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Amyloid beta 在湿性年龄相关性黄斑变性患者中的表达及意义*

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摘要 目的:探讨 Amyloid beta(Aβ)在湿性年龄相关性黄斑变性患者中的表达及意义。**方法:**2017 年 9 月到 2019 年 5 月选择在本院诊治的湿性年龄相关性黄斑变性患者 72 例(72 眼),检测血清 Aβ 含量,调查患者的一般资料、临床特征并进行相关性分析。**结果:**在 72 例患者中,平均血清 Aβ 含量为 203.29±14.29 ng/mL,其中 Aβ 含量≥180 ng/mL 40 例。Aβ 阳性组的脉络膜厚度显著高于 Aβ 阴性组($P<0.05$)。Aβ 阳性组的患眼动脉舒张末期血流速度和收缩期峰值血流速度都显著低于 Aβ 阴性组($P<0.05$)。Aβ 阳性组的性别、年龄、眼压、血压、体重指数、病程等与 Aβ 阴性组对比差异无统计学意义($P>0.05$)。直线相关性分析显示血清 Aβ 含量与脉络膜厚度、患眼动脉舒张末期血流速度和收缩期峰值血流速度都有显著相关性($P<0.05$),其中 Aβ 含量与脉络膜厚度呈正相关($r=0.566, P=0.003$),Aβ 含量与患眼动脉舒张末期血流速度和收缩期峰值血流速度呈负相关($r=-0.673, P=0.000; r=-0.455, P=0.010$)。**结论:**Aβ 在湿性年龄相关性黄斑变性患者中多呈现高表达状况,血清 Aβ 含量与脉络膜厚度、患眼动脉舒张末期血流速度和收缩期峰值血流速度相关,从而影响患者病情的进展。

关键词:Amyloid beta; 湿性年龄相关性黄斑变性; 脉络膜厚度; 血流速度

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Expression and Significance of Amyloid Beta in Patients with Wet Age-related Macular Degeneration*

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ABSTRACT Objective: To explore the expression and significance of Amyloid beta (Aβ) in patients with wet age-related macular degeneration. **Methods:** From September 2017 to May 2019, 72 patients (72 eyes) with wet age-related macular degeneration diagnosed and treated in our hospital were selected as the research subjects, the serum Aβ content were detected, and the general information and clinical characteristics of patients were investigated and were given correlation analysis. **Results:** The average serum Aβ content were in the 72 patients were 203.29±14.29 ng/mL, of which 40 patients were Aβ content ≥ 180 ng/mL. The choroid thickness of the Aβ positive group was significantly higher than that of the Aβ negative group ($P<0.05$). The end-diastolic blood flow velocity and peak systolic blood flow velocity in the Aβ-positive group were significantly lower than those in the Aβ-negative group ($P<0.05$). There were no significant difference in gender, age, intraocular pressure, blood pressure, body mass index, and duration of disease in the Aβ-positive group compared with the Aβ-negative group ($P>0.05$). Linear correlation analysis showed significant correlations between serum Aβ content and choroid thickness, end-diastolic blood flow velocity, and peak systolic blood flow velocity of the affected ophthalmic artery ($P<0.05$). The Aβ content was positively correlated with choroid thickness ($r=0.566, P=0.003$), and the Aβ content was negatively correlated with the end-diastolic blood flow velocity and peak systolic blood flow velocity of the affected ophthalmic artery ($r=-0.673, P=0.000; r=-0.455, P=0.010$). **Conclusion:** Aβ are highly expressed in patients with wet age-related macular degeneration. Serum Aβ content are related to choroid thickness, affected end-diastolic blood flow velocity and peak systolic blood flow velocity, and thus affects the progression of patients.

Key words: Amyloid beta; Wet age-related macular degeneration; Choroid thickness; Blood flow velocity

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前言

湿性年龄相关性黄斑变性(Age-related macular degeneration, AMD)是目前中老年人主要的致盲性眼病之一,其中 65 岁以上

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人群中年龄相关性黄斑变性的患病率在 10 % 以上, 80 岁以上人群患病率在 60 % 以上, 其中约有 15 % 具有严重的中心视力损伤^[1,2]。随着我国人口老龄化进程的逐步加剧, 因年龄相关性黄斑变性所致的盲人数量逐年增加, 可严重影响患者的生存质量, 也为整个社会带来巨大的精神及经济负担^[3]。该病在临床上常伴随有黄斑区出血渗出、盘状瘢痕形成等^[4,5]。其中早期病理特点是位于视网膜下细胞外基质异常沉积, 这种沉积物被称作玻璃膜疣, 其位于视网膜色素上皮细胞(Retinal pigment epithelium, RPE)和 Bruch 膜之间^[6,7]。Amyloid beta(A β)是玻璃膜疣的主要成分之一, A β 可以刺激 RPE 细胞分泌炎症因子和血管生成因子, 这可能是玻璃膜疣参与年龄相关性黄斑变性发病的重要原因^[8-10], 但是具体的作用机制还不明确。本文具体探讨了 A β 在 AMD 患者中的表达及意义, 以明确 A β 的作用价值。

1 资料与方法

1.1 研究对象

选择 2017 年 9 月~2019 年 5 月在本院诊治的 AMD 患者 72 例(72 眼), 纳入标准: 符合 AMD 的诊断标准; 年龄 55-75 岁; 单眼发病; 患眼最佳矫正视力(best correct visual acuity, BCVA)<0.1, 无全盲; 患者知情同意本研究且得到了本院伦理委员会的批准。排除标准: 妊娠与哺乳期妇女; 临床与检测资料缺乏者; 全身感染性疾病者; 合并有其它眼病病史者。

其中男 40 例, 女 32 例; 平均年龄 68.28 ± 2.19 岁, 其中 ≥ 70 岁 30 例; 平均眼压 14.22 ± 1.45 mmHg; 平均血压 123.98 ± 4.45 mmHg; 平均体重指数 22.33 ± 2.24 kg/m²; 眼别: 右眼 34 例, 左眼

38 例; 平均病程 5.08 ± 0.42 个月。

1.2 A β 表达检测

采集所有患者的空腹外周静脉血 3-5 mL, 室温条件下待外周血自然凝固(30 min 左右)后离心 5 min(1000 rpm), 取上层血清在 -80℃ 冰箱保存。采用酶联免疫法检测血清 A β 含量, A β 含量 ≥ 180 ng/mL 表示为阳性。

1.3 临床指标检测

(1) 使用蔡司 Cirrus HD-OCT, 选用巩膜内表面最清晰的一张图像, 脉络膜厚度为 Bruch 膜到脉络膜巩膜交界的垂直距离值, 取三次的均值。(2) 选择彩色超声多普勒显像仪 (美国产 ATL HDI 型) 测量患眼动脉(ophthalmic artery, OA) 的舒张末期血流速度 (end diastolic velocity, EDV) 和收缩期峰值血流速度 (peak systolic velocity, PSV)。

1.4 统计方法

应用 SPSS 19.00, 计量数据以 ($\bar{x} \pm s$) 表示, 计数数据以 % 表示, 对比用 t 检验和 χ^2 检验, 相关性分析采用直线相关性分析, 检验水准为 $\alpha=0.05$, $P<0.05$ 有统计学意义。

2 结果

2.1 A β 含量

在 72 例患者中, 平均血清 A β 含量为 203.29 ± 14.29 ng/mL, 其中 A β 含量 ≥ 180 ng/mL 的有 40 例。

2.2 两组脉络膜厚度对比

A β 阳性组的脉络膜厚度为 (183.48 ± 15.22) cm, 显著高于 A β 阴性组 (170.91 ± 26.11) cm, 两组对比有统计学意义 ($t=2.415$, $P=0.02$, $P<0.05$)。见表 1。

表 1 两组脉络膜厚度对比 ($\bar{x} \pm s$)

Table 1 Comparison of choroid thickness between the two groups ($\bar{x} \pm s$)

Groups	n	Choroidal thickness (cm)
A β positive group	40	$183.48 \pm 15.22^*$
A β negative group	32	170.91 ± 26.11

Note: Compared to the A β negative group, $*P<0.05$.

2.3 两组视网膜血流状况对比

A β 阳性组的患眼动脉舒张末期血流速度显著低于 A β 阴性组 ($t=8.196$, $P=0.000$), A β 阳性组的收缩期峰值血流速度显著低

于 A β 阴性组 ($t=6.631$, $P=0.000$), 两对比均有统计学意义 ($P<0.05$)。见表 2。

表 2 两组患眼动脉血流状况对比 (cm/s, $\bar{x} \pm s$)

Table 2 Comparison of blood flow in the ophthalmic artery between the two groups (cm/s, $\bar{x} \pm s$)

Groups	n	End diastolic blood flow velocity	Peak systolic blood flow velocity
A β positive group	40	$3.65 \pm 0.34^*$	$3.45 \pm 0.43^*$
A β negative group	32	5.22 ± 1.04	5.22 ± 1.46

Note: Compared to the A β negative group, $*P<0.05$.

2.4 两组一般资料对比

A β 阳性组的性别、年龄、眼压、血压、体重指数、病程等与 A β 阴性组对比差异无统计学意义 ($P>0.05$)。见表 3。

2.5 相关性分析

在 72 例患者中, 直线相关性分析显示血清 A β 含量与脉

络膜厚度、患眼动脉舒张末期血流速度和收缩期峰值血流速度都有显著相关性 ($P<0.05$), 其中 A β 含量与脉络膜厚度呈正相关 ($r=0.566$, $P=0.003$), A β 含量与患眼动脉舒张末期血流速度和收缩期峰值血流速度呈负相关 ($r=-0.673$, $P=0.000$; $r=-0.455$, $P=0.010$)。见表 4。

表 3 两组一般资料对比

Table 3 Comparison of two groups of general information

Groups	n	Sex (male/ female)	Age (years)	Intra-ocular tension (mmHg)	BMI (kg/m ²)	Course of course (months)	Blood pressure (mmHg)
A β positive group	40	22/18	68.33 $\pm$ 1.48	14.14 $\pm$ 1.49	22.19 $\pm$ 1.45	5.09 $\pm$ 0.32	124.09 $\pm$ 5.10
A β negative group	32	18/14	68.14 $\pm$ 1.22	14.32 $\pm$ 1.24	22.65 $\pm$ 2.14	5.07 $\pm$ 0.28	123.00 $\pm$ 4.14

表 4 湿性年龄相关性黄斑变性患者血清 A β 含量与临床指标的相关性(n=72)Table 4 Correlation between serum A β content and clinical indicators in patients with wet age-related macular degeneration (n=72)

Index	Choroidal thickness	Ophthalmic artery	
		End diastolic blood flow velocity	Peak systolic blood flow velocity
r	0.566	-0.673	-0.455
P	0.003	0.000	0.010

3 讨论

AMD 是一种黄斑细胞变性、死亡的进展性眼病^[1]。该病可损害视网膜微循环,影响视网膜的血流状况^[2]。随着基础研究的深入, A β 成为了 AMD 领域研究的热点,不仅仅在 AMD 中存在,同时在神经退行性疾病阿尔兹海默病大脑中沉积^[3]。A β 在视网膜中主要以两种形式存在, A β 1-40 和 A β 1-42, A β 1-42 较 A β 1-40 毒性更大^[4]。特别是在老年人视网膜中, A β 会介导炎症反应及诱导血管生成因子, A β 1-40 刺激 RPE 细胞, 会导致 IL-1 β 、IL-6、IL-8、IL-18、IL-33、TNF- α 表达上调^[5,16]。还有研究发现 A β 1-40 刺激人视网膜细胞后, 会造成血管生成因子 VEGF 表达上调^[17]。A β 1-42 可以增加视网膜细胞线粒体膜电位,促进活性氧的生成^[18]。本研究显示在 72 例患者中,平均血清 A β 含量为 203.29 $\pm$ 14.29 ng/mL,其中 A β 含量 $\geq$ 180 ng/mL 40 例; A β 阳性组的性别、年龄、眼压、血压、体重指数、病程等与 A β 阴性组无差异,表明 AMD 患者可伴随有血清 A β 的释放。

已有研究认为 AMD 的发病机制主要为血 - 视网膜屏障破坏而引起液体积聚,导致黄斑区视网膜增厚,从而引起黄斑变性^[19]。视网膜缺血和缺氧被认为是湿性年龄相关性黄斑变性的主要刺激因素,而在高眼压的作用下视网膜缺血情况会加剧,形成恶性循环^[20,21]。AMD 患者的视网膜微循环处于一种低灌注、高阻力;黄斑中心凹无视网膜毛细血管,其营养来自脉络膜血管,内层视网膜由中央动脉供应^[22,23]。本研究显示 A β 阳性组的脉络膜厚度显著高于 A β 阴性组; A β 阳性组的患眼动脉舒张末期血流速度和收缩期峰值血流速度都显著低于 A β 阴性组。从机制上分析, AMD 患者的玻璃膜疣成分 A β 可以激活 NLRP3 导致 Caspase-1 激活、IL-18 释放,引起视网膜色素上皮细胞萎缩,进而引起视网膜病变的形成,导致干性年龄相关性黄斑变性的发生^[24-26]。

AMD 是一种发病率随年龄增加而增加的眼部疾病,可引起一系列渗出、出血、瘢痕形成等,导致视力急速下降^[27,28]。本研究直线相关性分析显示血清 A β 含量与脉络膜厚度、患眼动脉舒张末期血流速度和收缩期峰值血流速度都有显著相关性,其中 A β 含量与脉络膜厚度呈正相关, A β 含量与患眼动脉舒张

末期血流速度和收缩期峰值血流速度呈负相关。从发病机制上分析,血清 A β 的增加可导致眼内自由基不断增多,破坏视网膜的脂质及多种酶体,从而导致视网膜血液供应降低,诱发形成 AMD^[29,30]。本研究也存在一定的不足,没有进行随访分析,且纳入样本数量较少,将在后续研究中深入探讨。

总之, A β 在湿性年龄相关性黄斑变性患者中多呈现高表达状况,血清 A β 含量与脉络膜厚度、患眼动脉舒张末期血流速度和收缩期峰值血流速度相关,从而影响患者病情的进展。

参 考 文 献 (References)

- [1] Kam JH, Weinrich TW, Shinhmar H, et al. Fundamental differences in patterns of retinal ageing between primates and mice [J]. Sci Rep, 2019, 9(1): e12574
- [2] Lennikov A, Saddala MS, Mukwaya A, et al. Autoimmune-Mediated Retinopathy in CXCR5-Deficient Mice as the Result of Age-Related Macular Degeneration Associated Proteins Accumulation [J]. Front Immunol, 2019, 10: e1903
- [3] Mallmann F, Canani LH. Intravitreal neurodegenerative and inflammatory mediators in proliferative diabetic retinopathy [J]. Arq Bras Oftalmol, 2019, 82(4): 275-282
- [4] Masuda N, Tsujinaka H, Hirai H, et al. Effects of concentration of amyloid beta (A β) on viability of cultured retinal pigment epithelial cells[J]. BMC Ophthalmol, 2019, 19(1): e70
- [5] Rosenfeld PJ, Berger B, Reichel E, et al. A Randomized Phase 2 Study of an Anti-Amyloid beta Monoclonal Antibody in Geographic Atrophy Secondary to Age-Related Macular Degeneration [J]. Ophthalmol Retina, 2018, 2(10): 1028-1040
- [6] Salobar-Garcia E, De Hoz R, Ramirez AI, et al. Changes in visual function and retinal structure in the progression of Alzheimer's disease[J]. PLoS One, 2019, 14(8): e0220535
- [7] Song XY, Wu WF, Gabbi C, et al. Retinal and optic nerve degeneration in liver X receptor beta knockout mice [J]. Proc Natl Acad Sci U S A, 2019, 116(33): 16507-16512
- [8] Van De Kreeke JA, Nguyen HT, Den Haan J, et al. Retinal layer thickness in preclinical Alzheimer's disease [J]. Acta Ophthalmol, 2019, 97(8): 798-804
- [9] Das TK, Jana P, Chakrabarti SK, et al. Curcumin Downregulates GSK3 and Cdk5 in Scopolamine-Induced Alzheimer's Disease Rats

- Abrogating Abeta40/42 and Tau Hyperphosphorylation [J]. *J Alzheimers Dis Rep*, 2019, 3(1): 257-267
- [10] Bodart-Santos V, De Carvalho L RP, De Godoy MA, et al. Extracellular vesicles derived from human Wharton's jelly mesenchymal stem cells protect hippocampal neurons from oxidative stress and synapse damage induced by amyloid-beta oligomers [J]. *Stem Cell Res Ther*, 2019, 10(1): e332
- [11] Deng L, Pushpitha K, Joseph C, et al. Amyloid beta Induces Early Changes in the Ribosomal Machinery, Cytoskeletal Organization and Oxidative Phosphorylation in Retinal Photoreceptor Cells [J]. *Front Mol Neurosci*, 2019, 12(8): e24
- [12] Feng L, Liao X, Zhang Y, et al. Protective effects on age-related macular degeneration by activated autophagy induced by amyloid-beta in retinal pigment epithelial cells [J]. *Discov Med*, 2019, 27(148): 153-160
- [13] Fancellu G, Chand K, Tomas D, et al. Novel tacrine-benzofuran hybrids as potential multi-target drug candidates for the treatment of Alzheimer's Disease [J]. *J Enzyme Inhib Med Chem*, 2020, 35(1): 211-226
- [14] Hata S, Omori C, Kimura A, et al. Decrease in p3-Alc-beta37 and p3-Alc-beta40, products of Alc-beta generated by gamma-secretase cleavages, in aged monkeys and patients with Alzheimer's disease [J]. *Alzheimers Dement (N Y)*, 2019, 5: 740-750
- [15] Leitao MJ, Silva-Spinola A, Santana I, et al. Clinical validation of the Lumipulse G cerebrospinal fluid assays for routine diagnosis of Alzheimer's disease [J]. *Alzheimers Res Ther*, 2019, 11(1): e91
- [16] Bhavsar AR, Baker CW, Guymer RE, et al. Subthreshold nanosecond laser intervention in age-related macular degeneration: The LEAD Randomized Controlled Clinical Trial [J]. *Ophthalmology*, 2019, 126(829-838): e91
- [17] Chen H, Deng H, Zou X, et al. Hypocrellin B Encapsulated in Triphenyl Phosphonium-Modified Cationic Liposomes for Photodynamic Treatment of Exudative Age-Related Macular Degeneration [J]. *J Biomed Nanotechnol*, 2019, 15(12): 2305-2320
- [18] Falavarjani KG, Au A, Anvari P, et al. En Face OCT of Type 2 Neovascularization: A Reappraisal of the Pitchfork Sign [J]. *Ophthalmic Surg Lasers Imaging Retina*, 2019, 50(11): 719-725
- [19] Horita S, Watanabe M, Katagiri M, et al. Species differences in ocular pharmacokinetics and pharmacological activities of regorafenib and pazopanib eye-drops among rats, rabbits and monkeys [J]. *Pharmacol Res Perspect*, 2019, 7(6): e00545
- [20] Lad EM. Does Aspirin Worsen Macular Degeneration in a Clinically Meaningful Way? [J]. *Ophthalmology*, 2019, 126(12): 1657-1658
- [21] Nowosielska A. Macular Hole Surgery in the Case of Wet Age-Related Macular Degeneration Treated with Intravitreal Aflibercept [J]. *Case Rep Ophthalmol*, 2019, 10(3): 369-373
- [22] Parfitt A, Boxell E, Amoaku WM, et al. Patient-reported reasons for delay in diagnosis of age-related macular degeneration: a national survey [J]. *BMJ Open Ophthalmol*, 2019, 4(1): e000276
- [23] Qi JH, Bell B, Singh R, et al. Sorsby Fundus Dystrophy Mutation in Tissue Inhibitor of Metalloproteinase 3 (TIMP3) promotes Choroidal Neovascularization via a Fibroblast Growth Factor-dependent Mechanism [J]. *Sci Rep*, 2019, 9(1): e17429
- [24] Raval V, Pathengay A, Narayanan R. Bilateral diffuse uveal melanocytic proliferation secondary to thyroid carcinoma [J]. *Indian J Ophthalmol*, 2019, 67(12): 2094-2097
- [25] Sharma A, Kumar N, Bandello F, Re Dugel, et al. HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brodalumab for neovascular age-related macular degeneration (Ophthalmology. 2019 Apr 12 [Epub ahead of print]) [J]. *Ophthalmology*, 2019, 126(12): e95-e96
- [26] Masdeu JC. Neuroimaging of Diseases Causing Dementia [J]. *Neurol Clin*, 2019, 38(1): 65-94
- [27] Ochiishi T, Kaku M, Kiyosue K, et al. New Alzheimer's disease model mouse specialized for analyzing the function and toxicity of intraneuronal Amyloid beta oligomers [J]. *Sci Rep*, 2019, 9(1): e17368
- [28] Vacher M, Porter T, Villemagne VL, et al. Validation of a priori candidate Alzheimer's disease SNPs with brain amyloid-beta deposition [J]. *Sci Rep*, 2019, 9(1): e17069
- [29] Weber-Adrian D, Kofoed RH, Chan J WY, et al. Strategy to enhance transgene expression in proximity of amyloid plaques in a mouse model of Alzheimer's disease [J]. *Theranostics*, 2019, 9(26): 8127-8137
- [30] Yang H, Li X, Zhu L, et al. Heat Shock Protein Inspired Nanochaperones Restore Amyloid-beta Homeostasis for Preventative Therapy of Alzheimer's Disease [J]. *Adv Sci (Weinh)*, 2019, 6(22): e1901844

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- [25] Platt DM, Bano KM. Opioid receptors and the discriminative stimulus effects of ethanol in squirrel monkeys: Mu and delta opioid receptor mechanisms [J]. *Eur J Pharmacol*, 2011, 650(1): 233-239
- [26] Lur G, Fariborzi M, Higley MJ. Ketamine disrupts neuromodulatory control of glutamatergic synaptic transmission [J]. *PLoS One*, 2019, 14(3): e213721
- [27] Miner JR, Moore JC, Austad EJ, et al. Randomized, double-blinded, clinical trial of propofol, 1:1 propofol/ketamine, and 4:1 propofol/ketamine for deep procedural sedation in the emergency department [J]. *Ann Emerg Med*, 2015, 65(5): 479-488
- [28] Pizon AF, Lynch MJ, Benedict NJ, et al. Adjunct ketamine use in the management of severe ethanol withdrawal [J]. *Crit Care Med*, 2018, 46(8): e768-e771
- [29] Ionescu DF, Felicione JM, Gosai A, et al. Ketamine-associated brain changes: a review of the neuroimaging literature [J]. *Harv Rev Psychiatry*, 2018, 26(6): 320-339
- [30] Mason KP, Seth N. Future of paediatric sedation: towards a unified goal of improving practice [J]. *Br J Anaesth*, 2019, 122(5): 652-661