

牙周炎与阿尔茨海默病的相关性研究进展

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摘 要

阿尔茨海默病作为引起老年人痴呆与认知能力下降的重要原因之一, 始终是学术界研究的重点问题。近年来, 研究发现牙周炎与阿尔茨海默病的发生密切相关, 因此, 本文就二者之间的关联展开探讨。

关键词

牙周炎, 阿尔茨海默病, 口腔健康, 认知障碍, 炎症反应

Research Progress on the Correlation between Periodontitis and Alzheimer's Disease

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Abstract

Alzheimer's disease, as one of the major causes of dementia and cognitive decline in the elderly, has always been a key research topic in the academic community. In recent years, studies have found that periodontal disease is closely related to the occurrence of Alzheimer's disease. Therefore, this article explores the correlation between the two.

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Keywords

Periodontitis, Alzheimer's Disease, Oral Health, Cognitive Impairment, Inflammatory Response

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1. 引言

阿尔茨海默病(Alzheimer's disease, AD)是老年人中常见的一种神经退行性疾病, 全球约有 3700 万人口受到 AD 的影响。有报道推测到 2050 年, 每 85 人当中就有一人患有 AD [1]。目前关于 AD 的病因尚不完全清楚, 1%~2%的 AD 病例来源于家族遗传性, 并遵循常染色体显性遗传模式[2]。除此以外, 大多数的 AD 病例是由遗传和环境的相互作用而导致, 受教育水平、高血压、糖尿病、高胆固醇饮食、载脂蛋白 E 可能是导致 AD 的危险因素[3]。AD 主要表现为记忆力、思维、学习能力等的下降, 是导致患者认知能力下降和痴呆的主要病因[4]。有研究报道称 AD 患者的认知能力下降与突触毒性 β -淀粉样蛋白(A β)肽斑块的形成以及过度磷酸化的 tau 蛋白组成的神经原纤维缠结有关[4]。先天免疫反应将上述物质从脑内清除的同时加剧体内神经变性过程[5] [6]。目前有研究发现[7] [8], 身体其他部位的感染可能会加剧大脑内的炎症反应过程, 从而导致 AD 的发生。

牙周炎(Periodontitis, PD)是由附着在口腔表面的牙菌斑中的细菌病原体引起的口腔炎症性疾病。主要破坏包括牙槽骨、牙龈、牙周韧带在内的口腔支撑结构。PD 会引起患者出现牙龈出血、牙齿脱落等口腔问题。除了引起口腔局部不良结局外, 近年来多项研究指出 PD 与心血管疾病[9]、结直肠癌[10] [11]、呼吸系统疾病[12]、糖尿病[13]以及神经退行性疾病, 如 AD 的发生发展[14] [15]有关。流行病学证据表明[16], 慢性 PD 存在 10 年或更长时间会使患散发性 AD 的风险增加一倍。AD 和 PD 都有共同的危险因素, 这表明这两种疾病之间存在某种关联。因此, 本文就 AD 与 PD 的之间的相关性进行了综述, 以期 AD 的预防及治疗提供新的思路。

2. AD 与 PD 危险因素

近年来, 研究报道[17] [18]指出年龄、肥胖、高血压、糖尿病、吸烟、受教育程度、体育活动、抑郁会增加患 AD 的风险。而上述几种因素中也与 PD 的发生相关, 本文将从 PD 与吸烟、糖尿病、肥胖之间的关系展开论述, 以期阐述 PD 与 AD 之间的潜在关系。

2.1. PD 与吸烟

现阶段的研究共识认为, 吸烟会加剧口腔健康状况, 是 PD 的危险因素。Zhang 等人指出[19]吸烟创造了有利于牙周病原体定植的环境, 并可调节牙周病原体毒力因子的表达和功能, 导致牙周病原体致病性的进一步增强。吸烟会通过调控牙周蛋白质的表达从而影响免疫力。一项纳入 17 名吸烟者、10 名戒烟者和 13 名非吸烟者的研究中发现吸烟者和戒烟者与不吸烟者相比, 前两者口腔龈沟液中多种免疫球蛋白表达不足。这种免疫抑制作用加剧了 PD 的病情进展。精氨酸代谢物参与体内多种炎症性疾病的发生。一项横断面研究[20]表示患有 PD 且吸烟的患者唾液中精氨酸代谢物($p = 0.033$, $p < 0.001$)和精氨酸($p = 0.030$, $p = 0.001$)水平高于吸烟者和不吸烟者, 进一步揭示了吸烟加速了体内炎症反应进程。

2.2. PD 与糖尿病

截至 2015 年[21], 全球共有 4.15 亿成年人患有糖尿病。体内的高血糖状态是众多微血管病变如视网膜病变、肾病和神经病变发生的主要原因。早有研究[22]指出, 糖尿病与 PD 之间存在双向关系。糖尿病引起牙周组织的免疫和炎症反应的激活, 增加患 PD 的风险。免疫和炎症反应的激活使体内促炎因子表达增加, 伴随氧化应激, 这些因素共同作用于牙周组织, 破坏结缔组织, 加速牙槽骨吸收, 进而加剧 PD 的进展[23]。动物实验[24]发现慢性糖尿病大鼠根尖 PD 的发病率较高。此外, 糖尿病会影响口腔菌群的组成, 使口腔菌群的致病性进一步增强。Qin 等人[25]发现同时患有 PD 与糖尿病的患者口腔微生物菌群丰度与糖尿病患者不同, 在对糖尿病进行干预性治疗后能部分缓解口腔微生物菌群的改变[26]。一项荟萃[27]分析认为与无 PD 人群相比, PD 患者患糖尿病的总体患病率和几率更高, 这进一步说明了二者之间的密切关系。

2.3. PD 与肥胖

肥胖, 以及超重, 已成为发展中国家和发达国家中一种新的流行病, 并且肥胖还与健康恶化、过早死亡的风险、残疾和慢性疾病有关[28]。多项分析表明肥胖和 PD 的发生有关[29] [30]。肥胖可能导致身体持续的促炎状态, 改变牙周部位的微环境, 有利于口腔微生物区系的生长。巴西开展的一项针对 345 名受试者(其中 74.2%的参与者患有 PD)的调查研究发现[31], PD 在腰围增加的个体中存在较为普遍。并且, 该研究在调整了年龄、吸烟习惯、教育水平、糖尿病和家庭收入后仍指出, 肥胖(即腰围 > 88 cm)与 PD 之间在女性中呈正相关。动物实验中发现[32], 肥胖会影响实验性 PD 的牙周膜组织蛋白质组, 这可能是肥胖导致 PD 潜在关联机制。一项系统回顾和荟萃分析[33]亦指出, 肥胖与 PD 风险增加之间存在显著关联。这表明肥胖可能是 PD 的一个危险因素。此外, PD 也会导致肥胖。牙周组织中革兰氏阴性菌产生的脂多糖能够刺激脂肪组织产生促炎细胞因子(肿瘤坏死因子- α 、白介素 6), 促进肝脏脂代谢紊乱, 降低胰岛素敏感性, 导致肥胖和 2 型糖尿病, 进一步说明了两者之间的相关作用。

3. PD 与 AD 发病机制的关联

3.1. 牙周病原菌的影响

口腔是仅次于肠道的第二大微生物聚集部位, 拥有超过 700 种微生物群落[34]。口腔微生物和 AD 之间的关系日益受到关注。Jiao 等人发现 AD 患者唾液微生物组的多样性明显低于健康人[35]。Maurer 等人[36]也发现与对照组相比, AD 患者牙菌斑中的伴生放线杆菌、牙龈卟啉单胞菌和核梭杆菌的细菌载量较高。有研究人员在 AD 病人大脑中检出了 PD 病原体如牙龈卟啉单胞菌和齿密螺旋体[37] [38]。齿垢密螺旋体通过上调 β 和 γ 切割酶(这些是处理 β 样淀粉样前体蛋白 APP 所需的宿主酶)增加 C57BL/6 小鼠海马体内 A β 40 和 A β 42 蛋白的积累, A β 样蛋白积聚导致神经细胞凋亡[39]。牙龈卟啉单胞菌作为 PD 的主要致病菌之一, 具有较强的毒力作用, 能通过血液循环进入大脑, 破坏大脑血脑屏障, 损害脑实质。研究人员在感染牙龈卟啉单胞菌的小鼠脑内观察到了包括淀粉样变性、脑萎缩和海马区和皮质区的神经变性在内的 AD 样病理改变。并且, 牙周病原菌外膜囊泡包裹着关键的致病因子如脂多糖、牙龈痛、胶囊、菌毛, 这些致病因子能够进入不同的器官, 影响免疫细胞吞噬作用并触发促炎信号级联反应的启动[40]。由此产生的炎症介质加剧了 AD 的疾病进展, 导致患者认知能力的下降。有研究人员[41]对 20 名 AD 病人进行了认知测试, 发现牙龈卟啉单胞菌与较低的简易精神状态检查分数相关($p < 0.05$), 并且与画钟测试中的分数较低的趋势相关。牙龈蛋白酶是牙龈卟啉单胞菌生存所必需的蛋白水解酶[42] [43]。Dominy 等人[37]在牙周组织和人体脑组织标本中都观察到该酶的存在。并且, 与未表现出认知功能障碍的对照脑标本相比, AD 脑尸检标本中牙龈蛋白酶的含量更高, 其含量与 tau 蛋

白和泛素病理相关[44]。牙龈蛋白酶抑制剂可以有效遏止牙龈卟啉单胞菌的生长和繁殖。研究发现[44]受牙龈卟啉单胞菌感染的小鼠口服牙龈蛋白酶抑制剂后,其脑中牙龈卟啉单胞菌 DNA 的丰度、 β -淀粉样蛋白、炎症介导肿瘤坏死因子- α 的含量明显降低,同时在使用该抑制剂治疗的感染小鼠的大脑中可以检测到比未治疗的感染小鼠更多的海马神经元[44]。上述研究揭示了牙周病原菌的存在对 AD 病理生理过程的影响。

3.2. 炎症反应的作用

PD 作为一种口腔慢性炎症疾病,是全身炎症的常见来源。PD 引起的全身炎症反应介导了多种促炎因子如 C 反应蛋白、白介素-1、白介素-6 的释放。这些促炎因子能激活中枢神经系统小胶质细胞,加速神经退变过程[7] [45]。并且,炎症期间产生的细胞因子,特别是肿瘤坏死因子- α ,在 AD 中起着重要作用。胶质增生、脱髓鞘、血脑屏障降解和细胞死亡是由肿瘤坏死因子- α 的夸大炎症过程引起的。血脑屏障能使大脑免受外来物质的干扰。有研究[46] [47]发现 AD 患者的血脑屏障结构发生了变化,这种变化能使白介素-6、白介素-1 跨过血脑屏障并与脑血管中的内皮受体结合,释放其它炎症介质进一步损伤血脑屏障的完整性。PD 的持续存在不仅能激活外周免疫反应,还会导致中枢神经系统神经炎症的发生。神经炎症是大脑或脊髓内的一种炎症反应,由胶质细胞、内皮细胞和外周来源的免疫细胞产生的细胞因子、趋化因子和其他介质介导[48]。这些介质通过细胞因子介导的神经胶质细胞和神经元之间的相互作用而导致认知损害,导致 AD 的发生。PD 产生的炎症因子能跨越 BBB,激活小胶质细胞。被激活的小胶质细胞又会产生促炎细胞因子,这些促炎因子能通过旁分泌或者自分泌途径刺激神经胶质细胞进一步产生额外的 A β 42、Tau 蛋白和丙氨酸炎症分子。因此,炎症介质可发挥双重作用,既刺激神经胶质细胞,又激活分子途径,导致神经炎症[49]。

3.3. 宿主遗传因素的作用

载脂蛋白 E(ApoE)的等位基因变异已被确认为晚发性 AD 的主要危险因素。研究发现,AD 患者的等位基因 ϵ 4 (ApoE- ϵ 4)的频率是认知正常的人的 2~3 倍[50]。此外,ApoE- ϵ 4 会加速衰老大脑中 AD 病理的发展[51]。单纯疱疹病毒和巨细胞病毒都是嗜神经性病毒,二者的激活会导致大脑中神经元的丢失,这与 AD 的发病密切相关[52] [53]。单纯疱疹病毒糖蛋白 β 与 AD 的 A β 沉积特征有显著的同源性,这可能会促进遗传易感个体的 β 沉积,从而导致认知障碍[54]。PD 患者牙周感染组织中可分离出单纯疱疹病毒和巨细胞病毒[55] [56]。并且,有研究发现 ApoE- ϵ 4 基因携带者在单纯疱疹病毒感染的情况下患 AD 的风险增加 15 倍[57],这进一步说明了 PD 患者未来患 AD 的风险较高。

4. 总结与展望

综上所述,目前 PD 与 AD 的相关性研究日益受到关注,大多研究从 PD 病原菌微生物以及所致的炎症反应方面阐述了 PD 与 AD 之间的潜在机制关联。但未来仍需从以下方面深入探讨:首先,开展针对 AD 人群大规模临床试验,以验证牙周治疗延缓认知能力下降的积极作用;其次,将进一步明确 PD 与认知能力下降之间的关系,以期开发基于唾液的生物标志物用于 AD 早期风险筛查的可能性;另外,神经科与口腔科医生应开展跨学科的研究合作,以充分揭示 PD 与 AD 之间的机制联系,并制定合理的治疗方案以延缓病情进展。

利益冲突

所有作者声明无利益冲突。

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