•专家论坛•

血液载脂蛋白作为神经退行性疾病潜在生物标志物的研究

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摘要: 神经退行性疾病 (neurodegenerative diseases, ND) 主要包括阿尔茨海默病、帕金森病、多发性硬化症、肌萎缩侧索硬化症和共济失调等疾病。神经退行性疾病患者人数不断增长, 但能早期诊治的患者比例不到30%, 并且ND的发病原因目前仍不明确。为了尽早对疾病进行干预, 研究者们致力于寻找便于早期诊断ND的生物标志物。其中, 脑脊液 (cerebrospinal fluid, CSF) 真实反映了脑细胞外空间的组成, 可能是评价ND的最灵敏的生物标记物。但取脑脊液的方法比较复杂, 在治疗ND患者的初级护理或老年医疗机构中不是一个普遍的方法。影像学检查价格高昂, 难以在社区人群中普及。而外周血采集方便、创伤小和费用低, 是具有潜力的早期筛查和随诊手段。血液中有多种成分可供分析研究, 本文就ND患者血液中载脂蛋白的变化作为标志物的研究进展进行综述。

关键词: 神经退行性疾病; 阿尔茨海默病; 帕金森病; 多发性硬化症; 肌萎缩侧索硬化症; 共济失调; 血液生物标志物; 载脂蛋白

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Study on blood apolipoprotein as a potential biomarker of neurodegenerative diseases

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Abstract: Neurodegenerative diseases (ND) mainly include Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, ataxia, and other diseases. The number of patients with ND is increasing, but the proportion of patients who can be diagnosed and treated early is less than 30% and the cause of ND is still unclear. In order to intervene in the disease as early as possible, researchers are committed to finding biomarkers that facilitate the early diagnosis of ND. Among them, cerebrospinal fluid (CSF) closely reflects the composition of the extracellular space of the brain, and may be the most sensitive biomarker for evaluating ND. However, the method of taking cerebrospinal fluid is more complicated, and it is not a common method in primary care or elderly medical institutions for the treatment of ND patients. Imaging examinations are expensive and difficult to spread among the community. The peripheral blood collection is convenient and less traumatic, which is a potential early screening and follow-up method. There are many components in the blood for analysis and research. This article reviews the research progress of the changes of apolipoprotein in the blood of ND patients as markers.

Key words: neurodegenerative disease; Alzheimer's disease; Parkinson's disease; multiple sclerosis; amyotrophic lateral sclerosis; ataxia; blood biomarker; apolipoprotein

随着人类寿命的增加以及人口老龄化程度的加深, 神经退行性疾病发病率逐年升高, 严重威胁着人类的健康。目前, 神经退行性疾病存在发病机制不清、有效治疗手段少、发病进程不可逆等特征。如果能对神经退行性疾病的早期阶段进行诊断与干预, 将对延缓神经退行性疾病的进展提供重要的干预机会。因此,

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利用血液生物标志物对神经退行性疾病实现早期诊断具有重要意义, 同时血液生物标志物也是疾病筛查和进展监测的最简便和最无创的方式。

已有很多神经退行性疾病血液生物标志物的文章发表, 涉及到蛋白、核酸和脂质等[1-6]。目前, 神经退行性疾病已提出的发病学说除了特定蛋白的变异如Aβ沉积、Tau蛋白过度磷酸化和α-突触核蛋白异常等, 还包括脂蛋白代谢、炎症、氧化应激和补体系统的改变等。其中脂质代谢紊乱可能会导致氧化应激、能量代谢失衡和神经炎症等。血液脂质与载脂蛋白在神经退行性疾病中的变化也成为了当今研究神经退行性疾病发病机制的一大热点方向。

脂蛋白 (lipoprotein) 是在血液中运送水不溶性脂类的超分子组装体 (球状微粒), 由富含固醇酯、甘油三酯的疏水性内核和由载脂蛋白、单层磷脂、胆固醇等组成的外壳构成 (如图1所示)。脂蛋白对于细胞外脂质的包装、储存、运输和代谢起着重要作用。脂蛋白代谢异常与心血管疾病、代谢性疾病以及神经系统疾病的发生发展密切相关。而载脂蛋白 (apolipoprotein, Apo) 是一组与脂蛋白代谢有关的蛋白质, 其可能参与神经退行性疾病病理的过程, 有可能成为ND患者血液潜在的生物标志物。

载脂蛋白Apo家族可分为ApoA、B、C、D、E、F、H、J、L和M等亚家族成员。高密度脂蛋白 (high-density lipoprotein, HDL) 中含有的载脂蛋白有ApoA、C、D、E、F、H、J、L和M等, 而低密度脂蛋白 (low-density lipoprotein, LDL) 中含有的载脂蛋白主要是ApoB和C。脂质代谢异常在心脑血管疾病中的研究已经相对成熟。HDL能够逆转运胆固醇, 是一种抗动脉粥样硬化的血浆脂蛋白, 是冠心病的保护因子; 而LDL是一种运载胆固醇进入外周组织细胞的脂蛋白颗粒, 当低密度脂蛋白尤其是氧化修饰的低密度脂蛋白 (OX-LDL) 过量时, 它携带的胆固醇便积存在动脉壁上, 容易引起动脉硬化, 造成心脑血管疾病。近年来脂蛋白代谢在神经退行性疾病中的作用, 也有越来越多的报道值得研究者进一步去探索。本文主要讨论与脂蛋白代谢密切相关的载脂蛋白在神经退行性疾病中的变化, 探讨载脂蛋白作为神经退行性疾病血液生物标志物的可能性。本文回顾了ND患者的血浆和血清载脂蛋白的研究现状。在这篇综述中, 主要总结了ApoA、B、E和J等载脂蛋白在ND患者血液中的变化, 以寻找最具潜力的血液生物标志物。

1 阿尔茨海默病 (Alzheimer's disease, AD)

AD是老年痴呆的最常见病因, 以功能进行性受损为特征的神经退行性疾病。主要引起患者的记忆、

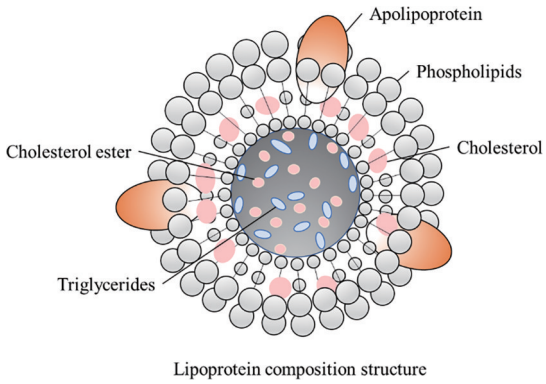

Figure 1 Lipoprotein composition

语言、视觉、计算和注意力障碍, 是最常见的痴呆类型。研究证实, 中年时总胆固醇水平升高是AD及其他类型痴呆的危险因素之一[7]。而载脂蛋白是一组与胆固醇和脂质代谢有关的蛋白质, 其可能参与神经退行性疾病的病理过程[8]。

载脂蛋白A-I (ApoA-I) 是HDL的主要组成部分, 约占总HDL蛋白的70%[9,10]。ApoA-I的功能主要涉及与细胞受体的相互作用, 激活卵磷脂/胆固醇酰基转移酶, 并赋予HDL多种抗动脉粥样硬化活性, ApoA-I还可与Aβ结合并在体外防止其聚集和毒性[11]。据报道, ApoA-I与转甲状腺素蛋白和补体蛋白结合是评估认知功能衰退早期的潜在血液生物标志物[12], 或许ApoA-I也可成为AD血液标志物的候选物。针对ApoA-I的多项研究结果一致性显示, 按照年龄和性别相匹配的原则, 与非AD的对照组相比, AD患者血浆/血清中ApoA-I蛋白的表达水平较对照组明显降低[12-24], 提示这种改变可能与AD的风险有关[8]。有文献[23]明确指出血清ApoA-I水平下降可能与认知能力下降和脑萎缩有关。另外, 早有报道发现日本迟发性非家族性AD患者血浆ApoA-I明显降低[25]。

除了研究ApoA-I, 载脂蛋白ApoA的其他亚型也受到关注, 包括载脂蛋白ApoA-II与ApoA-IV。有一项研究检测了44例散发性迟发性阿尔茨海默病患者的血清脂蛋白和载脂蛋白谱。在AD患者组中, ApoA-I和ApoA-II水平均降低, 且ApoA-I/ApoA-II的比率增加, 说明ApoA-II下降更明显。而且, 在患者组中ApoA-II水平成比例下降, 说明老年痴呆症患者的血清ApoA-II可能与AD的病理过程有关[13]。

ApoA-IV主要发挥抗氧化、预防动脉粥样硬化的作用。一项研究采用二维差异凝胶电泳结合质谱, 对轻度AD患者和非AD的对照组的血浆样品进行分析。结果显示在轻度AD患者中, ApoA-I下调, ApoA-IV上调[19]。在AD患者血清中ApoA-IV水平的上调与先前

的另一项研究[26]结果相一致。这些研究结果与本课题组在前期AD血清生物标志物的研究中得到的结果相反, 本课题组的研究结果显示AD患者血清中的ApoA-IV下降, 这与另一项研究结果相互验证。该项研究证实AD患者血清中的ApoA-IV及其mRNA水平呈下降趋势, 且ApoA-IV及其mRNA的水平与AD的进展呈负相关, 即AD进展越严重, ApoA-IV及其mRNA水平越低[17]。虽然有关ApoA-IV的研究结果存在矛盾性, 但ApoA-IV在AD的发生发展中的潜在作用, 已引起研究者的关注。

载脂蛋白E (ApoE) 是HDL的关键结构和功能糖蛋白成分, 但与载脂蛋白ApoA-I相比, 其在HDL颗粒中的含量要低得多[27]。ApoE可在多种组织和细胞中合成, 包括肝脏、内分泌组织、中枢神经系统和巨噬细胞等。自从1993年发现载脂蛋白E的ε4等位基因是迟发性AD的最强的已知遗传危险因素后, 人们开始逐渐意识到脂蛋白在中枢神经系统中的作用[28-30]。作为脑内最常见的脂蛋白, ApoE可能是AD的生物标志物候选物。有研究使用两种不同的检测方法即液质联用和荧光激活细胞分选术, 检测AD患者血清ApoE水平的差异。这两种方法得到的结果相当一致, 显示AD患者血清ApoE水平较非AD的对照组显著下降[31], 这与另一项研究结果相一致[15]。但也有研究报道在AD进程中, 血清ApoE水平没有显著变化[18], 甚至报道ApoE在AD患者血液中升高[21,32]。ApoE结果的差异性可能是因为ApoE存在不同基因型的原因[33,34]。已有研究报道ApoE4等位基因 (ε4) 的存在会导致AD中ApoE的水平降低, 而ApoE3等位基因 (ε3/ε3) 的存在会导致AD中ApoE的水平升高[35]。

ApoE主要存在3种亚型, 即载脂蛋白E2、E3和E4, 其中最常见的是ApoE3[36]。ApoE含3种等位基因, 即ε2、ε3和ε4, 据报道ε4才是AD最重要的遗传危险因子[37,38]。普通人群中的ε4等位基因频率为15%, 但在AD患者中为40%。具有1个ε4等位基因的人患AD的可能性是没有任何ε4等位基因的人的3～4倍, 具有2个ε4等位基因的人患AD的风险是没有任何ε4等位基因的人的12倍[28], 而且ε4等位基因携带者AD发作的年龄比ε3等位基因携带者早[39]; 另一方面, 与ε4等位基因携带者相比, ε2等位基因的携带者患AD的风险相对较低[40,41]。除此之外, ε4等位基因还与其他几种神经退行性疾病 [例如帕金森病 (Parkinson's disease, PD)[42]和多发性硬化症 (multiple sclerosis, MS)[43]] 的加速发展和进展有关。在考虑ApoE基因型的基础上采用等电聚焦和免疫印迹法检测ApoE表型, 结果显示与非AD的对照组相比, AD组ApoE4等位基因 (ε4) 的频率显著增高, ApoE2等位基因 (ε2) 的频率较对照组低[15,44-46]。因此, 脱离ApoE的基因型, 简单检测ApoE的血液含量对于AD的诊断标志物而言无重大意义, ApoE作为一种疾病血液生物标志物还需进一步的研究。

载脂蛋白J (ApoJ) 也称为簇蛋白和补体相关蛋白SP-40,40, 是一种反平行二硫键连接的异二聚糖蛋白。ApoJ的独特结构一方面可以与多种疏水分子结合, 另一方面可以与特定的细胞表面受体结合[47]。ApoJ存在于血浆中, 与HDL相关, 是HDL的组成成分[48]。据报道, ApoJ不仅能携带Aβ跨血脑屏障[49,50], 还能抑制Aβ在大脑中的沉积[51,52], 其遗传变异是散发性AD的危险因素[53]。在澳大利亚的一项老年人相关研究中发现, AD患者血液的ApoJ水平较非AD的对照组高[54], 这与另一项研究结果一致[55]。

载脂蛋白B (ApoB) 是低密度脂蛋白复合物 (LDL-C) 的主要组成成分。多项研究证实与非AD的对照组相比, AD患者的ApoB和LDL-C升高[20,24,56,57]。但是在一项日本迟发性非家族性AD患者的研究中, 发现表型为ApoE4/3的迟发型AD患者与同表型非AD的对照组相比, 血浆ApoB含量有下降趋势, 而表型为ApoE3/3的迟发型AD患者与同表型非AD的对照组相比, 血浆ApoB含量上升[25]。提示载脂蛋白ApoE的表型不同可能影响ApoB的血浆水平, 因此ApoB也有可能与其他载脂蛋白共同参与AD的诊断。

2　帕金森病 (PD)

PD也称为震颤麻痹, 是中老年人常见的神经系统变性疾病。其特征是运动迟缓、僵硬、静息性震颤和姿势不稳[58]。在PD的早期阶段, 对个体的进展状态与临床干预的效果进行评估, 并预测疾病的预后对患者具有重大意义。最近, 一些研究发现载脂蛋白如ApoA-I、ApoJ等在PD的起始、进展和预后中起着重要作用[59-63]。

ApoA-I与抑制炎症反应、保护血管内皮和调节免疫反应密切相关[11]。ApoA-I已被证实与多种神经退行性疾病有关, 最近ApoA-I被认为是PD发病年龄和运动受损严重程度的相关因素。在一项涵盖1 000多名患者的荟萃分析中证实, 低水平的血浆ApoA-I与PD发病年龄越早和运动受损严重程度越重显著相关[64]。为了更好地确定ApoA-I水平对PD发病年龄的影响, 在另一项研究中他们进行了Cox比例风险分析。采用三分位数法, 将研究人群根据ApoA-I的浓度分成3组即低 (0.15～0.26)、中 (0.27～0.37) 和高 (0.38～0.71), 这样不仅能反映数据的分布特征, 还能对多组数据进行分析比较。结果证实了ApoA-I浓度越低,

PD的发病年龄越早; 年龄相同时, ApoA-I浓度每三分位数增加 (从低三分位数到中三分位数到高三分位数), 可使PD发生风险降低26%[65]。在PD患者血液中, 与非PD的对照组相比, 血清ApoA-I表达水平下降, 尤其是在PD患者的早期[66-68]。在此基础上有研究者提出, 如果能够让血浆中的ApoA-I水平升高, 可能会降低PD的发生率。如他汀类药物与健康的生活方式均能改善ApoA-I的水平, 降低PD的发生率[65]。这些研究表明, ApoA-I或可作为PD中的保护性生物标志物和医学靶标[69]。

ApoJ是一种高度保守的异二聚糖蛋白, 参与许多生物学的过程, 例如脂质转运、细胞黏附、补体介导细胞裂解和细胞凋亡[70]。研究报道在许多神经退行性疾病, 如PD、路易体痴呆和AD中, ApoJ基因表达上调[71]。最近另外两项研究也发现了相同的现象, 即PD患者血浆中ApoJ水平高于非PD的对照组[72-74]。

3 多发性硬化症 (MS)

MS是一种慢性免疫性中枢神经系统疾病。早期症状表现为感觉障碍、虚弱无力、步态失调、躯体瘫痪等[75]。

血清ApoA-I被认为是一种免疫调节剂, 在某些自身免疫性疾病中可以抑制活化T细胞产生的促炎性细胞因子[76]。但是, MS患者血清ApoA-I水平如何变化尚不清楚。在一项研究中研究者们收集了包括41位非MS的对照组、76位复发缓解型MS受试者和37位进行性MS受试者。在5年的随访中获得了神经学检查、脑磁共振成像和血样。测得的胆固醇生物标志物包括血浆总胆固醇 (TG)、HDL-C、LDL-C和载脂蛋白ApoA-I等, 得出的结论是MS患者表现出较低的血清ApoA-I水平和较高的神经丝蛋白水平, 且较低的血清ApoA-I与较高的神经丝蛋白水平相关。通过检测神经丝蛋白水平, 说明较低的血清ApoA-I水平可能与更大的神经轴突损伤相关[77], ApoA-I在MS患者血液中显著降低这一结论与其他研究结果相一致[76,78,79]。不同的是, 也有研究报道MS患者血清中的ApoA-I水平与非MS的对照组相比无明显差异[80], 甚至升高[81,82]。

4 肌萎缩侧索硬化症 (amyotrophic lateral sclerosis, ALS)

ALS是一种致命的神经退行性疾病, 是由于运动皮层脑干和脊髓中运动神经元的变性导致[83], 其特征是进行性肌肉麻痹。ALS患者经常出现能量代谢异常, 包括葡萄糖和脂质代谢[84,85]。鉴于其高能量需求, 运动神经元可能比其他类型细胞对能量缺乏更为敏感[86]。能量代谢尤其是脂质代谢失衡可能是ALS运动神经元丢失的危险因素[87]。

ApoB升高与氧化应激增加有关, 而与ApoB相比, ApoA-I具有抗氧化、抗炎、抑制血栓形成和刺激一氧化氮生成并防止血管内皮损伤的作用[88]。ApoB/ApoA-I主要反映了所有潜在的致动脉粥样硬化和潜在的抗动脉粥样硬化脂蛋白颗粒之间的平衡, 即较高水平的ApoB和ApoB/ApoA-I可能会导致动脉壁脂质堆积增加, 动脉粥样硬化, 从而影响神经系统的能量供应[89]。在一项脂质和载脂蛋白代谢的血液生物标志物与ALS未来风险关系的研究中发现, 较低的ApoA-I和HDL-C, 较高的ApoB、LDL-C、ApoB/ApoA-I和LDL-C/HDL-C都与ALS的未来风险相关[88]。

5 共济失调

共济失调是一类遗传病, 该病是由于小脑及其传入和传出连接的功能障碍导致的平衡和协调障碍[90]。常表现为走路不稳、动作不灵、握物无力以及言语不清。共济失调主要包括了弗里德赖希共济失调 (Friedreich ataxia, FA) 和脊髓小脑共济失调 (spinocerebellar ataxia, SCA)[91]。

FA是一种常染色体隐性遗传性神经退行性疾病, 其主要原因是线粒体蛋白frataxin的表达降低[92-94]。FA的患病率估计为五万分之一, 这是最常见的遗传性共济失调[95]。矛盾的是, FA致死的原因最常见的是心肌病和心力衰竭, 而不是神经系统的影响[96-99]。普通人群中HDL和ApoA-I水平的降低与缺血性心肌病和心力衰竭的死亡风险增加相关。一项研究使用高度特异性的稳定同位素稀释质谱法进行测定, 与非FA的对照组相比, 证实了FA患者的血清ApoA-I降低了21.6%[95]。不幸的是, FA患者中ApoA-I的水平存在冲突的数据。另一项研究表明, 在血清载脂蛋白中, 仅ApoB在男性中减少, 而其他载脂蛋白包括ApoA-I并无明显差异[100]。

SCA是包括一大批以常染色体显性遗传方式遗传的异质性神经退行性疾病。它的特征是进行性小脑共济失调, 具有动眼功能障碍、构音障碍、锥体束征、锥体束外征兆、色素性视网膜病、周围神经病变和认知障碍等其他症状[101]。脊髓小脑共济失调3型 (spinocerebellar ataxia type 3/Machado-Joseph disease, SCA3/MJD) 的发病年龄不能完全由ATXN3基因上CAG区域的大小来解释, 这暗示着可能存在遗传修饰因子。研究证实, 与具有ApoE ε3/ε3或ε3/ε4基因型的患者相比, 具有ε2/ε3基因型的患者发病更早。在这一系列患者中, ApoE2等位基因 (ε2) 的存在意味着发病年龄提早了近5年[102], 这与其他研究结果相一致[103,104]。但也有研究表明, SCA3/MJD的发病年龄与ApoE基因型无关[105]。

6　小结

神经退行性疾病是一种表现为认知及运动功能障碍进行性加重的年龄相关性疾病, 随着中国快速老龄化, ND的疾病负担越发沉重。虽然目前临床对于ND的病因及发病机制仍不明确, 但早期对ND患者进行干预, 对于患者的预后具有重要作用。血液生物标志物的不断发展与更新, 为临床上ND的早期诊断和治疗提供了有力依据。

ApoA-I作为HDL的主要组成部分, 主要是激活卵磷脂/胆固醇酰基转移酶, 并赋予HDL多种抗动脉粥样硬化活性, 广泛被认为具有神经保护作用。已有大量的文献证明在AD、PD、ALS以及MS患者血液中, ApoA-I均表现为一致性下降, 因而它可作为这几种神经退行性疾病的早期诊断的潜在血液生物标志物。但ApoA-I缺乏疾病的特异性, 还需要与其他特异性蛋白或标志物联合使用, 提高其诊断的准确性。

作为脑内最常见的脂蛋白ApoE, 它存在3种亚型, 即载脂蛋白E2、E3和E4, ApoE4是AD最重要的遗传危险因子。由于不同ApoE基因型携带者的全血ApoE的水平不同, 因此在测量血液ApoE的表达量时, 还需要结合ApoE的基因型, 不能只检测ApoE表达量, 这可能会导致结果的差异性。有一些神经退行性疾病已明确与ApoE的亚型相关, 如SCA与AD。在SCA中, ApoE2等位基因 (ε2) 的存在意味着SCA发病年龄提前; 在AD中, AD患者血液ApoE4等位基因 (ε4) 的频率显著较高, 而E2等位基因的频率较低。因此, ApoE仅作为一种ND的风险因素。

ApoJ存在于血浆中, 参与HDL的组成。ApoJ可影响胆固醇的转运, Aβ的聚集和清除。在AD与PD患者血液中, 与对照组相比, ApoJ水平均升高, 因此ApoJ可作为AD与PD早期诊断的血液生物标志物。但ApoJ也存在诊断特异性的问题, 仍需结合其他载脂蛋白或标志物, 弥补特异性不足的缺点。此外, ApoB和ApoA-IV等也有报道在不同神经退行性疾病中的变化。ApoB是LDL-C的主要组成成分, 其在神经退行性疾病中的作用似乎与ApoA-I相反。

血液生物标志物作为神经退行性疾病的早期诊断, 具有采集方便、创伤小和费用低的优势。血液载脂蛋白只是一类潜在的血液生物标志物, 已经展现出一定的应用前景。但ND病因复杂, 难以用一类蛋白作为标志物进行诊断、治疗和预后预测。如前期已报道了大量与ND相关的血清和血浆蛋白, 如与能量代谢(线粒体) 相关、炎症免疫相关和神经营养相关的蛋白, 相信通过多种蛋白的组合, 进行ND的早期诊断和治疗评价, 将取得更好的预期结果。

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