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血清 α-syn、$A\beta_{1-42}$、SSA 在帕金森病患者中的表达及与认知功能损害的关系 *

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摘要 目的：探讨血清 α- 突触核蛋白（α-synuclein，α-syn）、β 淀粉样蛋白 1-42（β-amyloid 1-42，$A\beta_{1-42}$）、淀粉样蛋白 A（serum amyloid A，SSA）在帕金森病患者中的表达及与认知功能损害的关系。**方法：**收集本院 2018 年 7 月 ~2020 年 11 月收治的 136 例帕金森病患者为病例组，依据 Hoehn-Yahr（H-Y）分级分为早期组（n=76）与中晚期组（n=60）；依据蒙特利尔认知评估量表（Montreal Cognitive Assessment Scale，MoCA）分为认知功能正常组（n=94）与认知功能损害组（n=42）。另选同期本院体检正常者 105 例纳入对照组。对比各组血清 α-syn、SSA、$A\beta_{1-42}$ 水平及 MoCA，并用 Pearson 相关系数分析病例组患者血清 α-syn、SSA、$A\beta_{1-42}$ 水平与 MoCA 的相关性，用受试者工作特征曲线（receiver operating characteristic curve，ROC）分析血清 α-syn、SSA、$A\beta_{1-42}$ 水平对帕金森病和认知功能损害的诊断价值。**结果：**病例组血清 α-syn、SSA 水平高于对照组，差异有统计学意义（$P<0.05$）；病例组 $A\beta_{1-42}$、MoCA 评分低于对照组（$P<0.05$）。病例组晚期患者血清 α-syn、SSA 水平高于早期患者（$P<0.05$）；病例组晚期患者 $A\beta_{1-42}$、MoCA 评分低于早期患者，差异有统计学意义（$P<0.05$）。病例组有认知功能损害患者血清 α-syn、SSA 水平高于认知功能正常患者（$P<0.05$）；病例组有认知功能损害患者 $A\beta_{1-42}$、MoCA 评分低于认知功能正常患者（$P<0.05$）。病例组患者血清 α-syn、SSA 与 MoCA 均呈正相关（$P<0.05$），$A\beta_{1-42}$ 与 MoCA 呈正相关（$P<0.05$）。血清 α-syn、SSA、$A\beta_{1-42}$ 水平对帕金森病诊断的曲线下面积分别为 0.858、0.821、0.785；血清 α-syn、SSA、$A\beta_{1-42}$ 水平对帕金森病认知功能损害预测的曲线下面积分别为 0.877、0.825、0.783。**结论：**帕金森病患者血清 α-syn、SSA、$A\beta_{1-42}$ 水平较健康者变化明显，且可能和帕金森病的诊断、病情进展和认知功能损害有一定关系。

关键词：帕金森病；认知功能损害；α- 突触核蛋白；β 淀粉样蛋白 1-42；淀粉样蛋白 A

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The Expression of Serum A-Syn, AB_{1-42} and SSA in Patients with Parkinson's Disease and Their Relationship with Cognitive Impairment*

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ABSTRACT Objective: To investigate the expression of serum α-synuclein (α-syn), β-amyloid 1-42 ($A\beta_{1-42}$) and serum amyloid A (SSA) in patients with Parkinson's disease and their relationship with cognitive impairment. **Methods:** 136 patients with Parkinson's disease admitted in our hospital from July 2018 to November 2020 were collected as case group, and divided into early stage group (n=76) and middle and late stage group (n = 60) according to Hoehn-Yahr (H-Y) grading. According to Montreal Cognitive Assessment Scale (MoCA), the patients were divided into normal cognitive function group (n=94) and cognitive impairment group (n=42). Another 105 cases with normal physical examination in the same period were included in the control group. The levels of serum α-syn, SSA, $A\beta_{1-42}$ and MoCA in each group were compared. Pearson correlation coefficient was used to analyze the correlation between the levels of serum α-syn, SSA, $A\beta_{1-42}$ and MoCA. The receiver operating characteristic curve (ROC) was used to analyze the diagnostic value of serum α-syn, SSA, $A\beta_{1-42}$ in Parkinson's disease and cognitive impairment. **Results:** The levels of serum α-syn and SSA in case group were higher than those in control group, the difference was statistically significant ($P<0.05$). The $A\beta_{1-42}$ and MoCA scores in the case group were lower than those in the control group ($P<0.05$). Serum α-syn and SSA levels in patients with advanced stage were higher than those in patients with early stage ($P<0.05$). The scores of $A\beta_{1-42}$ and MoCA in late patients were lower than those in early patients, the difference was statistically significant ($P<0.05$). Serum α-syn and SSA levels in patients with cognitive impairment were higher than those in patients with normal cognitive function ($P<0.05$). The scores of $A\beta_{1-42}$ and MoCA in patients with cognitive impairment were lower than those in patients with normal cognitive function ($P<0.05$). Serum α-syn, SSA were positively correlated with MoCA ($P<0.05$), and $A\beta_{1-42}$ was positively correlated with MoCA ($P<0.05$). The areas under the curve of serum α-syn, SSA and $A\beta_{1-42}$ levels for diagnosis

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of Parkinson's disease were 0.858, 0.821 and 0.785. The areas under the curve for predicting cognitive impairment of Parkinson's disease by serum α-syn, SSA and $A\beta_{1-42}$ levels were 0.877, 0.825 and 0.783. **Conclusion:** Serum levels of α-syn, SSA and $A\beta_{1-42}$ in patients with Parkinson's disease are significantly different from those in healthy people, which may be related to the diagnosis, progression and cognitive impairment of Parkinson's disease.

Key words: Parkinson's disease; Cognitive impairment; α -synuclein; Beta amyloid protein 1-42; Serum amyloid A

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前言

帕金森病病为中老年最常见的神经变性疾病,可引起多种运动症状及非运动症状,其中认知功能损害为最常见的非运动症状,调查研究表明[1],认知功能损伤发生痴呆的风险较高。流行病学资料也报道[2],多数帕金森病病认知功能障碍患者可进展至帕金森病病痴呆,严重影响患者社会功能及生活质量。目前研究认为帕金森病认知功能损害的生化改变和神经递质有密切关系,α- 突触核蛋白(α-synuclein,α-syn)为大脑神经元蛋白质,其可减少多巴胺释放,引起多巴胺能神经元变性、丢失,参与帕金森病病发生、发展[3,4]。β 淀粉样蛋白(β-amyloid,Aβ)为阿尔茨海默病的典型生物标志物,其中 $A\beta_{1-42}$ 为其最主要亚型,有较强的神经毒性。近年来研究指出[5],帕金森病患者脑脊液中 $A\beta_{1-42}$ 含量明显降低,和 α-syn 浓度呈负相关。有学者通过研究发现 [6],α-syn 及 $A\beta_{1-42}$ 相互作用能够促进淀粉样斑块产生,导致认知功能损伤。淀粉样蛋白 A(serum amyloid A,SAA)为机体急性时相蛋白,动物实验报道[7],帕金森病小鼠 SAA 浓度显著上升。Jang S 等[8]研究表明,SAA 和内侧颞叶及额叶的灰密度降低有良好相关性,SAA 水平上升可导致执行功能及工作记忆损伤。本研究主要探讨血清 α-syn、$A\beta_{1-42}$、SSA 在帕金森病患者中的表达及与认知功能损害的关系。

1 资料与方法

1.1 一般资料

收集本院 2018 年 7 月 ~2020 年 11 月收治的 136 例帕金森病患者为病例组,入选标准:符合帕金森病诊断标准[9];年龄 41~78 岁;知情同意本研究。排除标准:其他诱因所致的继发性帕金森病;;可能导致认知功能减退的其他疾病;原发性精神障碍; 帕金森叠加综合征恶性肿瘤; 严重心肝肾等功能异常;文盲。136 例病例组患者中平均年龄(60.46±5.93)岁;女 58 例,男 78 例;病程 1~12 年,平均(6.44±1.25)年;受教育年限(8.95±1.42)年;Hoehn-Yahr(H-Y)分级:早期(H-Y 分级 <3 级)76 例;中晚期(H-Y 分级≥ 3 级)60 例。另选同期本院体检正常者 105 例纳入对照组,其既往体健,均无帕金森病家族史,神经系统查体排除阳性体征,无认知功能损害表现,蒙特利尔认知评估量表(Montreal Cognitive Assessment Scale,MoCA)≥ 26 分,年龄 43~76 岁,平均(58.99±6.13)岁;女 49 例,男 56 例;受教育年限(8.87±1.55)年。两组一般资料对比无显著差异(P>0.05)。

1.2 方法

1.2.1 血清 α-syn、$A\beta_{1-42}$ 和 SSA 检测 采集病例组与对照组空腹外周静脉血,分离血清并取上清液待检。用酶联免疫吸附法测定血清 α-syn、$A\beta_{1-42}$ 和 SSA 水平。所有操作均严格在说明书指导下进行。

1.2.2 认知功能评价 用 MoCA 评价患者认知功能情况,MoCA 包含计算及定向力、抽象思维、视结构技能、语言、记忆、执行功能、注意与集中 7 个方面,总分 30 分,其分值 <26 分判定为认知功能损害,≥ 26 分判定为认知功能正常,对于教育年限≤ 12 年者在总分值上加 1 分[10]。

1.3 统计学分析

数据处理选用 SPSS20.0 软件包,计量资料用($\bar{x}\pm s$)表示,选用 t 检验,计数资料用[例(%)]表示,用 χ^2 检验比较,用 Pearson 相关系数进行相关性分析,制作受试者工作特征曲线(receiver operating characteristic curve,ROC) 分析相关指标对帕金森病及认知功能损害的诊断价值,P<0.05 表示差异有统计学意义。

2 结果

2.1 病例组与对照组血清 α-syn、$A\beta_{1-42}$、SSA、MoCA 评分对比

病例组血清 α-syn、SSA 水平高于对照组(P<0.05);病例组 $A\beta_{1-42}$、MoCA 评分低于对照组(P<0.05),见表 1。

图 1 血清指标对帕金森病诊断的 ROC 曲线分析

Fig. 1 ROC curve analysis of serum indexes in diagnosis of Parkinson's disease

Groups	n	α-syn(μg/L)	$A\beta_{1-42}$(μg/L)	SAA(mg/L)	MoCA(points)
Case group	136	9.86±1.43	1.03±0.11	9.95±1.38	24.66±1.19
Control group	105	5.71±0.65	1.21±0.14	3.54±0.49	28.03±0.65
t		27.608	11.179	45.419	26.155
P		<0.001	<0.001	<0.001	<0.001

2.2 病例组早期、中晚期患者血清 α-syn、$A\beta_{1-42}$、SSA、MoCA 评分对比

病例组晚期患者血清 α-syn、SSA 水平高于早期患者(P<0.05); 病例组晚期患者 $A\beta_{1-42}$、MoCA 评分低于早期患者(P<0.05),见表 2。

表 2 病例组早期、中晚期患者血清 α-syn、$A\beta_{1-42}$、SSA、MoCA 评分对比($\bar{x}\pm s$)

Table 2 Comparison of serum α-syn, $A\beta_{1-42}$, SSA and MoCA scores of patients in early, middle and late stages of case group($\bar{x}\pm s$)

Groups	n	α-syn(μg/L)	$A\beta_{1-42}$(μg/L)	SAA(mg/L)	MoCA(points)
Early group	76	7.58±1.24	1.09±0.09	6.77±1.09	25.59±1.49
Middle and late stage group	60	12.75±1.67	0.96±0.13	13.98±1.75	23.49±1.16
t		20.715	6.879	29.423	8.977
P		<0.001	<0.001	<0.001	<0.001

2.3 病例组有无认知功能损害者血清α-syn、$A\beta_{1-42}$、SSA 对比

病例组有认知功能损害患者血清 α-syn、SSA 水平高于认知功能正常患者(*P*<0.05);病例组有认知功能损害患者$A\beta_{1-42}$、MoCA 评分低于认知功能正常患者(*P*<0.05),见表 3。

表 3 病例组有无认知功能损害者血清 α-syn、$A\beta_{1-42}$、SSA 对比($\bar{x}\pm s$)

Table 3 Comparison of serum α-syn, $A\beta_{1-42}$ and SSA in patients with cognitive impairment ($\bar{x}\pm s$)

Groups	n	α-syn(μg/L)	$A\beta_{1-42}$(μg/L)	SAA(mg/L)	MoCA(points)
Cognitive impairment group	42	13.61±1.59	0.92±0.12	15.02±1.87	20.07±3.32
Normal cognitive function group	94	8.18±1.36	1.08±0.11	7.68±1.16	26.71±0.23
t		20.398	7.619	27.937	19.376
P		<0.001	<0.001	<0.001	<0.001

2.4 分析病例组患者血清指标和 MoCA 评分的相关性

病例组患者血清 α-syn、SSA 与 MoCA 均呈正相关,r 值分别为 -0.556,-0.360,*P*<0.05;$A\beta_{1-42}$ 与 MoCA 呈正相关,r 值为 0.483,*P*<0.05。

2.5 血清指标对帕金森病的诊断价值分析

血清 α-syn、$A\beta_{1-42}$、SSA 对帕金森病诊断的曲线下面积分别为 0.858、0.821、0.785;最近临界值分别为 11.65 μg/L,0.94 g/L,10.37 mg/L,见表 4 和图 1。

表 4 血清指标对帕金森病的诊断价值分析

Table 4 Analysis of Diagnostic Value of Serum Indexes for Parkinson's Disease

Index	Area	Standard error	Progressive sig	Asymptotic 95% confidence region		Sensitivity	specificity	Optimum critical value
				lower limit	upper limit			
α-syn	0.858	0.024	0.000	0.810	0.905	68.90%	94.30%	11.65 μg/L
$A\beta_{1-42}$	0.821	0.029	0.000	0.764	0.878	94.10%	59.00%	0.94 μg/L
SAA	0.785	0.029	0.000	0.728	0.843	68.10%	83.80%	10.37 mg/L

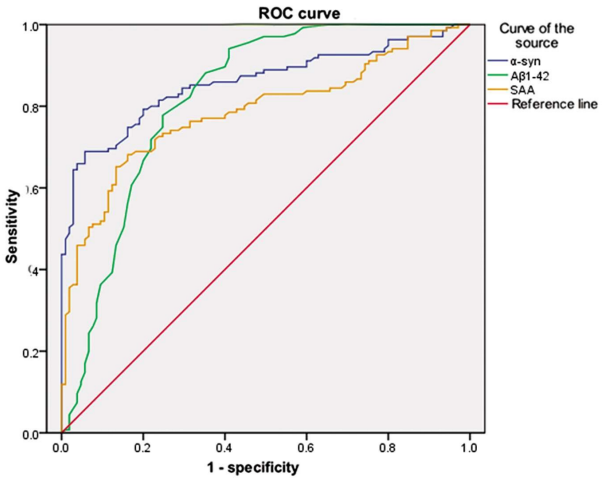

图 1 血清指标对帕金森病诊断的 ROC 曲线分析

Fig. 1 ROC curve analysis of serum indexes in diagnosis of Parkinson's disease

2.6 血清指标对帕金森病认知功能损伤的预测价值分析

血清 α-syn、$A\beta_{1-42}$、SSA 对帕金森病认知功能损害预测的曲线下面积分别为 0.877、0.825、0.783;最近临界值分别为 12.36 μg/L、0.92 g/L、11.73 mg/L,见表 5 和图 2。

3 讨论

帕金森病的起病隐匿,进展缓慢,近年来随着老龄化的加剧,帕金森病发生率不断上升,已成为影响中老年人群生活质量的主要疾病之一[12]。目前帕金森病的诊断主要依赖于病史、体格检查和多巴胺治疗反应,缺乏客观性的辅助指标。近年来有研究发现[13],部分血液指标可作为帕金森病早期诊断和病情监测的有效标志物。

目前有研究表明[14],α-syn 能够为帕金森病的诊断、疗效监测提供参考,可作为帕金森病的潜在生物标志物。α-syn 正常生理情况下呈可溶性,主要在突触前神经末梢分布,具有调节突触可塑性及突触多巴胺分布等生物学功能。病理情况下,α-syn 的表达明显增加,易发生错误折叠,形成寡聚体,并选择性的在特定脑区的胶质细胞及神经元内沉积,形成不溶性纤维结构,参与路易小体形成[15]。现有研究证实[16],神经元包浆路易小体(Louis corpuscle,LB)形成为帕金森病的典型病理特征。α-syn

表 5 血清指标对帕金森病认知功能损伤的预测价值分析

Table 5 Analysis of predictive value of serum indicators for cognitive impairment of Parkinson's disease

Index	Area	Standard error	Progressive sig	Asymptotic 95% confidence region		Sensitivity	specificity	Optimum critical value
				lower limit	lower limit			
伪 -syn	0.877	0.035	00.000	0.808	0.945	69.00%	91.49%	12.36 μg/L
A 尾 1-42	0.825	0.037	0.000	0.752	0.898	61.90%	88.30%	0.92 μg/L
SAA	0.783	0.045	0.000	0.696	0.871	62.30%	87.23%	11.73 mg/L

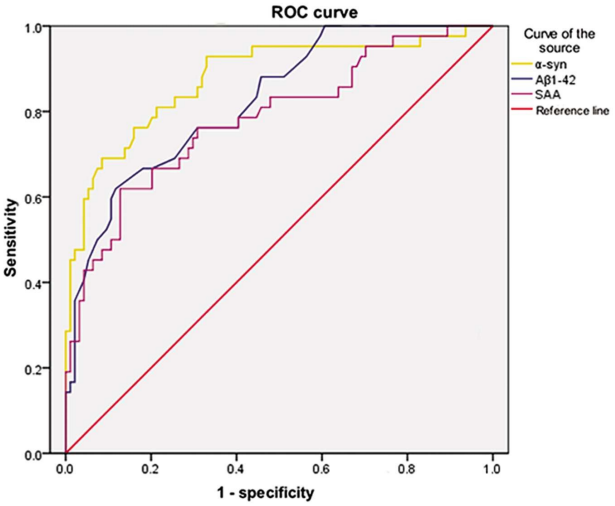

图 2 血清指标对帕金森病认知功能损害预测的 ROC 曲线分析

Fig. 2 ROC curve analysis of serum indexes predicting cognitive impairment of Parkinson's disease

寡聚体可引起细胞毒性，导致神经元变性，参与帕金森病发生[17]。本研究观察发现，帕金森病患者血清 α-syn 水平显著高于健康体检者，且中晚期帕金森病患者血清 α-syn 水平又高于早期患者，同时血清 α-syn 诊断帕金森病的 ROC 曲线下面积、特异度及灵敏度均较高，提示 α-syn 对帕金森病的诊断有较高价值，能够一定程度的反映疾病进展情况。

国外研究表明 [18]，α-syn 和 Aβ 的协同作用能够加重突触和神经元损伤，加重帕金森病的进展。正常情况下脑内 Aβ 生成与降解为相对平衡状态，血脑屏障中的 Aβ 经内外向转运保持外周血和大脑的 Aβ 水平平衡[19]。Aβ 可影响多巴胺能神经元摄取能力，并导致其形态改变。体外实验发现[20]，Aβ 在大脑皮质沉积能够激活神经胶质细胞，引起氧化应激和级联炎性反应，导致蛋白质和膜性结构损伤，使神经元坏死、凋亡，与帕金森病的神经炎性学说相符。$A\beta_{1\text{-}42}$ 为 Aβ 的最要亚型，其含量虽低，但更容易发生聚集，神经毒性也相应增加[21]。既往有研究报道[22]，晚期帕金森病患者血清 $A\beta_{1\text{-}42}$ 水平较健康人群显著下降。本研究结果显示，帕金森病患者血清 $A\beta_{1\text{-}42}$ 水平低于健康对照组，且中晚期患者血清 $A\beta_{1\text{-}42}$ 水平又低于早期患者，和临床研究结果相符。考虑 $A\beta_{1\text{-}42}$ 能够增加血脑屏障渗透性，导致紧密连接蛋白受损，导致脑内 $A\beta_{1\text{-}42}$ 水平异常增加，从而降低帕金森病患者血液中 $A\beta_{1\text{-}42}$ 水平。另外随着帕金森病的进展，中晚期患者海马和皮质区同时有 α-syn、Aβ 异常聚集，导致血脑屏障受损，减少脑脊液中可溶性 Aβ 水平，引起血清 $A\beta_{1\text{-}42}$ 降低。ROC 曲线发现，$A\beta_{1\text{-}42}$ 水平对帕金森病的诊断有较高价值。

近年来研究发现炎症因子在帕金森病发生、发展中可能有重要作用[23]。SAA 为机体主要炎性反应物，其主要由肝脏生产，组织发生炎症反应及受损时其浓度快速上升，是评价炎症状态的灵敏指标。Lee JY 等[24]研究表明，高水平的 SAA 可加重机体氧化应激反应，导致多巴胺能神经元变性，参与帕金森病发生。目前研究报道[25]，帕金森病患者血清 SAA 水平显著上升。本研究中，帕金森病患者血清 SAA 水平较健康对照组高，且中晚期患者血清 SAA 水平又明显高于早期患者，提示通过观察血清 SAA 水平可能有利于帕金森病的诊断和病情监测。

既往临床主要为帕金森病运动症状方面的研究，最近研究发现多数帕金森病患者伴非运动症状[26]。认知功能损害是非运动症状的主要类型，以视空间障碍、执行功能下降、回忆受损及记忆力下降等为主要表现[27]。相关研究发现[28]，帕金森病认知功能损害患者的痴呆风险明显高于帕金森病认知功能正常者，尽早诊治可能延缓帕金森病痴呆的发生。临床研究报道[29,30]，α-syn 可促进 tau 蛋白毒性低聚物的产生，引起纤维淀粉样蛋白形成，导致淀粉样斑块，参与认知功能损伤。既往有研究指出[31]，脑脊液中 $A\beta_{1\text{-}42}$ 和记忆力有良好相关性。最新研究发现 [32]，$A\beta_{1\text{-}42}$ 浓度降低为帕金森病认知功能降低的独立危险因素。又有研究认为[33]，α-syn 和 Aβ 有协同作用，能够进一步导致神经受损，快速降低认知能力。Facci L 等就血清 SAA 和帕金森病患者认知功能关系的研究发现，SSA 能够诱导相关炎性反应，促进胶质细胞释放炎症因子，引起脑组织内炎症反应，影响认知功能。另有文献报道，SAA 浓度上升可导致组织淀粉样蛋白沉积，引起神经元损耗及白质受损，参与痴呆发生。本研究中，帕金森病认知功能损害患者血清 α-syn、SAA 水平相对较高，$A\beta_{1\text{-}42}$ 则明显低于认知功能正常者，提示血清 α-syn、$A\beta_{1\text{-}42}$、SSA 可能和帕金森病认知功能损害有关。MoCA 是临床筛查认知功能情况的常用量表，临床研究证实，其敏感性高于简单精神状态量表，能避免轻度认知功能障碍的假阴性。本研究通过 MoCA 量表评估帕金森病患者认知领域，观察显示，帕金森病认知功能损害患者 MoCA 量表和血清 α-syn、SAA 均呈正相关，与 $A\beta_{1\text{-}42}$ 呈负相关，进一步提示此类指标和帕金森病认知功能损害有一定关系。ROC 曲线显示，血清 α-syn、$A\beta_{1\text{-}42}$、SSA 对帕金森病认知功能损害预测的曲线下面积均大于 0.5，表明血清 α-syn、$A\beta_{1\text{-}42}$ 和 SAA 可能为预测帕金森病认知功能损害的潜在生物指标。

综上所述，帕金森病患者血清 α-syn、SSA、$A\beta_{1\text{-}42}$ 水平较健康者变化明显，且可能和帕金森病的诊断、病情进展和认知功能损害有一定关系。

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