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颈深淋巴管/淋巴结–静脉吻合术治疗阿尔兹海默病的研究进展

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摘　要

阿尔兹海默病是一种与年龄相关，导致认知和功能障碍的神经退行性疾病，其特征为特定的神经病理变化。尽管阿尔兹海默病的发病机制与生物标志物研究已经取得了巨大的进展，但阿尔兹海默病到目前为止仍是一个不治之症。目前阿尔兹海默病的主要治疗方式是对症支持治疗，但并不能延缓疾病的进展。随着“脑膜淋巴管”概念的提出以及人们对它的进一步研究，发现脑膜淋巴管最终汇集于颈深淋巴结。近年来，手术治疗作为一种潜在的创新治疗方案受到越来越多的关注。本文综述了颈深淋巴管/淋巴结–静脉吻合术在阿尔兹海默病治疗中的潜力与应用。

关键词

阿尔兹海默病，病理机制，淋巴管/淋巴结–静脉吻合术，脑膜淋巴管，颈深淋巴管/淋巴结

Research Progress of Deep Cervical Lymphatic Vessel/Lymph Node-Venous Anastomosis in the Treatment of Alzheimer’s Disease

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Abstract

Alzheimer's disease is a central nervous system degenerative disease characterized by age-related cognitive decline and behavioral impairment. Despite significant progress in the pathogenesis and biomarker research of Alzheimer's disease, it remains an incurable disease to date. At present, the main treatment for Alzheimer's disease is symptomatic supportive treatment, but it cannot delay the progression of the disease. With the introduction of the concept of "meningeal lymphatic vessels" and further research, it has been found that meningeal lymphatic vessels ultimately converge in the deep cervical lymph nodes. In recent years, surgical treatment has gained increasing attention as a potential innovative therapeutic option. This article reviews the potential and application of deep cervical lymphatic vessel/lymph node-venous anastomosis in the treatment of Alzheimer's disease.

Keywords

Alzheimer's Disease, Pathogenesis, Lymphatic Vessel/Lymph Node-Venous Anastomosis, Meningeal Lymphatic Vessel, Deep Cervical Lymphatic Vessel/Lymph Node

1. 引言

阿尔兹海默病(Alzheimer's disease, AD)是一种常见的痴呆症，1906 年德国医师阿洛伊斯·阿尔兹海默(Alois Alzheimer)首次描述了这种痴呆症，后续将这种疾病命名为 AD。国际阿尔兹海默病组织于 2018 年估计全球约有 5000 万的 AD 患者，预计到 2050 年将增加 2 倍[1]。随着我国进入老龄化社会，60 岁及以上人口数量及占全国人口比重逐年攀升，预计到 2035 年左右将突破 4 亿，在总人口中的占比将超过 30%，我国 AD 患病率在逐年上升，现位居我国居民死亡原因的第五位[2]。

目前，AD 的主要治疗策略以对症支持治疗为主，治疗 AD 的药物主要是胆碱酯酶抑制剂和 N-甲基-D-天冬氨酸拮抗剂[3]，一般以延缓疾病的发展与进展为目的，改善患者的总体健康状况，但药物的治疗效果在时间上是有限的[4]。因此，研究者们开始探索基于病理通路的新型治疗方法。

2. 阿尔兹海默病的病理生理学

AD 是最常见的神经退行性疾病之一，其发病机制复杂，涉及多种病理生理变化[5] [6]。

(1) β-淀粉样蛋白(amyloid β-protein, Aβ)沉积：Aβ 是由 β-淀粉样前体蛋白(amyloid precursor protein, APP)在 β 分泌酶和 γ 分泌酶的作用下产生的[7]-[9]。正常情况下，Aβ 在脑脊液中被清除，但在阿尔兹海默病患者中，Aβ 逐渐聚集形成不溶性的淀粉样斑块[10]。这些斑块主要在大脑的皮质和海马区沉积，是阿尔兹海默病的标志性病理特征之一，淀粉样斑块的形成被认为通过神经毒性机制损害神经元功能和存活[11] [12]。

(2) Tau 蛋白异常磷酸化：Tau 蛋白是一种与微管稳定性相关的蛋白，正常情况下协助维持轴突运输[13]。在阿尔兹海默病中，tau 蛋白发生异常磷酸化，导致微管结构崩解，形成神经原纤维缠结[14]-[16]。这种缠结在神经元内的发展被认为会导致神经元的功能障碍和死亡[17]。

(3) 神经炎症：小胶质细胞是大脑中的免疫细胞，当 Aβ 斑块和 Tau 缠结积累时，小胶质细胞被激活，导致慢性炎症反应，持续的炎症会加重神经元损伤[18] [19]。激活的小胶质细胞和星形胶质细胞释放各种促炎性细胞因子，如 TNF-α、IL-1β 和 IL-6，这些因子进一步促进神经元损伤和细胞死亡[20] [21]。

(4) 血脑屏障功能障碍：血脑屏障(Blood-Brain Barrier, BBB)是保护脑组织不受血液内有害物质侵害的屏障[22]。研究表明，AD 患者的 BBB 通透性增加，这可能导致系统性炎症因子进入颅内，从而加重神经炎症和病变[23]。

(5) 线粒体功能障碍与氧化应激：AD 患者的线粒体功能常受到影响，导致能量代谢障碍[24]；由于抗氧化防御机制受损，患者脑内发生显著的氧化应激，这会损伤细胞膜、蛋白质和 DNA，最终导致神经细胞死亡[25] [26]。

3. 淋巴系统在中枢神经系统中的作用

淋巴系统是一个在人体常常被忽视的系统，但却扮演关键角色。除了心血管系统，淋巴系统代表了一个在体内独特的和突出的血管系统[27]。在“脑膜淋巴管”提出以前，人们认为中枢神经系统(Central Nervous System, CNS)缺乏淋巴系统[28]。然而，近年来的研究表明，大脑淋巴系统是存在的[29]。人和其他哺乳动物的脑膜中均存在淋巴管。有研究证明脑膜淋巴管起自双眼[29] [30]，脑膜淋巴管的淋巴引流始于脑毛细血管的基底膜，脑脊液(cerebrospinal fluid, CSF)通过筛状板后被鼻淋巴管吸收，然后排出到颈深淋巴结[31]。通过在小鼠左顶叶注射示踪剂，脑膜淋巴管的 CSF 流入下颌和腮腺淋巴结[32]。Martina 等[33]研究人员发现通过无创性检查 MRI 证明了人体及非灵长类生物脑膜中存在淋巴管。在 AD 的小鼠模型中，观察到 AD 小鼠与野生型小鼠相比，脑膜淋巴管(Meningeal lymphatic vessel, MLV)的引流量减少了 70% [34]。脑膜淋巴管(mLVs)是脑膜中存在的功能性淋巴系统，是负责清除分子，免疫细胞，细胞碎片从脑脊液和间质液进入颈深淋巴结。衰老和 ApoE4 是阿尔茨海默氏病(AD)的两个最重要的危险因素，可引起 MLV 功能障碍，减少脑脊液流入和流出，并加剧淀粉样蛋白病理和认知功能障碍。MlV 的功能障碍导致代谢产物的沉积，加速神经炎症，并促进大脑中促炎细胞因子的释放。因此，MLV 代表了用于治疗神经变性和神经炎性疾病的新型治疗靶标[35]。

胶质淋巴系统是一种依赖星形胶质细胞的脑脊液–间质液(Interstitial fluid, ISF)交换系统。此系统借助 CSF 的流动，通过围绕血管的空隙帮助清除脑内代谢废物。CSF 和 ISF 被蛛网膜颗粒吸收并释放到硬脑膜静脉窦[36]。然后 MLV 将 CSF 和 ISF 的混合物从硬脑膜静脉窦运输到颈深淋巴结，并能有效地从大脑排出带有分子和免疫细胞的液体。胶质淋巴系统为 CSF 和 ISF 的快速交换提供了血管周围通道。MLV 和胶质淋巴系统促进了 Aβ、Tau 和其他有毒蛋白从大脑间隙的清除。该引流系统的功能障碍是 AD 发病的关键[37]-[39]。在 AD 患者的尸检标本可以看到较多的由 Aβ 形成的老年斑，可以看出 Aβ 蛋白沉积和 AD 的发生有着密切的关系[40]。

CSF 是由脑腔系统中的软脑膜形成的脉络膜丛持续产生的“淋巴液”，CSF 在两个脑膜腔之间的蛛网膜下腔(SAS)循环，并通过动脉周围、静脉周围和毛细血管周围足端途径进入大脑，并通过许多途径离开大脑[31] [41]-[43]。CSF 持续而积极地产生，以维持颅内压(ICP)在正常水平。在大脑中，细胞碎片和毒性分子如 Aβ 的清除是通过 CSF 的跨细胞转运机制，驻留的小胶质细胞、单核细胞和巨噬细胞的吞噬和消化通过血管旁途径(淋巴)的 CSF 内流和 ISF 外流共同介导的[44] [45]。

脑膜淋巴管不仅参与了脑内代谢废物的清除，还涉及免疫细胞，如淋巴细胞和单核细胞的运输[46]。这些细胞通过淋巴管从 CNS 迁移到外周淋巴器官，参与免疫应答[47]。MLV 与 BBB 的完整性和功能密切相关。它们共同维持了 CNS 的免疫稳态和防止病原体入侵[48]。淋巴系统在 CNS 的免疫调节中扮演重要角色，通过调节免疫细胞的运输和活性，影响神经炎症反应，这在 AD 的病理过程中起到关键作用。

4. 颈深淋巴管/淋巴结–静脉吻合术的机制与理论基础

颈深淋巴管/淋巴结–静脉吻合术是一种通过超显微外科手术将颈部淋巴管/淋巴结与静脉系统相连的方法，其目的是通过改善淋巴回流来促进脑内代谢产物的清除。淋巴管静脉吻合术(Lymphatic Venous Anastomosis, LVA)通常是治疗肢体淋巴水肿的有效手术方法，通过吻合皮下功能性的淋巴管和血管，促进机体的淋巴循环，从而改善机体淋巴系统的循环[49]。随着超显微外科技术进步和显微镜的改进，以及在超声和荧光淋巴显像技术的支持下，LVA 作为一种术后并发症小、效果良好的手术已经越来越被大家所接受[50] [51]。手术的关键点并不在于淋巴管与静脉吻合数目的多少，而在于寻找功能性的淋巴管或淋巴结，减少或避免吻合口返流或堵塞[52]，术前在超声的辅助下在术中快速、便捷地定位到功能性的淋巴管或淋巴结[53]。颈部是脑的主要淋巴引流区域，直接将这一部位淋巴管/淋巴结与静脉连接，理论上可以增加全脑淋巴液的流通和排出效率，改善 BBB 的通透性[54]。

近年来的研究发现，脑膜淋巴管是中枢神经系统清除代谢废物(如 Aβ 和过度磷酸化的 Tau 蛋白)的关键途径[55]。LVA 手术通过连接颈部的功能性淋巴管/淋巴结与静脉，促进脑膜淋巴液的回流，改善脑部的淋巴循环。通过改善淋巴循环，LVA 可能有助于减少 Aβ 和 Tau 蛋白在脑内的积累。虽然 LVA 是一种侵入性手术，但已有研究显示其在治疗肢体淋巴水肿方面的安全性和有效性，为 LVA 治疗 AD 提供了一定的基础[56]。在 LVA 手术的作用下，可能通过神经炎症相关机制与信号通路调控和改善了脑部淋巴循环：1. 促炎细胞因子调控：AD 的神经炎症与促炎细胞因子(如 TNF-α、IL-1β、IL-6)的异常释放密切相关。LVA 可能通过改善淋巴引流功能，减少脑内炎症因子的积累。例如，淋巴系统清除功能的增强可能抑制小胶质细胞的过度激活，从而降低上述细胞因子的表达水平。也可能通过影响 JAK-STAT 信号通路：该通路在炎症反应中起核心作用，尤其在调节 IL-6、IL-4 等细胞因子的表达中。LVA 可能通过调节外周淋巴系统对炎症介质的清除，间接影响 JAK-STAT 通路的活性，但目前尚无直接证据支持这一假设。2. TGF-β 通路：通过 Smad 蛋白将信号转导至细胞核，参与免疫调节和抗炎反应。若 LVA 能够增强脑内代谢废物的清除，可能通过减少 Aβ 沉积引起的慢性炎症，间接激活 TGF-β/Smad 通路，抑制神经炎症。根据已有研究可知 LVA 治疗可能还会通过氧化应激与线粒体功能障碍以达到改善大脑淋巴回流的方式：1. PKC (蛋白激酶 C)通路在调节神经元抗氧化能力和线粒体功能中发挥重要作用。研究表明，PKC 的激活可增强神经元的抗氧化酶活性(如超氧化物歧化酶 SOD)，并改善线粒体能量代谢。若 LVA 通过改善脑内淋巴系统功能减少 Aβ 沉积，可能间接激活 PKC 通路，从而缓解氧化应激损伤。2. 胰岛素信号通路(PI3K/Akt)参与调节葡萄糖代谢和抗氧化反应。该通路的激活可促进 GLUT-4 转运体的膜定位，改善神经元能量供应，并抑制氧化应激相关蛋白的生成。LVA 对淋巴引流的改善可能通过调节外周代谢废物清除，间接影响中枢神经系统的 PI3K/Akt 通路活性。

改善大脑的淋巴引流有助于维持和恢复颅内液体的动态平衡，这样可能在一定程度上降低颅内压，从而可以减轻对中枢神经系统的压迫，减缓神经退行性病变的恶化[57]。通过淋巴引流，还可以减少脑水肿和相关炎症反应，有助于环境恢复及神经细胞功能维护[58]。加强 Aβ 等代谢废物的清除能力能够在理论上提供神经保护作用，减轻其对神经元的毒性影响，从而对长期的神经健康产生积极影响[58]。

颈深淋巴结分为颈深上淋巴结和颈深下淋巴结。颈深上淋巴结位于胸锁乳突肌深处的上部，主要引流头部和颈部上部的淋巴液；颈深下淋巴结位于胸锁乳突肌深处的下部，主要引流颈部下部、锁骨上区和肩部的淋巴液[59]。进行 LVA 手术时，我们要选择颈深上淋巴结及淋巴管进行吻合。

在对 AD 患者行 LVA 手术时，可能面临与治疗淋巴水肿相似的问题，例如术前淋巴管及静脉的定位、术中的监测与吻合的准确性、术后吻合口狭窄与梗阻的监测等。为了提高手术的准确性，我们可以借助吲哚菁绿(Indocyanine Green, ICG)红外荧光成像和彩色多普勒超声在术前对淋巴管及静脉进行精准

定位[60]。LVA 手术对精确度和显微外科技术的要求较高，因为淋巴管和静脉的直径通常非常细小。提高手术成功率的关键在于手术团队的专业培训和丰富的经验积累。通过引入显微镜和超显微手术技术，例如使用超显微缝线及显微镜下的实时荧光造影，可以进一步增强吻合的精确性。彩色多普勒超声作为一种实时、无创的成像技术，还能够在术后监测吻合口的并发症，并及时进行处理[61]。

此外通过对术后的随访，可以评定 LVA 对 AD 患者的疗效。可以通过迷你精神状态检查(MMSE, Mini-Mental State Examination)、阿尔兹海默病评定量表–认知部分(ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale)、蒙特利尔认知评估量表(MoCA, Montreal Cognitive Assessment)对 AD 患者进行病情监测和评估。

5. 结论

在颈深部进行淋巴管/淋巴结–静脉吻合术可以改善脑膜淋巴管的流出通道，重建淋巴系统并降低脑膜淋巴管的压力，在保持淋巴管静脉吻合口畅通的情况下，有望长期改善阿尔兹海默病患者的症状。对于颈深淋巴管/淋巴结吻合术在改善 AD 患者症状方面的长期效果，需要通过持续的术后跟踪和评估来进行深入研究。根据已发表的文献及统计学数据证明了，虽然 AD 患者患病因素有直接关系[35]，但根据所统计依据，患病比例逐渐年轻化。因此尽早治疗 AD，进行手术干预是有必要的[62]，但是由于一部分患者年纪较高，基础疾病过多，在原则治疗方法中仍需严格进行术前评估，排除手术禁忌症及麻醉风险后进行手术。因此本外科治疗方案仍具有部分局限性[63] [64]，未来的研究可以进一步探索 LVA 改善 AD 的具体机制，并增加多元治疗方案，包括其如何影响脑内免疫细胞的活性、神经营养因子的表达以及神经网络的可塑性等。

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