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头针调控炎症反应治疗血管性认知障碍的机制研究进展

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【摘要】 血管性认知障碍(VCI)是以脑血管病及其危险因素为核心病因的认知障碍综合征。近年来,头针在VCI治疗中的应用受到广泛关注。本文聚焦头针治疗VCI的作用机制,系统总结其通过调控促炎信号通路、抑制小胶质细胞过度活化与极化、调节星形胶质细胞功能,同时激活胆碱能抗炎通路、保护血脑屏障完整性、平衡神经-内分泌-免疫网络,进而抑制过度炎症反应、改善认知功能。此外,文章深入阐述头针在减轻神经损伤、延缓VCI进展中的关键作用,为进一步探究其抗炎机制及临床推广应用提供科学依据与参考。

【关键词】 血管性认知障碍;头针疗法;炎症反应;信号通路;综述

Research Progress on the Mechanism of Scalp Acupuncture in Regulating Inflammatory Response for Vascular Cognitive Impairment

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【ABSTRACT】 Vascular cognitive impairment (VCI) is a cognitive impairment syndrome with cerebrovascular disease and its risk factors as the core cause. In recent years, the application of scalp acupuncture in the treatment of VCI has received extensive attention. This article focuses on the mechanism of scalp acupuncture in the treatment of VCI, and systematically summarizes its regulation of pro-inflammatory signaling pathways, inhibition of excessive activation and polarization of microglia, regulation of astrocyte function, activation of cholinergic anti-inflammatory pathways, protection of blood-brain barrier integrity, and balance of neuro-endocrine-immune networks, thereby inhibiting excessive inflammatory response and improving cognitive function. Furthermore, it elaborates on the key role of scalp acupuncture in alleviating neural damage and delaying the progression of VCI, providing a scientific basis and reference for further investigation of its anti-inflammatory mechanism and clinical application.

【KEYWORDS】 Vascular cognitive impairment; Scalp acupuncture; Inflammatory response; Signaling pathway; Review

血管性认知障碍(VCI)是一类以脑血管病变及其危险因素为首要病因的连续临床谱系,范围涵盖轻度认知损害至血管性痴呆(VaD),为仅次于阿尔茨海默病的第2大认知障碍类型^[1-2]。其病程具有进行性发展特征,包括非痴呆性VCI(VCIND)和VaD两个阶段,VCIND可进一步进展为VaD^[3]。随着人口老龄化及脑卒中患病率升高,VCI患者数量不断攀升,且其认知损害涉及记忆力、执行控制能力等多个领域,严重损害患者日常生活自理能力与社会

功能,给家庭和社会造成沉重负荷^[4]。全球痴呆症患者人数预计到2050年将较2016年增长两倍以上,中国2019年65岁以上人群痴呆患病率达到5.60%^[5-6]。VCI的致病因素复杂多样,主要包括脑血管病危险因素、显性脑血管病及非显性脑血管病^[7]。其中,神经炎症级联反应在VCI的发生、发展进程中扮演核心角色^[8]。脑血管病变可诱发中枢神经系统及外周免疫系统的炎症反应,持续的炎症反应状态导致神经元损伤、突触可塑性降低,最终导

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致认知功能障碍^[9]。因此,有效调控炎症反应或成为治疗VCI的关键策略之一。

头针疗法是一种建立在现代大脑功能分区理论基础上的特色针刺技术,其核心作用机制在于依据大脑皮层功能定位在头皮的投影区,选择性地进行针刺刺激以调节相应脑功能^[10]。与传统体针全身取穴、整体调节的作用方式不同,头针强调对病变脑区的直接和特异性干预,具有显著的空间靶向性与神经调控精确性。该疗法通过刺激头颅表面特定区域,不仅能够改善局部脑血流循环、增强神经代谢活动,还可调节神经递质平衡、促进神经可塑性变化,从而在多层次发挥脑保护作用^[11]。近年研究^[12]结果显示,头针能有效抑制小胶质细胞(MG)活化、降低炎症信号通路活性,并减少促炎因子的释放,从而减轻神经炎症反应。此外,头针还可增强抗氧化能力、改善血脑屏障完整性,从多途径阻断VCI的炎症损伤。本文系统综述头针干预VCI相关神经炎症反应的分子机制,旨在为临床制定基于炎症调控的精准头针治疗策略提供理论依据。

1 VCI与炎症反应的关系

1.1 脑内炎症反应的激活

脑血管损伤(例如脑缺血、脑梗死、白质疏松等)会引发脑内缺血缺氧微环境的产生,此环境的主要特征为氧自由基释放及氧化应激。氧自由基的长期损伤能够直接作用于脑内固有免疫细胞,其中以MG和星形胶质细胞(AS)为主,促使其活化与增殖,并释放促炎细胞因子、趋化因子及其他炎症介质^[13]。炎症因子不仅可诱导白细胞浸润,刺激胶质细胞活化因子的表达,还能作为内皮细胞的活化信号分子,促进细胞黏附分子(CAM)的生成^[14]。除此之外,白细胞介素-1 β (IL-1 β)和肿瘤坏死因子- α (TNF- α)作为参与慢性脑缺血损伤过程的关键炎症因子,可造成中枢神经髓鞘脱失,引发胶质细胞凋亡,导致白细胞浸润及血脑屏障(BBB)的破坏^[15]。已有研究^[16]证实,TNF- α 水平与认知功能减退、神经元毒性及脑细胞凋亡存在密切关联;IL-1 β 的过量表达可加重神经炎症反应,提高神经元死亡率,从而诱发认知障碍性疾病。同时,活化的AS可通过与MG的相互作用被激活,而活化的MG亦可通过诱导与AS的相互激活,上调胶质纤维酸性蛋白(GFAP)的表达^[17],进而调节炎症反应强度。

1.2 外周炎症联动

血管病变(如动脉粥样硬化、高血压、糖尿病等

基础疾病)引发的慢性炎症反应可激活外周免疫系统,导致外周免疫细胞(如巨噬细胞、淋巴细胞)活化,并释放大量炎症因子(如C反应蛋白、IL-6、TNF- α)^[18]。这些炎症因子可通过血液循环穿透受损的BBB进入脑内,与脑内固有免疫细胞相互作用,加剧中枢神经系统炎症反应,加速神经退行性变,进而对认知功能产生负面影响^[19]。同时,基质金属蛋白酶表达上调可破坏BBB基底层及紧密连接,增加其通透性,促进炎症反应浸润微环境形成;神经胶质细胞极化活化相关的炎症信号通路被激活后,会将外周免疫细胞募集至大脑,导致细胞死亡及白质损伤等继发性组织损伤^[20]。此外,外周炎症反应还可影响神经-内分泌-免疫网络的平衡,通过神经递质、激素等信号分子间接调控脑内炎症反应状态,进而影响认知功能。

1.3 炎症反应对认知功能的损伤

炎症反应通过多通路级联损伤认知功能,且贯穿VCI发展全程。外周及中枢促炎因子(如IL-1 β 、TNF- α)经高通透性BBB浸润后,可激活核因子(NF)- κ B通路(核因子 κ B抑制蛋白 α 降解致核转位),诱导胶质细胞过度反应(GFAP表达上调、MG激活),释放活性氧、补体及兴奋毒性物质,导致少突胶质细胞变性、轴突脱髓鞘及白质完整性破坏;慢性低灌注会加剧内皮紧密连接蛋白表达下调及血管周围纤维化,促使外周炎症细胞(如T淋巴细胞)渗入并激活转化生长因子(TGF)- β 通路,导致神经血管单元解体^[21-22]。海马、前额叶等关键脑区的神经元突触后密度蛋白减少,线粒体氧化应激及补体依赖性突触消除机制可降低突触可塑性,导致默认网络功能连接异常^[23];同时,胆碱能抗炎通路(CAIP)失衡会削弱抗炎作用,直接损害记忆环路。炎症反应进一步促进 β 淀粉样蛋白(A β)沉积与tau蛋白磷酸化,形成神经纤维缠结,协同能量代谢障碍及凋亡信号,最终导致执行功能、信息处理速度及情景记忆进行性衰退,这构成了VCI的核心机制^[24]。

2 头针调控炎症反应治疗VCI的机制

2.1 抑制胶质细胞过度活化,调节炎症反应表型转化

2.1.1 抑制MG极化

脑缺血后,MG过度活化并呈现动态极化特征,即从短暂M2型(抗炎、促神经营养)向M1型(促炎、致损伤)转化,其过程受NF- κ B信号通路调控,是

M2向M1转化的分子开关,可放大炎症反应,此为缺血性脑卒中神经炎症反应的关键机制及干预靶点^[25]。区别于体针依赖全身免疫调节的间接效应,头针可通过抑制MG的M1型极化、诱导其向M2型转化,实现对过度活化的抑制及炎症反应表型的调节,发挥抗炎与神经保护作用^[26]。Peng等^[27]基于大鼠中动脉闭塞(MCAO)大鼠的研究进一步验证了头针的上述作用。电头针干预后,模型大鼠的神经功能缺损评分及相关神经行为学指标显著降低,脑梗死体积同步缩小;M1型MG特异性标志物CD32的表达水平明显下调,而M2型特异性标志物CD206的表达显著上调,提示电头针可能通过驱动MG由M1向M2表型转化,抑制神经炎症损伤,进而缓解缺血性脑卒中相关的认知功能减退。此外,边静等^[28]研究显示,针刺卒中后认知障碍(PSCI)大鼠“神庭”“百会”可显著改善认知功能,表现为海马区神经元密度增加、组织结构损伤减轻;同时,MG活化标记物离子钙结合衔接分子1及M1表型特异性标记CD197的表达水平显著下调,而M2表型特异性标记精氨酸酶1的表达明显上调。因此,头针或针刺头部特定腧穴可通过抑制脑内(尤其是海马区)MG的过度活化及M1型极化,减轻神经炎症损伤,从而改善缺血性脑卒中及PSCI模型动物的神经功能与认知缺损,为临床针刺干预缺血性脑损伤提供了可靠的实验依据。

2.1.2 调节AS功能

AS在VCI的炎症反应中同样扮演着重要角色。在VCI发生发展的病理过程中,AS迅速激活并释放TNF- α 、IL-1 α 、IL-1 β 、IL-6及CAM等大量炎症反应介质,该介质网络可通过直接或间接途径刺激一氧化氮等神经毒性物质生成,提高血脑屏障通透性,触发并放大炎症级联反应,从而加剧脑组织损伤,对VCI的病理进程及预后产生重要影响^[29]。头针在VCI的炎症反应中,对AS具有双向调节作用,能够因势利导发挥保护效应。一方面,头针可修复AS的形态结构,调控其功能状态,强化其在病理过程中的积极作用,如促进神经功能恢复等^[30];另一方面,针对AS被激活后释放大炎症介质引发炎症级联反应、加重脑损伤的问题,头针能抑制这一损伤途径,减少炎症介质及神经毒性介质的产生,降低BBB通透性,从而减轻炎症反应对脑组织的损害^[31]。Tian等^[32]研究显示头针可改善VaD大鼠的学习记忆能力,通过显著增加大鼠海马CA1区AS特异性标记物GFAP与抑凋亡因子B细胞淋巴

瘤-2(Bcl-2)共同表达的阳性细胞数目,上调海马AS中Bcl-2蛋白的表达,并通过抑制凋亡途径提升VaD大鼠的学习与记忆能力。

2.2 调控炎症反应相关信号通路

2.2.1 NF- κ B信号通路

NF- κ B是一种重要的转录因子,在炎症反应中处于核心地位。在正常情况下,NF- κ B与抑制因子I κ B结合,以非活性复合体形式滞留胞质;炎症反应刺激激活I κ B激酶,引发I κ B磷酸化并降解,释放的NF- κ B随即核转位,与 κ B序列结合,启动TNF- α 、IL-1 β 、IL-6等促炎基因转录,从而参与VCI诱导的认知障碍的发生及发展^[33]。Peng等^[27]研究提示,电针刺激MCAO大鼠双侧“顶颞前斜线”可明显抑制NF- κ B p65的活化,并伴随促炎因子及M1型标志物CD16表达下降,同时抗炎因子及M2型标志物CD206表达上升,提示头针可能通过抑制NF- κ B通路促使MG向M2表型极化,从而减轻神经炎症反应并缩小梗死体积。Wang等^[34]进一步指出,头针还可通过下调Toll样受体4(TLR4)的表达,阻断其介导的NF- κ B信号转导,最终改善认知功能。

TLR4作为NF- κ B的上游调控分子,在激活后不仅直接促进NF- κ B核转位,还可诱导NOD样受体家族含热蛋白结构域蛋白3(NLRP3)炎症反应小体的转录与组装。NLRP3炎症反应小体由NLRP3、凋亡相关斑点样蛋白和半胱天冬氨酸蛋白酶-1构成,在VaD中被认为是放大神经炎症反应与细胞焦亡的关键分子平台。该小体在MG、AS及神经元中均被报道高表达,可加剧BBB破坏并促进认知功能下降^[35]。头针疗法可显著抑制NLRP3通路,降低细胞焦亡水平,减轻炎症反应并保护神经元结构,从而改善认知缺损^[36]。Chen等^[37]选取“神庭”“百会”行带针有氧运动,通过下调海马区NLRP3表达及阳性细胞数量,抑制MG激活和促炎因子释放,促进神经恢复,改善大鼠认知功能障碍。

2.2.2 丝裂原活化蛋白激酶(MAPK)信号通路

MAPK信号通路在慢性脑缺血所致的神经炎症反应中扮演重要角色,尤其是p38 MAPK通路。该通路在缺血应激下发生磷酸化激活,进而促进TNF- α 、IL-1 β 等促炎因子的表达,启动并放大炎症反应级联反应^[38]。此外,细胞外信号调节激酶和c-Jun氨基末端激酶也参与这一过程,通过调控下游转录因子影响炎症反应介质生成、细胞增殖与凋亡^[39]。NF- κ B作为p38 MAPK下游的关键效应分子,其激活后可进一步结合于环氧合酶-2(COX-2)

基因启动子区域,显著提升COX-2表达。COX-2则催化前列腺素等炎性介质合成,扩大脑内炎性反应损伤^[40]。临床证据^[41]显示,慢性脑缺血患者脑中NF- κ B与COX-2的高表达与认知损伤严重程度呈正相关,表明该通路是VCI炎性反应机制的重要组成部分。王莹等^[42]研究指出,头针“神庭”“百会”可抑制VaD患者p38 MAPK磷酸化及NF- κ B核转位,进而降低TNF- α 、IL-1 β 释放与COX-2表达,最终减轻炎性反应损伤并改善认知功能。这一结果提示,头针可能通过调控MAPK/NF- κ B/COX-2信号轴发挥抗炎与神经保护作用。

2.2.3 CAIP激活

CAIP是传出迷走神经释放乙酰胆碱(ACh)并通过作用于相应受体调节炎性反应的通路。胆碱乙酰转移酶(ChAT)由CHAT基因编码,是ACh生物合成的限速酶,催化乙酰辅酶A与胆碱缩合生成ACh,构成CAIP的关键调控节点^[43-44]。ACh作为中枢关键递质,介导神经信息传递并参与学习记忆等认知活动,其受体分为毒蕈碱型(M型)与烟碱型(N型),其中 α 7烟碱型乙酰胆碱受体(α 7nAChR)在海马、下丘脑等认知相关区域呈高表达,通过调节突触可塑性发挥核心作用^[45]。在CAIP中,迷走神经释放的ACh激活 α 7nAChR后,可抑制NF- κ B信号通路,减少促炎因子释放,通过改善神经炎性反应进一步实现对认知障碍的调控^[46]。实验研究^[47]表明,头针干预可显著提高VaD大鼠海马区ChAT及AChE活性,促进ACh合成与代谢,增强CAIP功能,进而抑制NF- κ B通路并改善空间学习记忆能力。黄东挺等^[48]也报道头针丛刺可升高痴呆大鼠海马ACh水平,通过激活胆碱能受体增强CAIP信号,改善认知功能。上述结果表明,头针可能通过调节中枢胆碱能系统功能,增强CAIP抗炎效应,从而在VCI治疗中发挥重要作用。

2.3 保护BBB并减少炎性反应因子渗透

2.3.1 上调BBB相关蛋白表达

高血压、高血糖、急性缺血再灌注、慢性低灌注等因素可通过损害BBB导致血源性神经毒性物质、病原微生物等渗透入脑,引起多种免疫反应及神经炎性反应,损伤神经元及其他脑细胞,介导脑的结构与功能损害,导致VCI的发生及发展^[49]。BBB由毛细血管内皮、基底膜及AS终足共同构成,其中内皮细胞间的紧密连接(TJ)复合体是维持其选择通透性的关键结构。该复合体由闭合蛋白、闭合小环蛋白等跨膜及胞内蛋白构成,其表达与分布直接影

响BBB的完整性^[50]。头针干预可通过多途径增强TJ蛋白表达,促进BBB修复。在模型中,电针“百会”可促进脑缺血再灌注大鼠神经生长因子及BBB相关结构蛋白的表达,有助于恢复屏障功能^[51]。电头针处理不仅改善快速衰老模型(SAMP8)小鼠认知行为,还可降低海马区活性氧水平及神经炎性反应,其机制可能与抑制A β 沉积及调控TLR4/RAGE信号通路有关^[52]。邓畅等^[53]进一步研究显示,电针“百会”可显著改善VaD大鼠空间学习记忆能力,减轻BBB超微结构损伤,减少血清IL-1 β 和IL-18等促炎因子水平,表明其保护效应部分源于抗炎作用。综上,头针可能通过增强TJ蛋白表达、抑制炎性反应信号通路及减轻氧化应激等多重机制,协同保护BBB结构和功能完整性。

2.3.2 抑制血管内皮细胞黏附分子表达

炎性反应环境中,血管内皮细胞间黏附分子-1(ICAM-1)与血管细胞黏附分子-1(VCAM-1)表达显著升高,可介导外周免疫细胞黏附并跨越血管壁浸润至脑实质,加剧中枢炎性反应^[54]。已有研究^[55]证实,脑缺血后ICAM-1与VCAM-1表达上调,促进白细胞黏附并跨越内皮屏障浸润脑实质,从而放大缺血性炎性反应,该机制可能在VCI病理演进中发挥关键作用。头针疗法可通过抑制上述黏附分子的表达,减轻免疫细胞浸润及神经炎性反应。电针头穴能显著下调ICAM-1水平,同时增强内皮型一氧化氮合酶(eNOS)表达,改善脑血流灌注,从而缓解认知损伤^[56]。另一研究^[57]报道,电针“百会”可降低海马组织中晚期糖基化终末产物受体、VCAM-1和ICAM-1的表达,并上调低密度脂蛋白受体相关蛋白1和载脂蛋白E,促进A β 清除,最终改善认知功能。以上结果表明,头针不仅调控黏附分子表达以抑制外周免疫细胞入脑,还通过调节A β 代谢相关蛋白协同发挥神经保护作用。

总之,头针通过多重机制维护BBB稳态,包括增强紧密连接蛋白表达、抑制内皮黏附分子及调节A β 清除通路,从而减轻神经炎性反应、延缓VCI进展。这为头针临床应用提供了坚实的实验依据。

2.4 调节神经-内分泌-免疫(HPA)网络

2.4.1 激活HPA轴,调节抗炎激素分泌

HPA轴作为神经内分泌调控枢纽,主导机体应激反应;其过度激活既是缺血性卒中的典型特征,也与认知障碍进程紧密耦合^[58]。卒中后HPA轴功能紊乱可显著削弱记忆、理解与执行等认知维度,干扰日常活动并阻碍康复^[59]。头针可在下丘脑、垂

体及肾上腺多层次干预,调节促肾上腺皮质激素释放激素(CRH)、促肾上腺皮质激素(ACTH)及皮质醇(CORT)等关键激素水平,通过神经-免疫-肠道轴及脑区特异性炎症反应调控,影响认知相关脑区的神经炎症反应与神经可塑性,实现对认知障碍的调控^[60]。

周家荣等^[61]临床研究显示,针刺“百会”“神庭”等可显著降低PSCI患者血清中的CORT和ACTH水平,同时提高认知评分,表明头针能抑制HPA轴过度激活,缓解糖皮质激素对海马神经的抑制。过量CORT可损害海马神经前体细胞增殖与分化,从而影响学习记忆功能^[62]。白晶等^[63]研究显示,头穴丛刺能显著降低PSCI患者血清CORT水平,改善精神状态,其疗效优于单纯认知训练。唐强等^[64]进一步证实于氏头穴丛刺结合认知康复可更有效地调节HPA轴功能,降低CORT水平,且效果优于药物对照组。动物实验亦支持这一结果,LEE等^[65]报道头针可缓解由CORT诱导的大鼠记忆障碍,通过调控HPA轴功能及海马糖皮质激素受体信号,促进神经功能恢复。上述研究表明,头针通过调节HPA轴活性,降低应激激素水平,减轻神经损伤,从而为VCI的治疗提供了一种有效的神经内分泌干预策略。

2.4.2 增加脑源性神经营养因子(BDNF)表达

近年来,在对VCI的发病机制进行研究的同时,越来越多的研究关注到卒中后涉及的不同细胞因子在VCI发展中所起的作用。其中,BDNF作为中枢神经系统中含量丰富且功能关键的神经营养因子,在调节突触可塑性、促进神经元存活与修复及抑制神经炎症反应中发挥核心作用。其表达水平与认知功能呈正相关,已被广泛认定为评估认知状态的重要生物标志物^[66]。研究^[67]表明,BDNF能够穿越BBB,这为在治疗缺血缺氧性脑损伤中作为神经保护剂提供了理论依据。针刺干预可显著提升BDNF表达,从而发挥神经保护与抗炎效应。研究^[68]显示,头针能提高大鼠海马BDNF水平,抑制IL-6、TNF- α 等促炎因子释放,减轻神经胶质细胞过度活化,改善学习记忆能力。电针“四神聪”可通过调节谷氨酸代谢、减轻兴奋性神经毒性,激活BDNF信号通路,同时增加抗炎细胞因子IL-4和IL-10的表达,促进神经元存活与认知修复^[69]。临床研究进一步支持BDNF在头针治疗中的关键作用,如岭南头皮针可调节PSCI患者血清BDNF及IL-6水平,并显著提升其认知功能及日常生活能力^[70]。

因此,头针可能通过上调BDNF表达,协同抑制神经炎症反应和促进神经修复,最终改善VCI。

3 小结与展望

VCI的发生发展与炎症反应存在密切关联,其核心机制涵盖脑内炎症反应激活、外周炎症反应联动及由此引发的认知功能损伤。头针作为治疗VCI的有效干预手段,可通过多维度调控炎症反应发挥神经保护效应:一方面通过抑制胶质细胞表型极化、促进AS功能重塑、阻断经典炎症反应信号通路(如NF- κ B/MAPK)及激活CAIP,协同调节TJ蛋白及内皮黏附分子表达以修复血脑屏障完整性;另一方面通过HPA轴释放抗炎激素及上调BDNF,整合神经-内分泌-免疫网络,实现系统性抗炎及神经保护效应。头针通过多靶点、多途径调控炎症反应,为VCI的防治提供了重要的机制依据与潜在干预策略。

当前证据虽初步阐明头针可通过NF- κ B/MAPK/CAIP多轴抑制神经炎症反应、修复BBB及重塑神经-内分泌-免疫网络以改善VCI,但现有研究在深度与广度上仍存在局限:(1)基础研究多依赖动物模型(如MCAO大鼠、SAMP8小鼠),其与人类VCI病理特征存在物种差异,难以完全模拟人类VCI的复杂病理特征,导致临床转化证据链薄弱;(2)头针干预参数(如刺激频率、强度、穴位配伍方案等)尚未形成统一标准,研究方案差异显著,导致难以建立统一的疗效评价体系;(3)机制研究多聚焦于单一信号通路节点,缺乏对多靶点协同作用网络机制的系统解析;(4)临床试验普遍存在样本量偏小、循证医学证据等级偏低的问题,且研究多聚焦于短期认知功能改善,长期疗效及安全性数据仍较为匮乏。未来研究需针对上述局限进行突破,以推动头针在VCI干预中的临床转化与应用发展。基础研究需进一步优化动物模型,更贴近人类VCI病理特征,推动基础研究成果向临床实践的转化,并积累大样本长期随访数据;技术层面应推进头针干预参数的标准化研究,构建统一的疗效评价体系;机制研究需突破单一节点的局限,深入开展多靶点协同作用网络的系统研究;临床研究应扩大样本量、提升循证医学证据等级,重点关注长期疗效与安全性,为头针在VCI临床干预中的规范化应用提供更充分的证据支持。

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