

·综述·

红细胞异常与阿尔茨海默病的研究进展[☆]孟瑶^{*} 张巍^{*△◎}

【摘要】阿尔茨海默病(Alzheimer disease, AD)是最常见的认知障碍类型,但目前其确诊方法存在局限性。越来越多的研究表明,不同阶段AD患者的红细胞均出现异常,因此,本文对AD患者红细胞的改变及其与AD阶段、临床症状和生物标志物的关系以及靶向红细胞的治疗进行综述。研究发现,AD患者的红细胞数量、形态、物理特性等发生明显改变,并与认知功能、AD生物标志物和脑结构等改变相关,可预测AD风险、识别AD发生和评价疾病程度。针对性进行饮食补充可预防AD发生并改善患者的认知功能。本综述呈现了红细胞变化在AD诊断和治疗中的进展,以期AD的早诊早治带来新思路。

【关键词】阿尔茨海默病 红细胞 认知功能 生物标志物 脑结构 治疗

【中图分类号】R749.16

【文献标识码】A

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【Abstract】Alzheimer disease (AD) is the most common type of cognitive impairment, but its current diagnostic methods have limitations. Increasing studies have shown that the erythrocytes are abnormal in AD patients at different stages. Therefore, this article reviews the changes of erythrocytes and their relationships with disease stage, clinical symptoms, and biomarkers of AD and red blood cell – targeted therapies. Studies have indicated that AD patients have significant changes in the quantity, morphology, and physical characteristics of erythrocytes, which are related to cognitive level, AD biomarkers, and brain structural changes. These changes can predict AD risk, identify AD occurrence, and evaluate disease severity. Dietary supplementation by targeting erythrocytes may prevent AD occurrence and improve the cognitive function of patients. This review presents the progress of erythrocyte changes in the diagnosis and treatment of AD, aiming to bring new perspectives to the early diagnosis and treatment of AD.

【Keywords】Alzheimer disease Erythrocytes Cognitive function Biomarkers Brain structural Therapy

doi:10.3969/j.issn.1002-0152.2025.07.007

[☆] 国家自然科学基金面上项目(编号:81970992);首都卫生发展科研专项(首发)(编号:2022-2-2048);中国健康衰老与痴呆社区队列研究项目(编号:2022ZD0211600);脑疾病和神经调控的力生物材料学研究(编号:T2488101);北京市重大疑难疾病阿尔茨海默病中西医协同攻关项目(编号:2023BJSZDYNJBXTGG-018);首都临床特色应用研究(编号:Z121107001012161);北京市自然科学基金面上项目(编号:7082032);北京市教育委员会科技发展计划重点项目(编号:KZ201610025030);北京市中医药科技发展资金项目(编号:JJ2018-48);科技创新2030-脑科学与类脑研究重大项目(编号:2022ZD0213600)

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阿尔茨海默病(Alzheimer disease, AD)是最常见的老年期认知障碍性疾病,β淀粉样蛋白(β amyloid protein, Aβ)和过度磷酸化的tau(phosphorylated tau, P-tau)是诊断AD的生物标志物,脑脊液检测和正电子发射计算机断层扫描是目前确定生物标志物的金标准,但其有创和昂贵,临床难以普及,而无创和经济的血液生物标志物诊断AD仍存挑战^[1]。红细胞是血液系统重要的组成部分,是脑内氧代谢的主要场所。较多研究表明,AD患者血液中的红细胞在轻度认知障碍(mild cognitive impairment, MCI)、甚至临床前期即出现数量及形态异常^[2]。本文对AD患者的红细胞改变及其与疾病阶段、临床症状和生物标志物等关系进行综述,以期通过检测红细胞变化为早期预测、识别和干预AD提供新的切入点和依据。

1 AD患者红细胞的改变

1.1 红细胞数量的改变 AD患者的红细胞比容明显降低^[3-4],红细胞数量显著减少^[4-5],且在重度AD痴呆患者中减少得更突出^[3]。

1.2 红细胞形态的改变 AD患者的双凹形红细胞体积较健康者增加约1.5倍^[6-7];红细胞形态发生变化,部分呈月牙状(33%)和针状(5%~6%)^[7]。MCI患者红细胞膜的流动性降低^[8],AD痴呆患者红细胞膜的硬度和黏度增加,弹性及变形性降低,表面粗糙度降低^[6-7,9]。

以上红细胞的体积、形态及膜特性决定其变形性,影响其通过微循环将氧气运输至组织的能力,导致AD患者脑内氧供不足、A β 清除减少,最终加速AD进展。

1.3 红细胞组分的改变

1.3.1 AD病理蛋白

1.3.1.1 A β AD患者红细胞膜与A β 的结合率为98%,健康者仅为38%^[10]。MCI和AD痴呆患者红细胞内A β 42水平明显高于健康者,且与认知功能下降有关^[11]。基础研究表明,随着AD进展,A β 在红细胞中蓄积增加^[12]。

1.3.1.2 tau AD患者与健康者红细胞中总tau水平的研究结果存在分歧,有研究发现AD患者总tau水平较健康者显著降低,但校正年龄后差异消失^[13];有研究发现两者无明显差异^[14]。

1.3.1.3 α -突触核蛋白 AD、帕金森病及路易体痴呆患者的红细胞 α -突触核蛋白水平均显著低于健康者^[13-14]。因此,红细胞 α -突触核蛋白水平虽可区分AD患者与健康者,但不具有特异性。

1.3.1.4 病理蛋白聚集体 所有AD患者的红细胞膜中均存在AD病理蛋白聚集体,而仅在80~89岁AD患者的红细胞膜上观察到纤维聚集体转化为晶体结构,平均长度为(9.9 $\pm$ 4.4)nm,排列整齐^[15],检测脑脊液显示A β 阳性(A+)、tau阳性(T+)和神经变性阳性(N+),既往对A β 生成过程中原纤维-晶体相互转化的研究提示,该晶体结构可能与A β 终末形态有关^[16],但其诊断AD的准确性仍需深入研究。

AD病理蛋白可形成异质复合物^[17]。AD患者红细胞内异质复合物水平在疾病早期即降低,可区分AD患者和健康者,其中 α -突触核蛋白/总tau的鉴别性能较好(受试者操作特征曲线下面积=0.76)^[13-14],具有成为诊断AD生物标志物的潜力。

1.3.2 红细胞膜成分

1.3.2.1 脂肪酸 MCI和AD痴呆患者红细胞膜的脂质谱发

生改变,与认知功能下降有关,并可一定程度区分健康者、MCI和AD痴呆患者^[18]。

细胞膜 ω -3指数降低与脑内A β 增加相关^[19],可预测非痴呆人群认知功能显著下降,最佳临界值为5.3%(敏感性为51.65%,特异性为69.37%),提示 ω -3指数<5%的人群发生认知障碍的风险升高,可能是通过补充多不饱和脂肪酸(polyunsaturated fatty acids, PUFAs)预防认知障碍的理想人群^[20]。

脂肪酸在红细胞膜中稳定存在3个月^[21],反映长期营养状态,因此,其变化具有作为AD生物标志物的潜能,对识别临床前期AD具有一定的意义。

1.3.2.2 磷脂 与健康者相比,AD患者红细胞膜中鞘磷脂含量显著增加^[22],各甘油磷脂与鞘磷脂的比值显著降低^[23]。

磷脂酰肌醇是一种磷脂衍生物,可催化生成磷脂酰肌醇磷酸盐(phosphatidylinositol-phosphates, PIPs)家族,在脑的突触修饰和神经传递中发挥关键作用^[24]。MCI和AD患者红细胞膜中PIPs水平显著降低。PIPs综合指标区分MCI和AD痴呆的敏感性分别为83%和93%,特异性分别为90%和88%^[25]。

AD患者红细胞膜中磷脂水平降低,可能导致细胞氧化程度增加及抗氧化能力降低,影响红细胞功能,加速AD进展。因此,红细胞膜的磷脂变化对AD进展具有提示作用。

1.3.2.3 蛋白 AD患者红细胞膜中热休克蛋白90水平显著升高,Band 3蛋白水平显著降低^[26],这可能是导致红细胞变形性、弹性和稳定性降低的原因。早发性和晚发性AD患者红细胞膜中胰岛素受体和葡萄糖转运蛋白-1水平均显著高于健康者,晚发性AD患者红细胞膜中与高密度脂蛋白胆固醇形成及转运相关的三磷酸腺苷结合盒转运蛋白A1、与免疫相关的多药耐药转运体三磷酸腺苷结合盒转运蛋白G2水平也显著升高^[27],提示红细胞膜中蛋白水平可反映AD引起的代谢和免疫能力改变。

AD患者红细胞膜中的蛋白分子内部在吸收热后形成展开结构时得到的热焓(ΔH)、膜内血红蛋白的剩余热焓(C_p^{ex})和热转变的中点温度(T_m)^[28]均高于健康者,提示红细胞膜的蛋白构象和/或结合状态发生改变,导致热稳定性升高^[29],但其诊断AD的特异性和准确性仍需深入研究。

1.3.3 血红蛋白 血红蛋白水平降低是认知功能下降的独立危险因素^[30],AD患者的血红蛋白水平显著低于健康者^[3-4,31],且与额叶皮质、负责语言和记忆功能的外侧颞叶和内侧顶叶皮质萎缩有关^[32],而血红蛋白水平每升高1个标准差,AD风险降低5%^[4]。AD患者血液中血红蛋白水平降低

与硫胺素二磷酸(thiamine diphosphate, TDP)缺乏显著相关,而与叶酸和维生素B12水平无关。TDP是血红蛋白合成中琥珀酰辅酶A生成的关键辅酶(参与血红素合成),提示AD患者血液中TDP水平降低可导致血红素合成受阻、血红蛋白生成减少,从而引发贫血^[5]。

贫血增加痴呆的发生风险^[4, 33],导致认知功能下降^[34-36]。一项前瞻性研究表明,贫血患者全因痴呆风险较无贫血者增加56%,在校正高血压和糖尿病后,二者的关联仍然存在。孟德尔随机化分析发现,血红蛋白水平对AD具有显著影响($P_{IVW} = 0.03$),两者存在因果关系。血红蛋白降低与部分脑区(如眶额叶皮质、苍白球)体积缩小及白质完整性下降相关。以上结果提示,血红蛋白降低可因脑供氧和氧合不足而引起缺氧,进而通过能量代谢障碍、氧化应激和神经炎症损伤神经元,或通过损伤血管而减少脑灌注、损伤脑结构,二者协同加速神经变性^[4]。虽然贫血患者可通过提高血流量代偿性增加脑氧含量,但此代偿作用仅存在于脑灰质,而负责神经传导的脑白质仍处于缺氧状态,仍可导致认知功能下降^[37]。

也有研究发现,血红蛋白水平与AD等痴呆存在U型关联,低于14.2 g/dL或高于17.8 g/dL均显著增加痴呆风险,具体机制有待明确^[4, 38]。

综上,AD患者因营养不良(如TDP缺乏)导致血红蛋白合成受阻,引发贫血,进而降低脑组织供氧能力,促进A β 沉积及神经元变性。纠正健康人群及AD患者的营养不良及低血红蛋白水平可降低AD等痴呆的发生风险、提高认知水平。

1.3.4 红细胞代谢物 采用液相色谱-质谱法确定了12种与痴呆相关的红细胞代谢物^[39]。与健康者相比,MCI患者的麦角硫因水平显著降低^[40];AD等痴呆患者12种代谢物水平均显著降低,以三甲基色氨酸和三甲基酪氨酸降低得最显著,氧化型辅酶II、三甲基组氨酸、麦角硫因和S-甲基-麦角硫因区分痴呆患者和健康者的准确性较高^[39]。尸检研究发现,AD患者的多种鞘脂及其相关化合物水平较健康者显著降低,3-硫酸牛磺脱氧胆酸和多种氨基酸代谢产物水平显著升高^[41]。

红细胞数量多、寿命较长、且具有代谢活性,其代谢组学变化有望作为AD生物标志物并解释患者代谢失调的机制。

1.4 红细胞内信号通路的改变 与健康者相比,AD患者与红细胞膜结合的酪氨酸蛋白激酶数量显著增加、蛋白酪氨酸磷酸酶活性显著降低,Band 3蛋白的酪氨酸磷酸化水平

显著升高;采用A β 42处理健康者的红细胞也观察到上述变化^[42]。上述结果提示,AD患者血中A β 可能引起酪氨酸蛋白激酶数量增加,抑制蛋白酪氨酸磷酸酶的活性,提高Band 3蛋白磷酸化水平,降低膜骨架的稳定性,从而削弱红细胞的功能。

2 靶向红细胞的AD治疗进展

AD患者红细胞膜或胞内组分发生改变,靶向上述变化的AD治疗进展如下。

2.1 补充 ω -3 PUFAs ω -3 PUFAs主要通过饮食补充,具有降低胆固醇、抗炎和神经保护作用^[43]。

长期补充 ω -3 PUFAs[尤其是二十二碳六烯酸(docosahexaenoic acids, DHA)]可降低AD发生风险并延缓认知功能下降^[44]。红细胞膜中DHA水平高的健康人群AD的发生率更低,DHA比例>6.1%较<3.8%的健康者发生AD的风险降低49%^[45],且载脂蛋白E ϵ 4携带者低于非携带者^[45],表明补充 ω -3 PUFAs可预防AD发生,且载脂蛋白E ϵ 4携带者获益更多。

单纯口服补充DHA或联合补充花生四烯酸后,MCI患者的海马萎缩速度减慢,认知功能显著改善^[46]。补充 ω -3 PUFAs改善以记忆障碍为主诉和症状较轻的AD患者的认知功能,女性获益显著高于男性^[47]。B族维生素水平高的患者认知改善得更明显^[48]。因此,应注意检测同型半胱氨酸以评估B族维生素水平,采取个性化原则补充 ω -3 PUFAs可更好地改善认知功能。在结、直肠癌肝转移的患者中,静脉注射 ω -3 PUFAs可使红细胞膜中二十碳五烯酸水平持续升高5~12 d^[49],尚需对AD患者进行研究。

综上,单纯补充 ω -3 PUFAs或联合补充其他脂肪酸可一定程度预防AD发生或改善AD患者的认知功能,但对不同阶段AD患者的给药途径、理想剂量、疗效及其他因素的影响有待深入研究。

2.2 补充虾青素 虾青素是一种酮式类胡萝卜素,其对红细胞膜具有降低氧化应激反应、减轻炎症、诱导自噬和清除A β 等作用^[50]。

基础实验表明,给小鼠补充虾青素可减轻A β 诱导的红细胞膜氧化应激反应^[51]。临床研究显示,老年健康者红细胞中A β 42和A β 40水平均显著高于年轻人,补充虾青素后两组人群的A β 42和A β 40水平均显著降低^[52]。以上研究提示,虾青素降低红细胞中A β 水平,降低红细胞膜的氧化应激反应,进而提高红细胞对氧化损伤的抵抗力,可能成为预防AD的手段。

综上,大量基础实验和临床研究表明,红细胞的数量、形态、物理特性、细胞膜及胞内组分在 MCI 及 AD 痴呆患者中发生明显改变,与认知水平、体液生物标志物、脑内病理蛋白沉积和脑结构的变化相关,并可一定程度预测 AD 的发生风险、识别 MCI 及 AD 痴呆患者及评价认知障碍的严重程度。因此,红细胞可能具有成为新的 AD 生物标志物的潜能。针对红细胞膜及胞内变化的组分进行针对性饮食补充可一定程度预防 MCI 及 AD 痴呆的发生,并改善患者的认知功能。未来仍需在多中心、大样本的纵向队列中通过标准化检测技术和实验模型进行分层分析,明确红细胞改变与 AD 发生和发展的相关性及其机制,评估其早期识别和诊断 AD 的准确性和敏感性,探究通过改善红细胞治疗 AD 的前景,为 AD 的早诊早治提供新的思路 and 方向。

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(收稿日期:2024-12-26 录用日期:2025-07-27)

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论文描述统计检验结果时,应注意以下问题:

1. P 值指零假设成立的前提下,出现目前样本数据对应的统计量(如 t 值、 F 值、 χ^2 值等)乃至更极端数值的概率。因此,描述统计检验结果时应给出统计量(如 t 值、 F 值、 χ^2 值等)和 P 值。
2. 目前统计分析软件已可以计算精确的 P 值,文中应报告精确的 P 值。当 P 值过小,统计软件输出结果 P 值为“0.000”,是因为目前小数位数不足以显示有效数字,在文中描述结果应写为“ $P<0.001$ ”或“ $P<0.01$ ”。
3. 当 $P<0.05$ 时,其统计学含义为可以拒绝零假设,因此可以得到“组间差异有统计学意义(significant difference)”的结论,而不译作“有显著差异”。更不能因为 P 值较小,如 $P<0.01$,而称“差异非常显著”。