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血清 IGF–1，5–HT 及 TNF–α 水平与帕金森病伴发抑郁的相关性

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[摘　要]　**目的：**探究血清胰岛素样生长因子-1(insulin-like growth factor-1，IGF-1)、5-羟色胺(serotonin，5-HT)、肿瘤坏死因子-α(tumor necrosis factor-α，TNF-α)水平与帕金森病(Parkinson's disease，PD)伴发抑郁的相关性。**方法：**选取辽阳市中心医院2018年1月至2019年12月收治的PD伴发抑郁患者40例为抑郁组，并选取同期无抑郁的PD患者40例与健康体检人员40例分别为PD组与对照组。抽血测定各组血清IGF-1，5-HT及TNF-α水平。采用Pearson相关性分析研究血清指标与伴发抑郁的关系，采用logistic回归分析研究PD伴发抑郁的相关因素。**结果：**抑郁组、PD组与对照组血清IGF-1，5-HT及TNF-α水平比较差异均有统计学意义(P<0.05)，抑郁组患者血清IGF-1和5-HT水平均显著低于对照组与PD组(P<0.05)，TNF-α水平高于对照组与PD组(P<0.05)；汉密尔顿抑郁量表(Hamilton Depression Scale，HAMD)评分与血清IGF-1和5-HT水平呈负相关(P<0.001)，与TNF-α水平正相关(P<0.001)；血清IGF-1，5-HT与TNF-α水平呈负相关(P<0.05)；logistic回归分析显示：受教育时间长、血清IGF-1和5-HT水平高是PD伴发抑郁的保护因素(P<0.05)，病程长、血清TNF-α水平高是其危险因素(P<0.05)。**结论：**PD伴发抑郁患者血清IGF-1，5-HT低水平，TNF-α高水平，其危险因素包括病程长、高TNF-α水平、低IGF-1和5-HT水平。

[关键词]　帕金森病；抑郁；胰岛素样生长因子-1；5-羟色胺；肿瘤坏死因子-α

Correlation between serum IGF-1, 5-HT and TNF-α levels and Parkinson's disease with depression

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Abstract　**Objective:** To explore the correlation between serum insulin-like growth factor-1 (IGF-1), serotonin (5-HT) and tumor necrosis factor-α (TNF-α) levels and Parkinson's disease (PD) with depression. **Methods:** A total of 40 patients with PD complicated with depression who were admitted to the hospital between January 2018 and December 2019 were selected and included in the depression group. Meanwhile, 40 patients with PD and without depression, and 40 healthy persons were selected and included in the PD group and the control group, respectively. Serum IGF-1, 5-HT and TNF-α levels in each group were determined. The relationship between serum indicators and depression was analyzed by Pearson correlation analysis. Logistic regression analysis was performed to analyze related factors of PD with depression. **Results:** There were significant differences in serum IGF-1, 5-HT

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and TNF-α levels between the depression group, the PD group, and the control group (P<0.05). Serum IGF-1 and 5-HT levels in the depression group were significantly lower than those in the control group and the PD group (P<0.05), but the level of TNF-α was higher than the control group and the PD group (P<0.05). Hamilton Depression Scale (HAMD) score was negatively correlated with serum IGF-1 and 5-HT levels (P<0.001), but was positively correlated with TNF-α levels (P<0.001). Serum IGF-1 and 5-HT levels were negatively correlated with TNF-α levels (P<0.05). Logistic regression analysis showed that time of receiving education, high serum IGF-1 and 5-HT levels were protective factors for PD with depression (P<0.05), while long course of disease and high serum TNF-α levels were risk factors (P<0.05). **Conclusion:** Serum IGF-1 and 5-HT levels are low and TNF-α level is high in patients with PD complicated with depression. Risk factors include long course of disease, high TNF-α level, low IGF-1 and 5-HT levels.

Keywords Parkinson's disease; depression; insulin-like growth factor-1; serotonin; tumor necrosis factor-α

帕金森病(Parkinson's disease，PD)属于神经病变疾病，临床上易合并抑郁，由于PD抑郁躯体症状可能和疾病表现重叠，临床上易被忽略，而抑郁会加重PD患者功能障碍，影响其生活及家庭和谐[1-3]。为此早期诊断PD伴发抑郁十分重要。目前PD伴发抑郁机制还不明确，可能与炎症、5-羟色胺(serotonin，5-HT)异常表达、神经免疫等有关[4-6]。胰岛素样生长因子-1(insulin-like growth factor-1，IGF-1)被发现有非选择性神经营养特性，可促外周神经再生。当下关于IGF-1与PD的研究报道不多，其对PD伴发抑郁的影响更少。本研究对血清IGF-1，5-HT，肿瘤坏死因子-α(tumor necrosis factor-α，TNF-α)水平与PD伴发抑郁的相关性进行探讨，并进一步行Logistic多因素回归分析，旨在为疾病诊治提供参考。

1 对象与方法

1.1 对象

以辽阳市中心医院2018年1月至2019年12月收治的40例PD伴发抑郁患者为对象。患者均符合PD诊断标准[7]，年龄18~80岁，均接受汉密尔顿抑郁量表24项版本(Hamilton Depression Scale 24 item version，HAMD-24)[8]测定且总分≥20[(25.85±3.12)]分，体征稳定，表达正常。另选择同期40例无抑郁的PD患者为PD组，40例健康体检人员为对照组。排除帕金森综合征及叠加综合征、器质性病变、严重痴呆及抑郁、近14 d内有抗精神病药物使用史、近期感染、自身免疫异常、依从性差等患者。本研究经辽阳市中心医院医学伦理委员会审核批准，患者均签署知情同意书。

1.2 方法

PD患者于就诊次日(用药前)、健康人员在体检日清晨空腹抽取其静脉血4 mL，采用肝素抗凝，以3 000 r/min离心10 min，血清分离后保存到−80 ℃待测。通过酶联免疫吸附法测定血清IGF-1，5-HT及TNF-α水平，试剂盒均源于武汉博士德生物技术有限公司，步骤依据说明书执行。

1.3 统计学处理

采用SPSS 20.0软件处理数据。计数资料以例(%)表示，χ^2检验；计量资料均符合正态分布，以均数±标准差($\bar{x}\pm s$)表示，检验方差齐性，多组间行单因素方差分析，两两比较采用SNK-q检验；采用Pearson法分析血清IGF-1，5-HT及TNF-α水平与HMAD评分的相关性；采用logistic回归分析PD伴发抑郁的相关因素。检验水准α=0.05。P<0.05为差异有统计学意义。

2 结果

2.1 各组一般情况对比

3组性别、年龄、体重指数的差异无统计学意义(P>0.05)；3组受教育时间对比，差异有统计学意义(P<0.05)，其中抑郁组受教育时间明显短于PD组、对照组(P=0.026)；抑郁组病程明显长于PD组(P=0.002，表1)。

2.2 各组血清指标对比

抑郁组、PD组、对照组患者血清IGF-1，5-HT及TNF-α水平的差异有统计学意义(P<0.05)；与对照组相比，抑郁组、PD组患者血清IGF-1和5-HT水平均显著较低(均P<0.001)，TNF-α水平显

著高(P<0.001)；抑郁组与PD组对比，差异有统计学意义(P<0.05，表2)。

2.3 相关性分析

Pearson相关性研究发现：PD伴发抑郁患者HAMD评分与血清IGF-1和5-HT水平均负相关(r=−0.692，−0.640，均P<0.001)；HAMD评分与血清TNF-α水平呈正相关(r=0.751，P<0.001)；血清IGF-1与5-HT水平无相关性(r=0.296，P=0.064)；血清IGF-1，5-HT与TNF-α水平均呈负相关(r=−0.329，−0.536，P=0.038，P<0.001；图1~6)。

2.4 相关因素分析

Logistic回归分析显示：受教育时间长、血清IGF-1和5-HT水平高是PD伴发抑郁的保护因素(P<0.05)，病程长、血清TNF-α水平高是其危险因素(P<0.05，表1~3)。

表1 3组一般情况对比(n=40)

Table 1 Comparison of general data among the 3 groups (n=40)

组别	男/女	年龄/岁	体重指数/(kg·m^{-2})	受教育时间/年	病程/年
抑郁组	26/14	64.75 ± 5.38	25.13 ± 2.13	7.46 ± 2.00	3.40 ± 0.93
PD组	23/17	63.99 ± 6.03	24.87 ± 2.30	8.61 ± 2.46	2.75 ± 0.87
对照组	25/15	62.46 ± 6.12	25.00 ± 2.25	8.72 ± 2.35	—
$F/\chi^2/t$	0.703	1.589	0.180	3.753	3.228
P	0.704	0.209	0.835	0.026	0.002

表2 3组血清IGF-1，5-HT及TNF-α水平对比(n=40)

Table 2 Comparison of serum IGF-1, 5-HT and TNF-α levels among the 3 groups (n=40)

组别	IGF-1/(mg·mL^{-1})	5-HT/(ng·L^{-1})	TNF-α/(pg·mL^{-1})
抑郁组	117.22 ± 29.25*#	89.54 ± 9.26*#	15.53 ± 4.12*#
PD组	139.18 ± 30.79*	107.08 ± 12.13*	10.51 ± 3.28*
对照组	168.69 ± 34.71	129.95 ± 14.05	5.34 ± 1.57
F	26.607	114.512	103.164
P	<0.001	<0.001	<0.001

与对照组相比，*P<0.05；与PD组相比，#P<0.05。

Compared with the control group, *P<0.05; Compared with the PD group, #P<0.05.

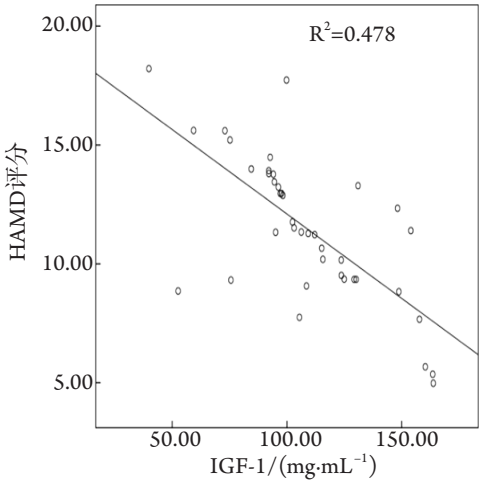

图1 HAMD评分与IGF-1水平的相关性

Figure 1 Correlation between HAMD score and IGF-1 level

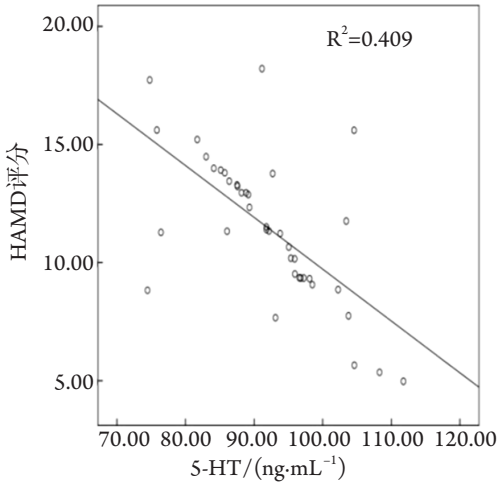

图2 HAMD评分与5-HT水平的相关性

Figure 2 Correlation between HAMD score and 5-HT level

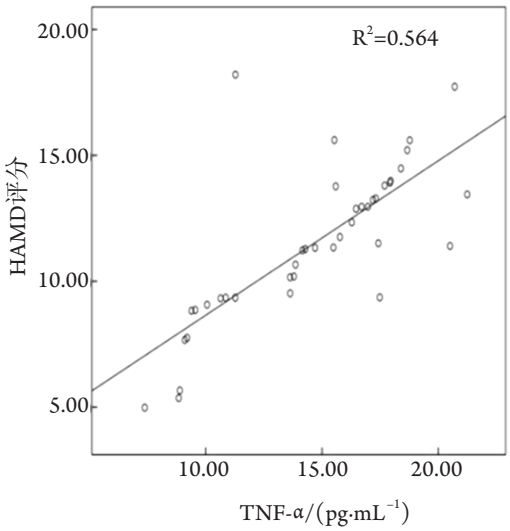

图3 HAMD评分与TNF-α水平的相关性

Figure 3 Correlation between HAMD score and TNF-α level

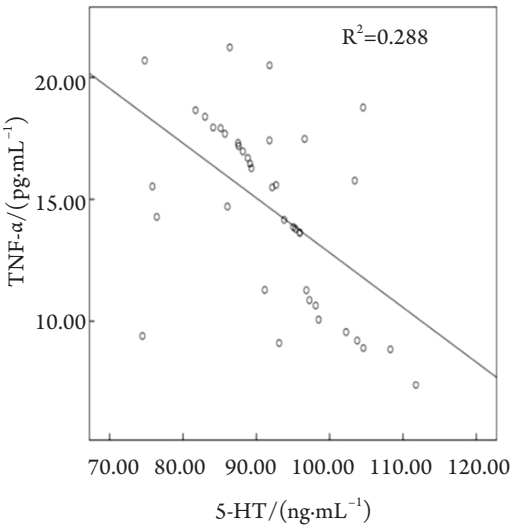

图5 TNF-α与5-HT水平的相关性

Figure 5 Correlation between TNF-α and 5-HT level

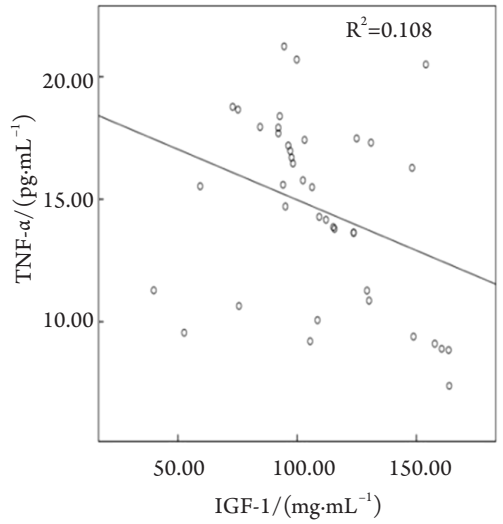

图4 TNF-α与IGF-1水平的相关性

Figure 4 Correlation between TNF-α and IGF-1 level

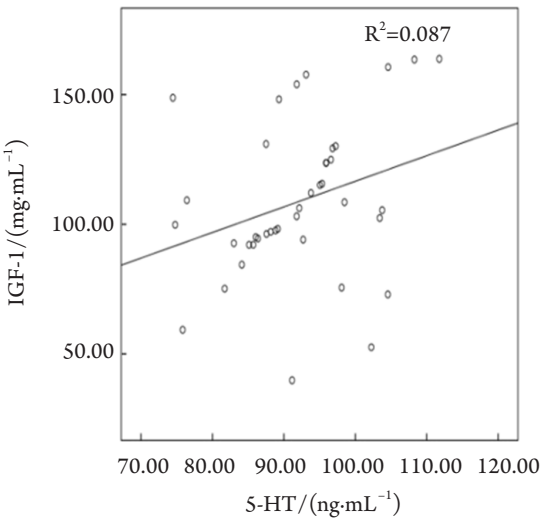

图6 IGF-1与5-HT水平的相关性

Figure 6 Correlation between IGF-1 and 5-HT level

表3 PD伴抑郁患者相关因素Logistic回归分析

Table 3 Logistic regression analysis of related factors of patients with PD and depression

变量	B	SE	Wald χ^2	*P*	OR (95%CI)
受教育时间	−0.583	0.250	5.438	0.020	0.558 (0.342~0.911)
病程	0.576	0.260	4.908	0.027	1.779 (1.069~2.961)
血清IGF-1	−1.496	0.513	8.504	0.004	0.224 (0.082~0.612)
血清5-HT	−1.420	0.518	7.515	0.006	0.242 (0.088~0.667)
血清TNF-α	2.025	0.864	5.493	0.020	7.576 (1.393~41.200)

3 讨论

PD伴发抑郁机制尚不明确，目前有神经病变、炎症、5-HT系统异常等学说[9]。IGF-1属于神经保护剂，在成熟脑组织中低表达，对神经细胞生长、分化有一定的调节作用，能有效抑制细胞凋亡，且能修复损伤细胞，其表达下降被认为是疾病发生或进展的信号之一[10]。本研究结果显示：与健康人相比，PD患者血清IGF-1水平显著低，与黄嵘等[11]研究结果一致。同时相比单纯PD患者，伴发抑郁者血清IGF-1水平更低，提示血清IGF-1水平可能促PD、抑郁发生，脑组织退变越明显，血清IGF-1水平下降越明显。分析其可能原因：PD、抑郁发病与氧化应激密切相关，高浓度多巴胺能诱导之，而IGF-1能减轻多巴胺造成的细胞凋亡[12]。IGF-1能加重脑损伤，增加PD发生风险[13]。抑郁患者呈现海马结构、神经元变化特点，而IGF-1促进神经再生，保护脑神经功能，血清IGF-1水平低，将不利于神经保护，进而导致发生抑郁。

5-HT属于神经递质，多于大脑皮质层、神经突触内表达，可能在睡眠等多种生理功能中发挥作用，中枢神经系统5-HT表达异常可能参与精神病的发病[14]。Lee等[15]研究发现：多巴胺、5-HT系统相互作用异常影响人体大脑，导致抑郁出现。有学者[16]指出PD患者血清5-HT水平下降与抑郁程度有关。Qamhawi等[17]研究发现：PD、抑郁患者均会发生5-HT水平异常表达，且与病情严重程度有关。本研究结果与之结论一致，结果显示：相比健康人员，PD患者血清5-HT水平显著降低，且伴发抑郁患者水平更低。可见5-HT系统异常可能是PD、抑郁发生的机制。朱文明等[18]研究发现：PD伴发抑郁患者血清5-HT水平低，而TNF-α水平高，与本研究结果一致。TNF-α为常见炎性因子之一，其对多巴胺能神经元存在潜在毒性。TNF-α通过促小胶质细胞合成集落刺激因子至中枢神经系统炎症部分，参与、放大炎症反应，且可能导致细胞内钙离子失衡，进一步损伤细胞。另外，细胞表面两种TNF受体影响细胞内信号级联反应激活，影响神经元发育[19]。赵雪晴等[20]研究表明：TNF-α可能通过影响细胞表面TNFR1受体，激发细胞内信号级联反应，损伤多巴胺能神经元，参与PD炎症反应。本研究结果显示：与健康人相比，PD患者血清TNF-α水平显著升高，且伴发抑郁患者血清TNF-α水平更高，提示血清TNF-α水平可能通过参与、扩大炎症反应以促PD、抑郁发生。本研究还分析了各血清指标间、血清指标与抑郁的相关性，结果显示：血清IGF-1，5-HT水平与HAMD评分均呈负相关，TNF-α水平与HAMD评分呈正相关，提示PD患者抑郁发生可能与血清IGF-1和5-HT水平低表达、TNF-α水平高表达有关，这可能与上述指标与多巴胺、5-HT系统异常相关。同时本研究发现血清IGF-1，5-HT与TNF-α水平呈负相关，而血清IGF-1和5-HT水平不相关。究其原因可能是多巴胺、5-HT系统异常相互作用最终导致炎症反应，而血清IGF-1与多巴胺关联源于氧化应激反应，后者则源于5-HT系统。另外，本研究进行多因素logistic回归分析发现：血清IGF-1和5-HT水平低表达、TNF-α水平高表达、病程长、受教育时间短是PD伴发抑郁的危险因素。

综上所述，PD伴发抑郁患者血清IGF-1和5-HT水平低表达，TNF-α水平高表达，其是PD伴发抑郁相关因素，对此建议从5-HT再摄取抑制剂等方面防治PD伴发抑郁。

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