinson’s disease with depression; water cold resulting in inhibition of the wood; pathogenesis

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帕金森病(Parkinson's disease, PD)是一种发病率仅次于阿尔茨海默病的慢性进展性神经系统退行性疾病,主要临床表现包括静止性震颤、肌强直、运动迟缓、姿势平衡障碍等运动症状,以及抑郁、睡眠障碍、便秘等非运动症状^[1]。其中抑郁是PD最常伴发的非运动症状^[2]。研究发现帕金森病抑郁(PDD)的患病率为40%~50%。与不伴抑郁的PD患者相比,PDD患者疾病进展更速,认知下降更著,依从性更差,致残率更高,照料起来更困难^[3]。PD患者生活质量的下降有40%的原因是由抑郁症状所致^[4]。西医对于PDD的发病机制尚未完全明晰,现多从去甲肾上腺素(Norepinephrine, NE)、多巴胺(Dopamine, DA)、5-羟色胺(5-hydroxytryptamine, 5-HT)等神经递质水平降低^[5-6],神经肽-Y水平降低^[7],额叶-纹状体-DA通路受损^[8],氧化-抗氧化系统失衡^[9]等方面论。中医对于PDD的认识有一定的历史,近年来有关PDD的临床报道也日益增多。我们发现“水寒木郁”病机在PDD的发病中起重要作用。

1 “水寒木郁”病机溯源

“水寒木郁”即指肾阳虚水寒,无以上腾温暖肝木,肝郁升发不能而为病的病机观。此说源于《黄帝内经》,《素问·生气通天论篇》载“阳气者,精则养神,柔则养筋。”率先指出阳气与人的精神状态、筋脉柔僵均密切相关。明代医家张介宾在《类经》中亦言“神之灵通变化,阳气之精明也;筋之运动便利,阳气之柔和也……阳气去则神气乱,筋骨废。”^[10]至清朝,黄元御明确提出了“水寒土湿木郁”病机,其著作《四圣心源》有载“盖厥阴肝木,生于肾水而长于脾土。水土温和,则肝木发荣,木静而风恬;水寒土湿,不能生长木气,则木郁……凡病之起,无不因于木气之郁。”^[11]该病机观现已被众多医家接受并发展运用,如吴荣祖教授提出了“三阴脏寒,水寒土湿,木郁不达”的病机观^[12];高体三教授提出了“水暖土和木达”的学术思想等^[13]。该病机思想也指导了神经系统、消化系统、内分泌系统等临床多系统疾病的治疗。我们在首都临床特色应用研究项目资助下进行的前期临床研究发现,由该病机观演化而来的“水寒木郁”病机与PDD的发病十分契合。

2 “水寒木郁”导致PDD的理论探索

2.1 PDD多为“拘病”“郁证”之合病

PDD通常被认作是“颤证”“郁证”之合病。然

PD可分为震颤型、少动和强直型、震颤或少动和强直型伴痴呆型、震颤或少动和强直型不伴痴呆型4类^[14],且60%的PDD由少动和强直型PD进展而来^[15]。而少动和强直型PD以肌张力增高为突出特点,无肢体震颤或震颤不明显,故将PD统归为“颤证”的做法并不严谨。关于肌张力增高的症状,早在《内经》中就有相关描述,如《灵枢·刺节真邪论》载“虚邪之中人也……搏于筋,则为筋挛”;《素问·至真要大论篇》亦载“厥阴在泉,客胜则大关节不利,内为痉强拘瘓,外为不便”等。其中“挛”“拘瘓”即指肌张力增高、关节拘急不利之态,“痉强”则为强直之象。后书中又出现了专门论述肌张力增高的病证,如元代程杏轩的《医述·痿》提出“拘挛属肝,肝主筋……盖阴血受伤则血燥,血燥则筋失所养,为拘为挛,势所必至。”^[16]清代王肯堂的《证治准绳》、张璐的《张氏医通》更是单列“挛”为一节,并详细描述了其症状及病因病机。但上书所述病证也包含了风湿痹症、中风所致的肢体拘挛不舒,概念过宽,且仅含筋脉挛急之态,而并无PD肌强直的特征性症状。直至2003年,由罗云坚、张英哲主编的《常见病中西医结合诊疗常规》首次将PD按临床表现分属于中医的“颤病”“拘病”及“颤拘病”,明确指出了少动和强直型PD的中医病名为“拘病”^[17]。而PDD多继发于少动和强直型PD,故大多PDD应属“拘病”与“郁证”之合病。

2.2 “肾虚水寒”为拘病的中心病机

少动和强直型PD最易继发PDD,此型PD属中医“拘病”的范畴,其运动症状主要表现为四肢拘急、活动笨拙、运动迟缓、表情淡漠、易疼痛^[15]等。《伤寒六书》载“拘急者,手足不能自如,屈伸不便,如蜷卧恶风之貌。四肢诸阳之本,因发汗亡阳,阳虚而有此证。”^[18]可见阳虚可致筋脉挛缩而拘急。活动笨拙具体表现为起步行走或前进过程中步伐短暂、突然中止或明显减少,常持续数秒至数分钟不等^[19],西医称之为“冻结步态”,恰如其分地说明了此症的寒象;肌肉僵硬所致的表情淡漠也正如寒冰封冻不解,俱因阳虚生寒,而寒性凝滞所致。至于运动迟缓,《素问·阴阳别论篇》载“静者为阴,动者为阳,迟者为阴,数者为阳。”说明阳气不足则迟缓少动。《素问·举痛论篇》有言“寒气入经而稽迟,泣而不行……客于脉中则气不通,故卒然而痛。”指

出寒性凝滞而主痛,故阳虚生寒易发疼痛。

由此可见少动和强直型PD最突出的中医病机特点为阳虚寒生。而肾为先天之本,其内所藏阳气为真阳、元阳,为一身阳气之根本,正如张介宾在《类经附翼·大宝论》中所言“天之大宝,只此一丸红日,人之大宝,只此一息真阳。”^[20]故人身阳气不足,或为肾阳真火虚弱牵连他脏生寒,或为他脏阳虚久病及肾,总以肾阳为一身阳气之最重。相关研究亦发现,在少动和强直型PD发病过程中,阳虚这一病理要素贯穿始终,且随着病情进展,其阳虚、气虚之像愈显,寒象渐多,火热之象渐少^[15]。故肾阳不足极可能为少动和强直型PD易进展为PDD的关键所在。

2.3 “水寒木郁”导致“郁证”的机制

PDD患者的抑郁症状与其他继发性抑郁有所不同,以持久的情绪低落、工作和生活兴趣丧失、冷漠、悲观等^[21]为主要表现,而自责、自罪及自杀行为相对少见。中医将之归于“郁证”的范畴。郁证与肝最为相关,究其因,肝主疏泄,喜调达而恶抑郁,疏泄不及则郁而寡欢。正如《景岳全书·郁证》载:“至若情志之郁,则总由乎心,此因郁而病也……一曰怒郁,二曰思郁,三曰忧郁……忧郁病者,则全属大虚,本无邪实,此多以衣食之累,利害之牵,及悲忧惊恐而致郁者,总皆受郁之类……凡此之辈,皆阳消证也……使不知培养真元,而再加解散,真与鹭鸶脚上割股者何异?”显而易见,PDD属“思郁”“忧郁”之类,且患者多为病痛及治疗费用所苦,与“忧郁”之因“利害之牵”“悲忧”相合,依其言,此“皆阳消”所致。说明情志异常不仅与肝气郁结相关,阳气不足也是一个重要的致病因素。

综上所述,肾阳亏损则筋急失柔,又诸筋主束骨、利机关,筋病则关节活动不利,故见四肢拘急、活动笨拙、运动迟缓等运动症状。而从五行生化论,肝属木,肾属水,且水能生木而为其母,肾损及子,肝亦受害。又肝为刚脏,体阴而用阳,所谓“体阴”即言肝肾同归人体下焦而属阴;所谓“用阳”即言肝为风木之脏,外应春生之气,其气主升、主动,以调达舒畅为顺。石寿棠之《医原》有载“肾中真阴之气,即因肾阳蒸运上通于各脏腑之阴,阳助阴升,以养肝木,则木气敷荣。”^[22]肾阳虚无力蒸腾肾阴则致肝体失濡;再则肝为甲木之脏,阳中之少阳,性喜调达而恶抑郁,只有阳气充沛方能助其调达,而肾为先天之本,其中真阳不足可牵涉各脏,肝阳也损,则肝木失助而调达不能,发荣无力。故肾阳虚水寒则“肝体”失涵无发荣之基石,“肝用”失助无发荣之动力,终致肝木郁郁不伸,肝

气郁结而疏泄失司,故可出现情志异常而继发抑郁。可见PDD以阳虚水寒为发病之根本,肝木郁滞为发病之肇始。因此在治疗上应肝肾同调,既要疏肝解郁以散结,还应温补肾阳以培元。

3 “水寒木郁”导致PDD的相关研究验证

目前已有不少医家从温阳解郁的角度治疗PDD并取得了良好效果。如肖榕等人自拟温脾益肾解郁方(干姜、制附子、柴胡等)联合盐酸帕罗西汀片治疗PDD,利用帕金森氏病综合评分量表(UPDRS)、汉密顿抑郁量表(HAMD)及帕金森患者生活质量问卷(PDQ-39)评价疗效,结果显示有效率可达89.28%,显著高于仅用盐酸帕罗西汀片治疗者^[23]。钱昱璇等人自拟熄风解郁汤(刺五加、醋柴胡、白芍等)治疗PDD,并在治疗前后统一UPDRS、HAMD、PDNMS问卷量表、简短精神状态量表(MMSE)及中医证候积分评价疗效,发现治疗后患者各项评分均优于治疗前,且与盐酸普拉克索缓释片治疗者相比,其PDNMS评分下降更明显^[24]。陈路等人在原有抗PD西药治疗基础上加用滋肾益髓方(肉苁蓉、沙苑子、龟甲等)治疗PD,以UPDRS、帕金森病运动功能评定量表(MDRSPD)及30项非运动症状筛查问卷(NMS30题)评价疗效,发现与单用抗PD西药相比,联合该方能明显改善帕金森病患者的运动及非运动症状,二者疗效具有统计学意义($P < 0.05$)^[25]。我们在首都临床特色应用研究项目的资助下,基于PDD“水寒木郁”病机拟定了温阳解郁方(制附子、巴戟天、柴胡等)并进行了小样本临床研究,结果显示该方能改善PDD患者的运动功能、抑郁状态并提高日常生活质量,有效率可达70%。

药理学研究表明,一些有温肾或疏肝作用的中药能通过调节神经递质和神经营养因子、改善氧化应激等与PDD发病有关的多个途径治疗PDD。如附子能上调自由基清除相关基因表达水平,从而减少自由基生成,降低其对脑组织的损害^[26]。巴戟天甲素可增加脑组织中DA、NE、5-HT含量^[27];巴戟天多糖可清除活性氧(ROS)、减少丙二醛(MDA)的生成,使超氧化物歧化酶(SOD)含量增多、活性增强并减少SOD的消耗,同时减少机体超氧阴离子自由基的生成,从而减轻脑组织的氧化损伤,起到保护神经的作用^[28];巴戟天寡糖能显著增加海马脑区脑源性神经营养因子(BDNF)、磷酸化糖原合酶-3 β (p-GSK-3 β)及GluR1、突触后致密蛋白95(PSD95)、突触蛋白1(Synapsin 1)的表达,从而调节神经营养通路中的关键节点^[29]。柴胡可通过抑制线粒体凋亡

保护神经元细胞,起到抗抑郁样作用^[30]等。上述研究从临床和基础两方面为“温阳解郁”法提供了依据,从而反向证明了PDD“水寒木郁”病机的正确性。

4 小结

PDD的发病机制目前尚未完全明确,我们基于前期研究结果发现该病的发生主要涉及肝、肾二脏,中心病机为“水寒木郁”,病理性质总属本虚标实,其中肾阳不足为发病之本,肝气郁滞为发病之标。这为PDD的病机研究及临床治疗提供了新的思路和借鉴,以期充分发挥中医药的特色优势。

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