从因瘀致郁论治卒中后抑郁

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摘要:卒中后抑郁是脑卒中后常见的并发症,对脑卒中患者的预后产生深远影响。介绍了因瘀致郁理论渊源,因瘀致郁病机内涵主要包括两点:脑络瘀阻,神机失用;心神失养,郁证乃生。并对因瘀致郁与卒中后抑郁的现代生物学机制进行探讨,认为卒中后抑郁病理机制与低脑血流量、血小板功能障碍、内皮功能损伤、脂代谢异常、炎症反应等因素密切相关。从形神共治的角度提出卒中后抑郁的治疗以活血解郁为主,不仅要对卒中本身进行治疗,还要重视因病而导致的心理障碍的识别与干预。

关键词:卒中后抑郁;郁证;血瘀;形神共治
中图分类号:R277.7　　**文献标志码**:A　　**文章编号**:1672-0482(2023)06-0507-06
DOI:10.14148/j.issn.1672-0482.2023.0507
引文格式:谭艳,曹洋,罗敏辉,等.从因瘀致郁论治卒中后抑郁[J].南京中医药大学学报,2023,39(6):507-512.

Treating Poststroke Depression from the Perspective of Depression Caused by Stagnation

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ABSTRACT: Poststroke depression is a common complication after stroke, which has a profound impact on the prognosis of stroke patients. The article introduced the origin of the depression caused by stagnation theory. The pathogenesis connotation of the theory mainly includes two points: cerebral collateral stasis leading to vital activity dysfunction; nourishment deprivation of heart spirit leading to depression. The article also explored the modern biological mechanisms of depression caused by stagnation as well as poststroke depression. It is believed that the pathological mechanism of poststroke depression is closely related to factors such as low cerebral blood flow, platelet dysfunction, endothelial dysfunction, abnormal lipid metabolism, and inflammatory response. From the perspective of the joint treatment of body and spirit, it is proposed that the treatment of poststroke depression should mainly focus on promoting blood circulation and relieving depression. It is not only necessary to treat the stroke itself, but also to pay attention to the identification and intervention of psychological disorders caused by the disease.

KEYWORDS: poststroke depression; depression syndrome; blood stasis; co-governance of form and spirit

脑卒中是一种突然起病的脑血液循环障碍性疾病,又叫脑血管意外,分为缺血性脑卒中和出血性脑卒中,是世界第二大死亡原因,也是致残的主要原因[1]。早在《肘后备急方》一书中就有“救卒中恶死方”“治卒中风诸急方”等[2]关于“卒中”的记载。卒中后抑郁症(Post-stroke depression,PSD)是脑卒中后常见并发症,会对卒中患者的预后产生负面影响。卒中后 5 年内 PSD 的发生率可高达 39%~52%[3],与普通人群的抑郁症一样,卒中幸存者的抑郁症通常未被发现。据保守估计,超过三分之一的患者在卒中后出现抑郁的体征和症状[4]。PSD 的临床表现为抑郁、内疚或低自我价值、睡眠障碍、疲劳、注意力不集中和自杀倾向等[5],不利于卒中后运动功能和认知功能的恢复,并已成为严重的社会和公共卫生问题,降低了卒中后患者的存活率,并延迟了卒中患者的后期康复[6]。

中医认为 PSD 可归属于“中风”与“郁证”合病,中风是一种由风、火、痰、瘀、虚等多种病理因素导致病邪上扰清空、闭阻脑脉,或血溢脑脉,瘀阻脑络的一种病证。血瘀是中风后持续发生的一种病理

收稿日期:2022-05-24
基金项目:国家自然科学基金面上项目(81973956)
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状态,中风后病理产物滞留于脑内,气血不通,因而由瘀致郁,涉及单胺系统改变、下丘脑-垂体-肾上腺轴异常、神经可塑性改变、谷氨酸神经传递、炎症反应等病理变化。郁证有广义、狭义之别,广义郁证即前人所说的"百病皆兼郁"状态,可发于各种外感内伤,以及继发于其他疾病;狭义郁证指的是由七情创伤导致的精神障碍的一类疾病,如脏躁、百合病等[7]。本文所探讨的卒中后抑郁属于前者。本文围绕血瘀与郁证的理论渊源,系统探讨卒中后抑郁的生物学机制研究进展,以期为心脑同治法防治卒中后抑郁的研究提供理论依据。

1　因瘀致郁理论渊源

《景岳全书·郁证》云:"凡五气之郁,则诸病皆有,此因病而郁也"[8],提出了因病致郁理论。多数学者认为卒中后抑郁属于因病而郁状态,卒中后抑郁是在中风的基础上,由风、瘀、痰、火等病理因素交搏郁,结致使气血郁滞不畅,神明失其清展而致[9]。另有学者提出中风疾病过程中,瘀血的病机贯穿始终,瘀血既影响气机条畅,又能影响新血化生[10]。王清任在《医林改错》中曰:"平素和平,有病急躁,是血瘀"[11],明确了郁证可由血瘀所致。卒中后的病理因素以瘀为主,伴随风、火、痰等因素,而这些病理因素,随着疾病日益迁延,也易发展为瘀,瘀滞郁结,抑郁状态又可进一步加重,并形成血瘀,两者之间相互影响。由此笔者在因病致郁理论基础之上提出因瘀致郁。现代中医学者结合当今医疗实践,对 PSD 的形成及脑卒中与抑郁症之间的关系有了更加深刻的认识,脑卒中可以引发抑郁症,抑郁症亦可影响脑卒中患者神经功能缺损的恢复,甚至加重神经功能损害和患者的精神痛苦,两者之间相互作用致使病情进一步发展[12]。

2　因瘀致郁病机内涵

2.1　脑络瘀阻,神机失用

卒中发生的病位在脑,本病的发生非一因所致,而是多因素联合作用于机体,长期不解,脏腑功能失调,正气虚弱,外有所触,内有所动,体内气血溢乱所致。轻者,经络受损,血脉不利,络脉绌急,血液壅滞,凝结为瘀,则血脉瘀塞,神机失用而成瘀塞经络的缺血性中风。重者,邪盛正衰,脏气不平,腑气不通,经络不用,络破血溢则为出血性中风。轻者为闭,重者为脱,危者则亡。其病机归纳起来,主要是风、火、痰、气、虚、瘀此六者相互影响,合而为病,卒中发生后病机以瘀为主。

《黄帝内经素问集注》曰:"诸阳之神气,上会于头,诸髓之精,上聚于脑,故头为精髓神明之府。"[13]《三因极一病证方论》云:"头者,诸阳之会,上丹产于泥丸宫,百神所聚。"[14]《医宗金鉴》曰:"头为诸阳之首,位居至高,内涵脑髓,脑为元神之府,以统全体者也"[15],脑是精髓神明汇聚的地方,神居于脑,具有统御全身的作用。血滞脑络则为瘀血,瘀血阻络进一步导致气络病变。瘀血既是病理产物,又是致病因素,脑络瘀阻,则脑神失用,从而出现精神神志方面的症状,所谓脑络瘀阻,神机失用。

2.2　心神失养,郁证乃生

卒中后瘀血阻滞脑络不仅造成脑功能损伤,且对心神亦有损害。《素问·灵兰秘典论》云:"心者,君主之官也,神明出焉"[16]。《灵枢·邪客》曰:"心者,五脏六腑之大主,精神之所舍也。"[17]心藏神,具有统帅人体生理活动,主司意识、思维、情志等精神活动,是五脏六腑之大主。《黄帝内经太素》中提到"头是心神所居"[18],卒中病变部位在头,头伤而致心神无所居。另外卒中后血脉瘀阻,气血无以濡养,心神失养。

瘀血损伤可扰动心神,心神失养则神无所藏。《类经》云:"心为脏腑之主,而总统魂魄,并赅意志"[19],五志藏于心,魂神意魄志皆为心所统。《诸病源候论》曰:"心有所存,神有所止,气留而不行,故结于内"[20],心神耗伤,神无所止,则易气结而郁。《景岳全书·郁证》曰:"情志之郁,则总由乎心"[8],心神调和则神志清明,心神不调则情志郁结。卒中后血瘀扰神,心神失养,发为郁证。

3　因瘀致郁与卒中后抑郁的现代生物学机制探讨

PSD 发病机制复杂,涉及多方面因素,并非单一病理机制可以解释,涉及低脑血流量、血小板功能障碍、内皮功能损伤、脂代谢异常、炎症反应等。中医血瘀的生物学实质与其中多项机制相互交叉[21]。

3.1　低脑血流量与卒中后抑郁

人体正常生理状态下需要适当的脑血流量(Cerebral blood flow,CBF)来维持大脑的结构和功能完整性[22]。若人体在 CBF 自动调节缺陷的情况下,轻微的 CBF 减少便有可能损害认知和情感过程[23]。一项横断面临床研究发现,全脑平均脑血流量与抑郁症密切相关,其中扣带皮层中低 CBF 与特质性抑郁之间呈强关联性,并且研究结果表明,CBF 的减少更有可能与潜在的神经血管后遗症性抑郁症有关[24]。另一项研究表明,双侧基底神经节灌注不

足可能导致中风后情感淡漠,这是中风患者常见的神经精神症状[25],尽管冷漠在临床现象学上不同于抑郁症,但两者的症状有相当大的重叠,中风后冷漠常伴有抑郁症。在一项对卒中后患有抑郁症和卒中后无抑郁症的患者研究中,单光子发射计算机断层成像术测量显示抑郁症患者的 CBF 值较低[26],该研究得到了颞叶低灌注可能反映边缘系统功能障碍假设的支持,推测卒中后抑郁机制可能是通过影响中断的皮质-皮质下连接而导致[27]。由此可知,血流量的不足易导致血虚则瘀,而低脑血流量易导致抑郁症的形成。

3.2　血小板功能障碍与卒中后抑郁

血小板功能障碍可能是参与抑郁症和脑血管疾病关联的病理生理过程[28]。有研究发现,抑郁症与血小板聚集密切有关,血小板黏性的增加可能解释了抑郁症患者对中风的易感性增加,也导致中风后合并抑郁症的不良预后[29]。平均血小板体积(Mean platelet volume,MPV)作为血小板功能的标志,被视为血小板活性的生物学指标[30],在抑郁症患者血液中也观察到高 MPV 水平,明确 MPV 与抑郁症的病理生理机制有关[31]。中风伴随着血小板功能的改变,高 MPV 水平与缺血性中风的风险增加以及中风幸存者的不良预后相关[32]。一项临床研究结果显示高水平的 MPV 与 PSD 的发展显著相关[33],可被视为 PSD 的独立预后标志物,而血瘀证模型动物也表现出血小板聚集率增加的现象[34]。由上可知,血小板功能障碍是卒中后的显著特征,是卒中后抑郁发生的重要因素。血小板聚集和活化会促进郁证的发生。

3.3　内皮功能损伤与卒中后抑郁

血管内皮细胞是一类十分活跃的代谢及内分泌细胞,许多血管活性因子都由血管内皮细胞所分泌。各种诱因引起血管内皮细胞激活,从而引起了机体微环境中血管内皮细胞的腔面与血管周围的变化,血管内皮细胞合成、释放多种活性物质,参与血管舒缩、血栓形成等过程[35]。临床研究发现抑郁症患者与无抑郁症患者相比明显存在内皮功能障碍[36]。内皮细胞损伤是血栓形成增加的重要机制[37],改善血管内皮功能损伤与抑郁症和脑梗死的治疗效果密切相关[38-39]。一项关于缺血性脑卒中的临床随机对照试验发现,急性缺血性卒中与体循环中激活的内皮细胞标志物升高相关,以及循环中内皮祖细胞的减少,并伴有全身内皮功能障碍的损害,并且脑卒中早期使用改善内皮功能药物可以促进神经功能缺损的程度,可以预防 PSD 的发生[40]。内皮功能损伤是脑卒中发生后的结果现象,也是导致血栓形成的高危因素,是卒中后抑郁形成的重要生物学机制之一。

3.4　炎症反应与卒中后抑郁

研究发现一些炎症反应会破坏身体的内部平衡,引起代谢紊乱,导致神经递质分泌异常,从而导致抑郁症的发生[41]。Spalletta 等[42]认为 PSD 的发生可能与免疫激活有关,导致细胞因子分泌增加,提出了“细胞因子假说”,一种免疫激活和细胞因子增加的现象,即中风后中枢神经系统中的星形胶质细胞和小胶质细胞会产生细胞因子及其受体,包括白细胞介素-1(Interleukin1,IL-1)、白细胞介素-6(Interleukin-6,IL-6)、肿瘤坏死因子-α(Tumor necrosis factor α,TNF-α)和 γ 干扰素(Interferon γ,IFN-γ)。炎症因子相互作用形成调节免疫反应的网络系统[43],这些因素刺激单胺神经递质系统并产生毒性作用,导致抑郁症发生[44]。PSD 大鼠海马中发现 TNF-α、IL-1 和皮质醇释放因子表达增加[45]。一项队列研究发现当缺血性中风发生时,中性粒细胞释放促炎生物标志物,这些炎症介质引发一系列兴奋毒性炎症反应,同时将血小板募集在病变点[46]。由此可知,卒中发生后炎症因子激发炎症反应会募集血小板聚集,产生瘀毒,导致抑郁症的发生。

3.5　脂代谢紊乱与卒中后抑郁

脂质代谢失调是导致中风等中枢神经系统损伤的关键事件,由于大脑含有高浓度的多不饱和脂肪酸,容易发生脂质过氧化,消耗相对大量的氧气来产生能量,并且与其它器官相比,具有较低的抗氧化防御能力[47-48]。脂质代谢紊乱共同参与了抑郁症[49]和脑卒中[50]的病理生理过程。例如,在中风和 PSD 动物模型中观察到粪便中短链脂肪酸(Short chain fatty acid,SCFA)浓度降低[51]。研究表明,细菌衍生的短链脂肪酸,例如乙酸盐、丁酸盐和丙酸盐,可能有助于缓解 PSD 患者的抑郁症状[52]。动物实验发现高脂饮食摄入引起的脂质代谢紊乱加速小鼠抑郁样行为的形成[53]。使用大脑中动脉阻塞动物模型研究发现,中风会导致脂质谱的改变,表现为血浆游离脂肪酸和甘油三酯增加,并且诱发了小鼠抑郁和焦虑样行为[54]。血瘀证人群的蛋白组学研究提示脂代谢异常是血瘀证的一种生物学表现[55]。上述

研究表明中风可引起脂代谢失调,而脂代谢紊乱可导致抑郁症的形成。

4　卒中后抑郁的中医治法

卒中后发生抑郁不利于卒中后运动功能和认知功能的恢复,并延迟了卒中患者的后期康复,抑郁也会增加再次脑卒中的风险[56]。选择性 5-羟色胺重摄取抑制剂(SSRIs)类抗抑郁药是 PSD 治疗的首选药物,可以降低激动剂诱导的血小板活化、聚集和促凝活性,从而调节血小板的血栓形成,降低动脉闭塞事件的风险[57]。然而对于中风患者来说,情况较为复杂,因为 5-羟色胺对脑血管也有收缩作用,理论上可以抵消 SSRI 的抗血栓活性,并可能导致缺血性中风[58-59]。近年来,SSRIs 与出血性中风和/或死亡率之间的可能联系一直备受争议。因此,探究中医中药在此领域的相关应用具有重要临床价值。

卒中后抑郁属于中医中风、郁证合病,在中医药手段治疗卒中后抑郁上,多采用兼具化瘀和解郁功效的中药汤剂。解郁活血方[60]能改善脑梗死后的抑郁症状,其中当归、赤芍、鸡血藤、桃仁、红花活血化瘀,柴胡、郁金疏肝解郁,共奏活血解郁之效。醒脑解郁胶囊[61]具有醒脑解郁、活血化瘀之效,可以减轻神经炎症[62]和抗抑郁作用[63]。补阳还五汤可通过促进神经营养通路介导的神经保护和神经发生来改善 PSD[64];通窍活血汤在增殖活性和膜通透性方面对谷氨酸损伤的神经细胞具有明显的保护作用[65],这些证据表明活血化瘀治疗郁证的潜力。某些中药既有抗抑郁作用,又具有活血化瘀功效,可兼具血瘀和郁证的治疗,如郁金中生物活性成分姜黄素具有抗抑郁作用[66],莪术醇能明显改善血瘀证的血液高凝状态[67]。故卒中后抑郁的中医药治疗应以活血解郁为主,在治疗上需兼顾瘀与郁。

5　思考与展望

目前已知许多躯体疾病会伴发抑郁症状,患有严重内科疾病的患者,其抑郁症患病率更高,患有脑卒中、癌症、慢性肾功能衰竭、心肌梗死、帕金森病以及其它各种老年躯体性疾病的患者中约有 40% 可并发抑郁症,比不伴发抑郁症的患者死亡率高 3~4 倍[68]。中医学认为人的心理和生理各自成系统,又相互联系,共同组成统一体。躯体结构和生理机能是心理活动的物质基础,但都需要在心神的作用,生理和心理两大机才能被有机地整合成一体,即形神合一。卒中后抑郁发生于中风后,中风之后,脑络瘀阻,躯体功能障碍,伤的是形,以瘀为主要病理因素;而后心神失养,郁证乃生,伤的是神,以气郁为主要病理因素,瘀郁结合,心身共患。因此,心身医学理念下不仅要对卒中本身进行治疗,还要重视因病而导致的心理障碍的识别与干预,这也是中医的形神一体观的要求。目前兼顾活血和解郁治疗卒中后抑郁的临床疗效明显,且不良反应少,但目前此方面的研究尚少,具体机制尚未明确,因此,从因瘀致郁的角度开展卒中后抑郁的临床及机理研究,充分发挥形神共治的理念,对卒中后抑郁的治疗尤其具有重要意义。

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(编辑:叶亮)