

· 论著·临床 ·

精神分裂症患者外周色氨酸-犬尿氨酸代谢通路中代谢物水平与临床症状的关系

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【摘要】 背景 精神分裂症是一种常见的重性精神障碍,其发病机制复杂,目前关于精神分裂症外周血清和尿液犬尿氨酸(KYN)代谢物相关性的研究有限。目的 分析精神分裂症患者外周血清和尿液色氨酸(TRP)-KYN代谢物与白细胞介素-6(IL-6)的浓度以及血清与尿液KYN代谢物的相关性以及代谢物水平与临床症状的相关性,以期探索精神分裂症的潜在生物标志物提供参考。方法 纳入2021年12月—2022年12月在杭州市第七人民医院住院治疗或门诊就诊的、符合《精神障碍诊断与统计手册(第5版)》(DSM-5)精神分裂症诊断标准的38例患者为研究对象,同期在杭州市社区招募健康对照组共26例。采用阳性和阴性症状量表(PANSS)评定患者的精神病性症状,采用超高效液相色谱串联三重四极杆质谱技术检测所有受试者血清和尿液TRP、KYN、犬尿喹啉酸(KYNA)、喹啉酸(QUIN)、吡啶甲酸(PIC)、黄尿酸和5-羟色胺(5-HT)水平,采用酶联免疫分析检测血清和尿液IL-6水平。采用Pearson相关分析考查精神分裂症患者血清与尿液TRP-KYN代谢物之间的相关性以及代谢物水平与临床症状的相关性。结果 精神分裂症患者血清IL-6水平高于健康对照组,差异有统计学意义($U=798.500, P<0.01$)。精神分裂症患者尿液PIC水平低于健康对照组,差异有统计学意义($U=253.000, P=0.013$)。精神分裂症患者血清KYN水平与尿液QUIN/KYNA、QUIN/PIC均呈正相关($r=0.562, 0.438, P$ 均 <0.05)。精神分裂症患者血清5-HT/KYN与PANSS总评分和阴性症状分量表评分均呈正相关($r=0.458, 0.455, P$ 均 <0.01)。结论 精神分裂症患者血清TRP-KYN代谢物水平与尿液中神经毒性代谢物比值有关,并与阴性症状严重程度呈正相关。

【关键词】 精神分裂症;血清;尿液;色氨酸;犬尿氨酸;代谢物;临床症状

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Relationship between metabolites of peripheral tryptophan-kynurenine metabolic pathway and clinical symptoms in patients with schizophrenia

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【Abstract】 **Background** Schizophrenia is a common severe mental disorder with complex pathogenesis. There are few studies on the correlation between kynurenine metabolites in peripheral serum and urine in schizophrenia. **Objective** To investigate the concentration of tryptophan-kynurenine metabolites and interleukin-6 (IL-6) in serum and urine in patients with schizophrenia, and their correlation with clinical symptoms, so as to explore potential biological characteristics related to schizophrenia. **Methods** A total of 38 patients with schizophrenia who met the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), and were hospitalized or attended outpatient clinic at Hangzhou Seventh People's Hospital from December 2021 to December 2022 were included in the study. Additionally, 26 healthy individuals were concurrently recruited from the community of Hangzhou to serve as a control group. All participants were requested to complete the Positive and Negative Symptom Scale (PANSS). The levels of tryptophan (TRP), kynurenine (KYN), kynurenic acid (KYNA), quinolinic acid (QUIN), picolinic acid (PIC), xanthurenate and 5-hydroxytryptamine (5-HT) in both serum and urine were measured using ultra-high-performance liquid

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chromatography-triple quadrupole linear ion trap mass spectrometry. Serum and urine IL-6 were measured using enzyme-linked immunosorbent assay. Pearson correlation analysis was conducted to examine the correlation between serum and urinary KYN metabolites, as well as the correlation between metabolite levels and clinical symptoms in the patient group. **Results** Patients with schizophrenia had significantly higher level of IL-6 in serum ($U=798.500$, $P<0.01$) and lower level of PIC in urine ($U=253.000$, $P=0.013$) compared with the control group. Additionally, level of serum KYN was positively correlated with QUIN/KYNA ratio and QUIN/PIC ratio ($r=0.562$, 0.438 , $P<0.05$) in patients with schizophrenia. 5-HT/KYN ratio in serum was positively correlated with PANSS total score and negative symptom subscale score ($r=0.458$, 0.455 , $P<0.01$) in patients with schizophrenia. **Conclusion** Serum TRP-KYN pathway metabolite levels in patients with schizophrenia were associated with neurotoxic metabolite ratios in urine and the severity of negative symptoms. [Funded by Zhejiang Medical and Health Science and Technology Program Exploratory (number, 2022KY990)]

【Keywords】 Schizophrenia; Serum; Urine; Tryptophan; Kynurenine; Metabolites; Clinical symptoms

精神分裂症是一种常见的重性精神障碍,临床表现多样,异质性较高,病理机制复杂^[1]。精神分裂症终生患病率约为0.6%^[2],给家庭和社会带来沉重的负担。既往研究结果显示,犬尿氨酸(kynurenine, KYN)代谢通路失调是精神分裂症发病机制的假设之一^[3-5]。精神分裂症患者色氨酸(tryptophan, TRP)水平较低,可能与脑结构完整性较差有关^[6]。TRP是一种人体必需的氨基酸,主要通过犬尿氨酸通路代谢,形成多种具有神经活性的代谢产物,参与调节精神疾病相关的氧化应激,并与免疫炎症过程密切相关^[7-8]。TRP-KYN代谢通路与精神分裂症患者精神病性症状及认知功能受损有关,也与抗精神病药物疗效及疾病预后有关^[9-11]。既往研究显示,脑脊液和脑组织中犬尿喹啉酸(kynurenic acid, KYNA)水平异常与精神分裂症发病机制有关^[12-14]。KYN水平升高,黄嘌呤酸水平降低,可能是精神分裂症的生物标志物^[15-16]。KYN作为TRP-KYN代谢通路的第一步产物,本身无神经活性,在相关酶的作用下迅速降解为具有神经活性的下游代谢产物^[17]。在正常生命活动状态下,该代谢通路的下游代谢产物处于平衡状态;当下游代谢产物之间失去平衡时,会导致神经可塑性改变,影响精神疾病的发生发展。目前关于精神分裂症血清KYN和KYNA水平的研究较多,缺乏对KYN下游代谢物水平异常以及代谢物之间平衡状态的全面分析。此外,目前研究主要集中于外周血KYN代谢物,尚缺乏同时分析外周血和尿液TRP-KYN代谢通路代谢物对精神分裂症影响的研究。故本研究检测首发未服药的精神分裂症患者与健康对照组血清和尿液TRP-KYN代谢物及白细胞介素-6(interleukin-6, IL-6)水平,比较两组血清和尿液TRP-KYN代谢物及IL-6水平的差异,并分析精神分裂症患者血清和尿液代谢物之间的相关性以及代谢物水平与临床症状的相关性,为进

一步探索精神分裂症相关的潜在生物标志物提供参考。

1 对象与方法

1.1 对象

选取2021年12月—2022年12月在浙江大学医学院附属精神卫生中心(杭州市第七人民医院)住院或门诊治疗的精神分裂症患者为研究对象(患者组)。入组标准:①符合《精神障碍诊断与统计手册(第5版)》(Diagnostic and Statistical Manual of Mental Disorders, fifth edition, DSM-5)精神分裂症诊断标准;②汉族;③年龄16~46岁;④小学及以上受教育程度;⑤首次发病且未服药。排除标准:①符合DSM-5其他诊断标准者;②合并躯体疾病者。符合入组标准且不符合排除标准共38例。

同期在杭州市社区招募与患者组年龄和性别相匹配的健康人群为健康对照组。入组标准:①汉族;②年龄16~46岁;③小学及以上受教育程度。排除标准:①目前或既往符合DSM-5任何诊断;②两系三代精神疾病家族史阳性;③既往有颅脑损伤且伴昏迷史。符合入组标准且不符合排除标准共26例。

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1.2 评定工具

采用自制问卷收集被试的一般资料,包括年龄和性别。

采用阳性和阴性症状量表(Positive and Negative Syndrome Scale, PANSS)^[18]评定患者的精神病性症状。该量表共30个条目,包括阳性症状(7项)、阴性症状(7项)、一般精神病理(16项)3个分量表。采用1~7分7级评分,总评分为各分量表评分之和,总评

分范围 30~210 分,总评分越高表明精神病性症状越严重。本研究中,该量表 Cronbach's α 系数为 0.871。

1.3 实验室检测

血清样本采集:于 8:00 抽取被试空腹肘静脉血 3 mL,静置 1 h 后,3 500 r/min($r=4$ cm)离心 5 min,取上清液,于 -80°C 冰箱冻存待测。尿液样本采集:收集随机尿(中段)3 mL,3 500 r/min($r=4$ cm)离心 5 min,取上清液,于 -80°C 冰箱冻存待测。

采用超高效液相色谱串联三重四极杆质谱技术检测色氨酸/犬尿氨酸代谢物,使用 Agilent 1290 Infinity UHPLC 系统进行分离,使用 QTRAP 5500 质谱仪在正/负离子模式下进行质谱分析。检测代谢物包括 TRP、KYN、KYNA、QUIN、吡啶甲酸(picolinic acid,PIC)、黄尿酸和 5-羟色胺(5-hydroxytryptamine, 5-HT)。采用酶联免疫吸附检测 IL-6 水平。

1.4 评定方法与质量控制

由两名经过一致性培训的精神科医师在安静的评估室进行 PANSS 评定。评定耗时 30~40 min。

1.5 统计方法

采用 Python Pingouin 进行统计分析。采用 Shapiro-Wilk 检验原始数据是否符合正态分布。计数资料以 $[n(\%)]$ 表示,组间比较用 χ^2 检验或 Fisher 确切概率检验;计量资料均不符合正态分布,故以 $[M(Q_1\sim Q_3)]$ 表示,组间比较采用 Mann-Whitney U 检验;比较患者组与健康对照组 TRP-KYN 通路代谢物比值(5-HT/KYN、KYN/TRP、KYNA/KYN、QUIN/KYNA 和 QUIN/PIC)。对原始数据进行自然

对数转换,控制年龄和性别的影响后,对数据进行 Z -score 标准化处理。采用 Pearson 相关分析考查患者组血清和尿液 KYN 代谢物之间的相关性以及代谢物水平与 PANSS 评分的相关性。经 FDR 校正 $P<0.05$,认为差异有统计学意义。

2 结 果

2.1 一般资料

患者组共 38 例,其中男性 26 例(68.42%),女性 12 例(31.58%),年龄 16~46 岁 $[(24.39\pm 8.30)$ 岁]。健康对照组共 26 例,其中男性 16 例(61.54%),女性 10 例(38.46%),年龄 16~46 岁 $[(27.73\pm 5.27)$ 岁]。两组年龄和性别差异均无统计学意义(P 均 >0.05)。

2.2 两组 IL-6 及 TRP-KYN 代谢通路代谢物水平比较

患者组血清 IL-6 水平高于健康对照组,差异有统计学意义 $[0.74(0.41\sim 1.64)$ vs. $0.41(0.22\sim 0.43)$, $U=798.500$, $P<0.01$]。两组血清 TRP-KYN 代谢通路代谢物水平及其比值差异均无统计学意义(P 均 >0.05)。见表 1。

患者组尿液 PIC 水平低于健康对照组,差异有统计学意义($U=253.000$, $P=0.013$)。见表 2。

2.3 相关分析

患者组血清 KYN 水平与尿液 QUIN/KYNA($r=0.562$, $P<0.05$)、QUIN/PIC($r=0.438$, $P<0.05$)均呈正相关。患者组血清 5-HT/KYN 与 PANSS 总评分($r=0.458$, $P<0.01$)和阴性症状分量表评分($r=0.455$, $P<0.01$)均呈正相关。

表 1 两组血清 TRP-KYN 代谢通路代谢物水平及其比值比较 $[M(Q_1\sim Q_3)]$
Table 1 Comparison of Serum tryptophan-kynurenine pathway metabolites level and ratios between two groups

组 别	TRP	KYN	KYNA	QUIN	PIC	黄尿酸	5-HT
患者组 ($n=38$)	7 946.68 (7 349.07~9 231.64)	286.54 (238.44~428.50)	0.14 (0.11~0.15)	47.11 (45.47~50.73)	40.47 (35.55~58.78)	2.89 (2.41~3.96)	93.94 (63.29~134.38)
健康对照组 ($n=26$)	8 244.74 (7 623.89~9 165.16)	298.41 (208.67~406.81)	0.16 (0.14~0.19)	47.02 (45.39~49.25)	37.51 (31.09~53.91)	3.71 (2.93~4.95)	100.78 (72.34~139.20)
U	452.000	538.000	332.000	550.000	592.000	333.000	433.000
P	0.571	0.571	0.090	0.571	0.396	0.090	0.571
组 别	5-HT/KYN	KYN/TRP	KYNA/KYN	QUIN/KYNA	QUIN/PIC		
患者组 ($n=38$)	0.32 (0.19~0.49)	0.04 (0.03~0.05)	0.00 (0.00~0.00)	0.00 (0.00~0.00)	1.15 (0.79~1.35)		
健康对照组 ($n=26$)	0.32 (0.25~0.68)	0.04 (0.03~0.04)	0.00 (0.00~0.00)	294.10 (261.64~340.44)	1.29 (0.87~1.57)		
U	427.000	536.000	339.000	672.000	419.000		
P	0.571	0.571	0.090	0.090	0.571		

注:TRP,色氨酸;KYN,犬尿氨酸;KYNA,犬尿喹啉酸;QUIN,喹啉酸;PIC,吡啶甲酸;5-HT,5-羟色胺

表2 两组尿液TRP-KYN代谢通路代谢物水平及其比值比较[M(Q₁-Q₃)]
Table 2 Comparison of urine tryptophan-kynurenine pathway metabolites level and ratios between two groups

组别	TRP	KYN	KYNA	QUIN	PIC	黄尿酸	5-HT
患者组 (n=38)	15 154. 30 (9 794. 69~27 895. 75)	824. 73 (439. 77~1289. 27)	0. 61 (0. 46~1. 27)	4 083. 28 (1 705. 2~6 174. 33)	177. 58 (125. 88~219. 35)	797. 97 (439. 95~1 367. 10)	117. 78 (51. 27~186. 95)
健康对照组 (n=26)	18 433. 06 (14 589. 55~25 334. 92)	781. 39 (385. 36~1292. 52)	0. 90 (0. 53~1. 21)	3 977. 12 (3 052. 05~4 817. 86)	243. 32 (184. 50~298. 30)	987. 80 (671. 80~1 599. 60)	115. 88 (90. 82~155. 44)
U	434. 000	524. 000	418. 000	510. 000	253. 000	406. 000	486. 000
P	0. 554	0. 812	0. 491	0. 902	0. 013	0. 430	0. 918
组别	5-HT/KYN	KYN/TRP	KYNA/KYN	QUIN/KYNA	QUIN/PIC		
患者组 (n=38)	0. 13 (0. 08~0. 18)	0. 05 (0. 04~0. 06)	0. 00 (0. 00~0. 00)	5 607. 98 (3 423. 23~8 027. 64)	22. 50 (15. 00~37. 90)		
健康对照组 (n=26)	0. 17 (0. 09~0. 23)	0. 04 (0. 03~0. 06)	0. 00 (0. 00~0. 00)	3 994. 07 (3 267. 17~6 118. 40)	14. 94 (11. 99~21. 70)		
U	390. 000	628. 000	394. 000	596. 000	665. 000		
P	0. 377	0. 295	0. 377	0. 377	0. 129		

注:TRP,色氨酸;KYN,犬尿氨酸;KYNA,犬尿喹啉酸;QUIN,喹啉酸;PIC,吡啶甲酸;5-HT,5-羟色胺

3 讨 论

本研究中,精神分裂症患者尿液PIC水平低于健康对照组。PIC作为KYN下游代谢物,具有神经保护、免疫和抗增殖作用^[19-20]。TRP-KYN代谢过程中,2-氨基-3-羧基甲酸酯-6-半醛(2-amino-3-carboxymuconate-6-semialdehyde, ACMS)代谢生成QUIN,同时在2-氨基3-羧基粘康酸-6-半醛脱羧酶(2-amino 3-carboxymuconate 6-semialdehyde decarboxylase, ACMSD)的作用下代谢生成PIC^[21]。ACMSD是代谢过程的关键酶,能维持QUIN和PIC之间的平衡^[22]。PIC水平降低可能是因为ACMSD活性改变,引起QUIN和PIC两种代谢产物失衡。

本研究结果还显示,精神分裂症患者血清KYN水平与尿液QUIN/KYNA和QUIN/PIC均呈正相关。血清KYN水平改变会影响尿液KYN代谢物之间的平衡,引起QUIN的神经毒性增加。QUIN是一种N-甲基-D-天冬氨酸(N-methyl-D-aspartate, NMDA)受体激动剂,可以直接刺激突触末梢谷氨酸(glutamate, Glu)释放,抑制星形胶质细胞对Glu的再摄取,增加兴奋性神经毒性^[23]。KYNA和PIC能够对抗QUIN的神经毒性作用,QUIN与KYNA和PIC的失衡会引起神经损害,加重精神分裂症患者的精神病性症状。QUIN增加可能导致精神分裂症患者阴性症状加重^[24]。此外,KYNA是NMDA受体拮抗剂,具有神经保护作用^[25],外周KYNA水平降低可能导致精神分裂症患者的临床症状加重^[26]。

相关分析结果显示,精神分裂症患者血清5-HT/KYN与PANSS总评分及阴性症状分量表评分均呈正相关,提示精神分裂症患者血清5-HT和KYN的比值与临床症状严重程度有关,尤其与阴性

症状严重程度有关。既往研究显示^[27],KYN通路和5-HT通路失衡与社交孤立等阴性症状有关。外周及中枢5-HT水平改变及5-HT合成限速酶基因多态性与精神分裂症的发病有关,且与患者的阳性症状和阴性症状相关^[28-30]。精神分裂症患者中枢5-HT激活水平与阴性症状严重程度呈正相关^[29],外周5-HT水平升高与精神疾病患者攻击行为增加有关^[30]。

综上所述,精神分裂症患者存在外周TRP-KYN代谢通路异常,血清KYN代谢物水平与尿液KYN神经毒性代谢物比值有关,并与阴性症状严重程度呈正相关。本研究存在一定局限性:①横断面研究无法推论因果关系,且样本量较小;②未结合其他表型数据(如脑影像、脑电等);③本研究中的TRP-KYN通路代谢物水平为单个时点数据。在未来研究中,可以进一步增加研究样本量,进行多时点随访,同时结合其他表型数据进行更深入的研究。

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