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血清 5-HT、TNF- α 、补体 C1q 对重性抑郁障碍急性期患者抗抑郁疗效的影响*

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摘要目的: 探讨血清 5-羟色胺(5-HT)、肿瘤坏死因子- α (TNF- α)、补体 C1q 对重性抑郁障碍急性期患者抗抑郁疗效的影响。**方法:** 选择 2020 年 1 月至 2022 年 1 月新疆精神卫生中心收治的 185 例首发重性抑郁障碍急性期患者,所有患者均接受抗抑郁药物治疗,根据疗效将患者分为无效组(32 例)和有效组(153 例)。治疗前、后检测血清 5-HT、TNF- α 、补体 C1q 水平,收集相关资料,多因素 Logistic 回归分析影响重性抑郁障碍急性期患者抗抑郁疗效的因素,受试者工作特征(ROC)曲线分析血清 5-HT、TNF- α 、补体 C1q 预测重性抑郁障碍急性期患者抗抑郁疗效的价值。**结果:** 无效组治疗后血清 5-HT、TNF- α 、补体 C1q 与治疗前比较差异无统计学意义($P>0.05$),有效组治疗后血清 5-HT 较治疗前增高($P<0.05$),TNF- α 、补体 C1q 较治疗前降低($P<0.05$)。无效组治疗后血清 5-HT 低于有效组,血清 TNF- α 、补体 C1q 高于有效组($P<0.05$)。多因素 Logistic 回归分析结果显示有自杀意念、高 TNF- α 、高补体 C1q 是重性抑郁障碍急性期患者抗抑郁治疗无效的危险因素,高 5-HT 是其保护因素($P<0.05$)。联合 5-HT、TNF- α 、补体 C1q 三项指标预测重性抑郁障碍急性期患者抗抑郁治疗无效的曲线下面积为 0.828,高于单独指标预测的 0.732、0.658、0.677。**结论:** 重性抑郁障碍急性期抗抑郁治疗后无效患者血清 5-HT 偏低,TNF- α 和补体 C1q 偏高,且与抗抑郁治疗无效有关,联合检测血清 5-HT、TNF- α 和补体 C1q 可预测抗抑郁疗效。

关键词: 5-羟色胺;肿瘤坏死因子- α ;补体 C1q;重性抑郁障碍;急性期;抗抑郁;疗效

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Effects of Serum 5-HT, TNF- α and Complement C1q on Antidepressant Efficacy in Patients with Acute Stage of Major Depressive Disorder*

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ABSTRACT Objective: To investigate the effects of serum 5-hydroxytryptamine (5-HT), tumor necrosis factor- α (TNF- α) and complement C1q on antidepressant efficacy in patients with acute stage of major depressive disorder. **Methods:** 185 patients with acute stage of first-episode major depressive disorder who were admitted to Xinjiang Mental Health Center from January 2020 to January 2022 were selected. All patients received antidepressant therapy, and the patients were divided into non-effective group (32 cases) and effective group (153 cases) according to the efficacy. The levels of serum 5-HT, TNF- α and complement C1q were detected before and after treatment. Relevant data were collected, and the multivariate Logistic regression analysis was conducted to analyze the factors that affect the antidepressant efficacy in patients with acute stage of major depressive disorder. The value of serum 5-HT, TNF- α and complement C1q in predicting the antidepressant efficacy in patients with acute stage of major depressive disorder were analyzed by receiver operating characteristic (ROC) curve. **Results:** There were no significant differences in serum 5-HT, TNF- α and complement C1q between the non-effective group after treatment and before treatment ($P>0.05$), while serum 5-HT in the effective group after treatment increased compared with before treatment ($P<0.05$), and TNF- α and complement C1q decreased compared with before treatment ($P<0.05$). After treatment, the serum 5-HT in the non-effective group was lower than that in the effective group, and the serum TNF- α and complement C1q were higher than those in the effective group ($P<0.05$). Multivariate Logistic regression analysis showed that with suicidal ideation, high TNF- α and high complement C1q were risk factors for the failure of antidepressant treatment in patients with acute stage of major depressive disorder, and high 5-HT was protective factor ($P<0.05$). The area under curve of the combination of 5-HT, TNF- α and complement C1q predicted the efficacy of antidepressant treatment in patients with acute stage of major depressive disorder was 0.828, which was higher than 0.732, 0.658 and 0.677 predicted by the single index. **Conclusion:** Serum 5-HT in patients with acute

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stage of major depressive disorder who have failure of antidepressant therapy is lower, and TNF- α and complement C1q are higher, which are related to the failure of anti-depression treatment. Combined detection of serum 5-HT, TNF- α and complement C1q could predict the antidepressant efficacy.

Key words: 5-hydroxytryptamine; Tumor necrosis factor- α ; Complement C1q; Major depressive disorder; Acute stage; Antidepressant; Efficacy

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前言

重性抑郁障碍是一种常见的、严重的精神疾病,通常与主动自杀意念、自杀行为有关;严重影响患者人际关系、工作表现和生活^[1]。口服抗抑郁药物是重性抑郁障碍急性期的主要治疗方法,可有效抑制抑郁症状,稳定患者情绪,但是患者对抗抑郁药物治疗的反应性差异较大,部分患者在治疗后抑郁症状仍得不到有效缓解^[2]。因此有必要探讨抗抑郁疗效的因素和标志物,以寻求改善临床结局。5-羟色胺(5-HT)是一种抑制性神经递质,在大脑皮层及神经突触内含量较高,可调节情绪、精力、记忆力等一系列神经活动,促使愉悦情绪的产生,5-HT的缺乏与抑郁、酗酒、自杀行为等有关^[3,4]。肿瘤坏死因子- α (TNF- α)是一种促炎细胞因子,可破坏血脑屏障的完整性,诱导抑郁样行为^[5],并激活肿瘤坏死因子受体1/核因子- κ B信号通路,诱导过度小胶质细胞激活和神经炎症反应,与抑郁的发生密切相关^[6]。补体C1q在补体激活、清除免疫复合物和坏死细胞、刺激细胞因子产生、调节淋巴细胞功能和情绪调节等方面发挥作用^[7],双相情感障碍血清补体C1q水平显著增高^[8]。本研究拟探讨血清5-HT、TNF- α 、补体C1q与重性抑郁障碍急性期患者抗抑郁疗效的关系,以期为临床治疗提供参考。

1 资料与方法

1.1 临床资料

选择2020年1月至2022年1月新疆精神卫生中心收治的185例首发重性抑郁障碍急性期患者,男63例,女122例,年龄28~45岁,平均(37.45 \pm 7.06)岁;受教育年限7~16年,平均(10.57 \pm 2.91)年。纳入标准: $\textcircled{1}$ 符合《中国抑郁障碍防治指南(第二版)解读:评估与诊断》^[9]中重性抑郁障碍急性期诊断标准; $\textcircled{2}$ 17项汉密尔顿抑郁评分量表(HAMD-17)总分 $>$ 24分^[10]; $\textcircled{3}$ 年龄18周岁及以上。排除标准: $\textcircled{1}$ 合并精神分裂症、双相情感障碍、强迫症、反社会人格障碍、边缘性人格障碍等精神疾病; $\textcircled{2}$ 患有痴呆、癫痫、帕金森综合征等神经系统疾病; $\textcircled{3}$ 合并严重肝、肾、心、肺等重要脏器功能障碍且病情不稳定; $\textcircled{4}$ 近期接受抗抑郁药物治疗。本研究已经获得我院伦理委员会批准,患者知情同意本研究并签署同意书。

1.2 血清5-HT、TNF- α 、补体C1q水平检测

治疗前、治疗后采集患者空腹静脉血3 mL注入真空试管(不含抗凝剂),室温静置后取上层液于离心管(相对离心力3260 \times g,时间5 min),取上层血清置于-80 $^{\circ}$ C冰箱中保存。采用Cobas e601型全自动电化学发光免疫分析系统(瑞士罗氏公司)运用电化学检测血清5-HT水平。采用Multiskan FC酶标仪(美国赛默飞公司)运用酶联免疫吸附试验检测血清TNF- α 、补

体C1q水平,TNF- α 试剂盒购自上海酶联生物科技有限公司,补体C1q试剂盒购自武汉菲恩生物科技有限公司。

1.3 抗抑郁治疗和疗效评估

所有患者均接受草酸艾司西酞普兰片治疗,草酸艾司西酞普兰片(浙江金华康恩贝生物制药有限公司,国药准字H20130105,规格:5 mg)剂量为10-20 mg/d治疗8周,8周后根据HAMD-17总分减分率评价治疗效果,减分率=(治疗前HAMD-17总分-治疗后HAMD-17总分)/治疗前HAMD-17总分 \times 100%,减分率 \geq 25%为有效(有效组),减分率 $<$ 25%为无效(无效组)^[11]。

1.4 临床资料收集

收集患者年龄、性别、吸烟状态[不吸烟、过去吸烟(戒烟3个月以上)、目前吸烟]、饮酒状态[不饮酒、过去饮酒、目前饮酒]、受教育年限、婚姻状态、基线HAMD-17评分、治疗依从性、自杀意念、是否接受心理治疗以及血清5-HT、TNF- α 、补体C1q。治疗依从性采用Morisky服药依从性量表^[12]测评,该量表包括8个问题,比如,"您是否有时会忘记服药?您是否有时会因其他原因不服药?当您服药自觉症状更糟糕时是否自行减药或停药?"等,量表总分0~8分, $<$ 6分为依从性差,6~7分为依从性中等,8分为依从性好。自杀意念采用Beck自杀意念量表中文版(BSI-CV)^[13]测评患者自杀意念,量表第4(主动尝试自杀)或者5项(希望外力结束自己生命)若测评受试者有"弱"或"中等到强烈"倾向为有自杀意念,若无倾向则为无自杀意念。

1.5 统计学分析

SPSS 25.0进行数据分析,计量资料符合正态分布以($\bar{x}\pm s$)表示采用独立样本t检验。计数资料以例(%)表示采用 χ^2 检验。多因素Logistic回归分析影响重性抑郁障碍急性期患者抗抑郁疗效的因素,受试者工作特征(ROC)曲线分析血清5-HT、TNF- α 、补体C1q预测重性抑郁障碍急性期患者抗抑郁疗效的价值。检验水准 $\alpha=0.05$ 。

2 结果

2.1 有效组和无效组治疗前血清5-HT、TNF- α 、补体C1q比较

治疗8周后,无效组32例,有效组153例。两组治疗前血清5-HT、TNF- α 、补体C1q比较差异无统计学意义($P>0.05$)。无效组治疗后血清5-HT、TNF- α 、补体C1q与治疗前比较差异无统计学意义($P>0.05$)。有效组治疗后血清5-HT较治疗前增高($P<0.05$),TNF- α 、补体C1q较治疗前降低($P<0.05$)。无效组治疗后血清5-HT低于有效组($P<0.05$),血清TNF- α 、补体C1q高于有效组($P<0.05$),见表1。

表 1 有效组和无效组治疗前、后血清 5-HT、TNF-α、补体 C1q 比较($\bar{x}\pm s$)
Table 1 Comparison of serum 5-HT, TNF-α and complement C1q before treatment and after treatment
between effective group and non-effective group($\bar{x}\pm s$)

Groups(n)	Time	5-HT(ng/mL)	TNF-α(pg/mL)	C1q(ng/mL)
Non-effective group(n=32)	Before treatment	102.35±16.23	97.12±13.42	8.02±2.67
	After treatment	103.05±16.42	97.58±13.59	8.19±2.49
<i>t/P</i>		0.172/0.864	0.136/0.892	0.263/0.793
Effective group(n=153)	Before treatment	102.41±15.83	97.23±13.06	8.03±2.53
	After treatment	172.54±31.57	50.27±9.15	2.12±0.41
<i>t/P</i>		24.562/0.000	36.426/0.000	27.943/0.000
Comparison of <i>t/P</i> values between the two groups before treatment		0.019/0.985	0.043/0.966	0.201/0.841
Comparison of <i>t/P</i> values between the two groups after treatment		12.096/0.000	24.238/0.000	28.626/0.000

表 2 影响重性抑郁障碍急性期患者抗抑郁治疗无效的单因素分析
Table 2 Univariate analysis of factors affecting the efficacy of antidepressant therapy in patients with acute stage of major depressive disorder

Factors	Non-effective group(n=32)	Effective group(n=153)	<i>t/χ²</i>	<i>P</i>
Age(years, $\bar{x}\pm s$)	37.15±6.26	37.51±6.38	-0.291	0.771
Gender[n(%)]				
Male	12(37.50)	51(33.33)	0.205	0.651
Female	20(62.50)	102(66.67)		
Smoking status[n(%)]				
No smoking	6(18.75)	35(22.87)	1.327	0.515
Smoking in the past	8(25.00)	49(32.03)		
Currently smoking	18(56.25)	69(45.10)		
Drinking status[n(%)]				
Do not drink alcohol	8(25.00)	40(26.14)	0.135	0.935
Drinking in the past	7(21.88)	37(24.18)		
Currently drinking	17(53.12)	76(49.68)		
Years of education(years, $\bar{x}\pm s$)	10.02±2.35	10.69±2.47	-1.407	0.161
Marital status[n(%)]				
Married	21(65.63)	91(59.48)	0.419	0.518
Unmarried or divorced or widowed	11(34.37)	62(40.52)		
Baseline HAMD-17 score(scores,)	29.35±3.06	27.12±2.03	5.126	0.000
Treatment compliance[n(%)]				
Bad	15(46.88)	21(13.72)	20.845	0.000
Medium	11(34.38)	55(35.95)		
Good	6(18.74)	77(50.33)		
Suicide ideation[n(%)]				
Yes	23(71.88)	52(33.99)	15.760	0.000
No	9(28.12)	101(66.01)		
Psychotherapy[n(%)]				
Accept	12(37.50)	92(60.13)	5.507	0.019
Not accepted	20(62.50)	61(39.87)		

2.2 影响重性抑郁障碍急性期患者抗抑郁治疗无效的因素分析

无效组治疗依从性差、有自杀意念、未接受心理治疗比例高于有效组,基线 HAMD-17 评分高于有效组($P < 0.05$),两组年龄、性别、吸烟状态、饮酒状态、受教育年限、婚姻状态比较差异无统计学意义($P > 0.05$),见表 2。以表 1 及表 2 中差异有统计学意义的指标:治疗依从性(赋值:0=中等和好,1=差)、自杀

意念(赋值:0=无,1=有)、心理治疗(赋值:0=接受,1=未接受)及基线 HAMD-17 评分、治疗前后 5-HT、TNF- α 、补体 C1q (均为连续性变量,原值输入)为自变量,重性抑郁障碍急性期患者抗抑郁治疗疗效为因变量(赋值:0=有效,1=无效),采用向后逐步法排除无关变量,最终有自杀意念、高 TNF- α 、高补体 C1q 是重性抑郁障碍急性期患者抗抑郁治疗无效的危险因素,高 5-HT 是其保护因素($P < 0.05$),见表 3。

表 3 影响重性抑郁障碍急性期患者抗抑郁治疗无效的多因素 Logistic 回归方程

Table 3 Multivariate Logistic regression equation affecting the efficacy of antidepressant therapy in patients with acute stage of major depressive disorder

Variable	β	SE	Wald χ^2	OR(95%CI)	P
Constant term	10.659	3.911	7.428	-	0.000
With suicidal ideation	1.592	0.469	11.522	4.914(1.960~12.320)	0.000
High 5-HT	-0.495	0.143	11.982	0.610(0.461~0.807)	0.000
High TNF- α	0.612	0.271	5.100	1.844(1.084~3.137)	0.006
High complement C1q	0.525	0.236	4.949	1.690(1.064~2.675)	0.010

2.3 治疗后血清 5-HT、TNF- α 、补体 C1q 预测重性抑郁障碍急性期患者抗抑郁治疗价值的价值

治疗后血清 5-HT、TNF- α 、补体 C1q 预测重性抑郁障碍急

性期患者抗抑郁治疗无效的曲线下面积为 0.732、0.658、0.677,联合三项指标预测重性抑郁障碍急性期患者抗抑郁治疗无效的曲线下面积为 0.828,高于单独指标预测,见表 4 和图 1。

表 4 治疗后血清 5-HT、TNF- α 、补体 C1q 预测重性抑郁障碍急性期患者抗抑郁治疗效果的 ROC 参数

Table 4 ROC parameters of serum 5-HT, TNF- α and complement C1q after treatment to predict the efficacy of antidepressant therapy in patients with acute stage of major depressive disorder

Factors	Area under curve(95%CI)	Critical value	Sensitivity(%)	Specificity(%)	Youden index
5-HT	0.732(0.662~0.794)	140.42ng/mL	65.63	75.16	0.4079
TNF- α	0.658(0.585~0.726)	72.49pg/mL	68.78	71.24	0.4002
Complement C1q	0.677(0.604~0.744)	5.19ng/mL	62.50	77.12	0.3962
Unite	0.828(0.766~0.880)	-	90.63	71.90	0.6253

3 讨论

重性抑郁障碍是临床常见的精神障碍之一,急性期以持续抑郁情绪、心境变化、兴趣减退甚至完全丧失等为特征;抗抑郁药物是主要的治疗方法,但是效果并不理想,部分患者对抗抑郁治疗反应欠佳,为改善抗抑郁治疗方法和预防抑郁症复发,探讨与抗抑郁疗效相关的生物标志物十分必要^[14]。研究显示重性抑郁障碍的发病机制复杂,与大脑结构和功能改变,免疫炎症反应,中枢神经递质紊乱、神经营养因子缺乏、氧化应激等有关^[15]。

5-HT 作为神经递质,主要分布于松果体和下丘脑,通过与细胞表面受体结合调节痛觉、睡眠、情绪、记忆力等多种生理功能,5-HT 含量及功能异常与焦虑、抑郁、精神分裂症等各种神经精神疾病有关^[16]。研究显示冠心病伴焦虑抑郁患者^[17]、中度抑郁患者^[18]血清 5-HT 偏低,经临床抗抑郁治疗后血清 5-HT 增高,可见 5-HT 与抗抑郁治疗密切相关。本研究发现重性抑郁障碍急性期患者治疗后低血清 5-HT 与抗抑郁治疗无效有关,并可预测抗抑郁治疗效果。分析原因为 5-HT 通过能量梯度移动到神经元和星形胶质细胞,与突触外高亲和力 5-HT 受体结合

促使神经递质传导和情绪调节,5-HT 活性增高可促使愉悦情绪的产生^[19],因此高 5-HT 可预防抑郁的发生,在中性抑郁障碍中发挥保护作用。

TNF- α 是一种关键的炎症因子,可引起炎症、细胞凋亡,并介导受刺激巨噬细胞释放白细胞介素(IL)-6、IL-8 和 IL-1 β 等多种细胞因子,诱导炎症反应^[20]。TNF- α 在神经性疼痛和抑郁样疾病中表达增加,通过与肿瘤坏死因子受体 1 结合影响海马神经发生、神经可塑性、髓鞘重塑^[21]。有荟萃分析表明与健康对照组相比,抑郁症患者血清 TNF- α 显著增高^[22]。动物研究显示 TNF- α 中枢给药可导致啮齿动物出现抑郁样症状^[23]。本研究发现血清 TNF- α 增高与重性抑郁障碍急性期患者抗抑郁治疗后反应性差有关,高 TNF- α 是抗抑郁治疗无效的危险因素。推测可能的机制为 TNF- α 过度表达可促使小胶质细胞活化并释放促炎细胞因子,诱导神经炎症反应,破坏血脑屏障,影响神经内分泌功能、区域脑活动和神经递质代谢,导致抑郁样症状和行行为^[24],因此高 TNF- α 可提示抗抑郁治疗效果较差的可能。

补体系统介导先天免疫系统和获得性免疫系统之间的免疫反应,启动免疫调节过程,补体系统的异常会导致免疫功能障碍和炎症反应,补体 C1q 参与经典补体通路的启动,是自然

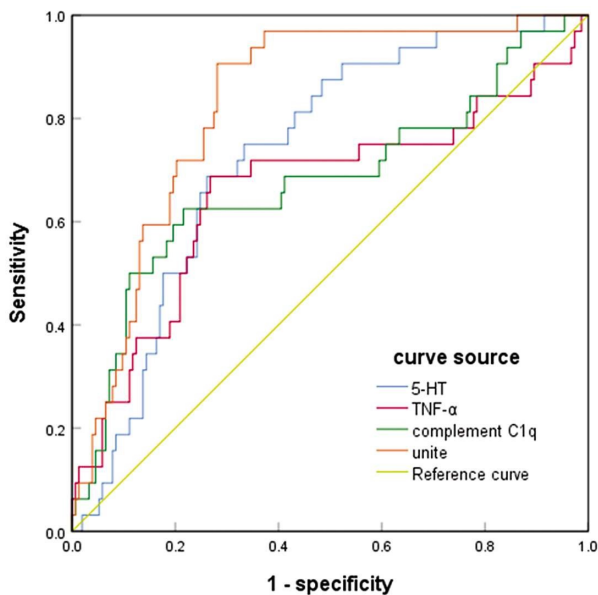


图 1 血清 5-HT、TNF- α 、补体 C1q 预测重性抑郁障碍急性期患者抗抑郁治疗效果的 ROC 图

Fig. 1 ROC chart of serum 5-HT, TNF- α and complement C1q predicting the efficacy of antidepressant therapy in patients with acute stage of major depressive disorder

免疫系统的重要组成部分,对补体系统激活,单核细胞活化,炎症反应和细胞凋亡至关重要^[25]。补体 C1q 可增加吞噬性小胶质细胞的数量,加重早期突触丧失程度,诱发神经炎症^[26,27]。本研究发现重性抑郁障碍急性期患者血清补体 C1q 显著增高,高补体 C1q 是抗抑郁治疗无效的危险因素。分析补体 C1q 可能通过激活补体通路,诱导免疫功能障碍和神经炎症,导致突触丧失,神经细胞凋亡和大脑结构缺陷,引起重性抑郁障碍^[28],因此高补体 C1q 提示抗抑郁治疗后抑郁症状未得到有效缓解,与治疗结果偏差有关。本研究多因素 Logistic 回归分析显示自杀意念与重性抑郁障碍急性期患者抗抑郁治疗无效也有关,研究表明抑郁程度越重,自杀意念越强,自杀意念加重认知功能损害,影响抗抑郁治疗效果^[29]。

ROC 分析联合血清 5-HT、TNF- α 和补体 C1q 预测重性抑郁障碍急性期患者抗抑郁治疗无效的曲线下面积为 0.828,提示三者联合预测的价值较高。

综上,重性抑郁障碍急性期抗抑郁治疗后无效患者血清 5-HT 偏低,TNF- α 和补体 C1q 偏高,高 TNF- α 和补体 C1q 是重性抑郁障碍急性期患者抗抑郁治疗无效的危险因素,高 5-HT 是保护因素,联合检测血清 5-HT、TNF- α 和补体 C1q 对重性抑郁障碍急性期患者抗抑郁疗效的预测价值较高。

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