·论著·

血清Klotho、KLK6、NCAM水平对老年癫痫患者病情严重程度的评估价值

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摘要 **目的** 探讨血清Klotho、激肽释放酶6（KLK6）及神经细胞黏附因子（NCAM）水平对老年癫痫患者病情严重程度的评估效能。**方法** 选取2022年1月至2024年2月间我院收治的118例老年癫痫患者作为癫痫组，同期124例健康老年人作为健康组。根据脑电图结果将118例患者分为轻中度组（$n = 83$）及重度组（$n = 35$）。用Spearman相关分析老年癫痫患者血清Klotho、KLK6及NCAM水平与国立医院癫痫发作严重程度量表（NHS3）评分的相关性；用多因素logistic回归分析老年癫痫病情严重程度的影响因素；用受试者操作特征曲线分析血清Klotho、KLK6及NCAM诊断老年重度癫痫的效能。**结果** 与健康组比较，癫痫组血清Klotho、NCAM水平降低（$t = 10.427$、13.052，$P < 0.05$），KLK6水平升高（$t = 15.107$，$P < 0.05$）。与轻中度组比较，重度组血清Klotho、NCAM水平降低（$t = 9.576$、7.598，$P < 0.05$），NHS3评分、KLK6水平升高（$t = 14.546$、6.183，$P < 0.05$）。老年癫痫患者血清Klotho、NCAM水平与NHS3评分呈负相关（$r = -0.429$、-0.401，$P < 0.05$），KLK6水平与NHS3评分呈正相关（$r = 0.435$，$P < 0.05$）。血清Klotho（$OR = 0.942$，95%CI：0.909~0.976）和NCAM（$OR = 0.869$，95%CI：0.773~0.977）为癫痫病情严重程度的保护因素（$P < 0.05$），KLK6（$OR = 1.264$，95%CI：1.058~1.511）为危险因素（$P < 0.05$）。血清Klotho、KLK6及NCAM联合诊断重度癫痫的灵敏度及特异度分别为91.43%、81.93%，曲线下面积为0.902，高于Klotho（$Z = 2.080$，$P = 0.038$）、KLK6（$Z = 2.634$，$P = 0.008$）及NCAM（$Z = 2.373$，$P = 0.018$）单独诊断。**结论** 老年癫痫患者血清Klotho和NCAM水平较低，KLK6水平较高，三者与患者病情严重程度密切相关，且具有一定评估价值。

关键词 癫痫；病情严重程度；Klotho；激肽释放酶6；神经细胞黏附因子
中图分类号 R742.1 **文献标志码** A **文章编号** 0258-4646（2026）07-0609-05
网络出版地址 https://link.cnki.net/urlid/21.1227.R.20260709.1704.006
DOI：10.12007/j.issn.0258-4646.2026.07.007

Evaluation value of the serum Klotho, KLK6 and NCAM levels for determining the disease severity in older patients with epilepsy

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Abstract **Objective** To evaluate the efficacy of serum Klotho, kallikrein-releasing enzyme 6 (KLK6), and neural cell adhesion molecule (NCAM) levels in determining the disease severity in older patients with epilepsy. **Methods** A total of 118 older patients with epilepsy who were admitted to our hospital between January 2022 and February 2024 were included in the epilepsy group, and 124 healthy older people were included in the healthy group. The 118 patients were assigned to a mild-to-moderate group ($n = 83$) and a severe group ($n = 35$). Spearman's correlation analysis was used to determine the correlations between the serum Klotho, KLK6, and NCAM levels and the National Hospital Seizure Severity Scale (NHS3) score in older patients with epilepsy. Multivariate logistic regression was used to determine the factors influencing the severity of epilepsy in the older patients. Receiver operating characteristic (ROC) curve analysis was used to determine the efficacy of the serum Klotho, KLK6, and NCAM levels in the diagnosis of severe epilepsy in the older patients. **Results** Compared with the healthy group, the epilepsy group had lower serum Klotho and NCAM levels ($t = 10.427$, 13.052, both $P < 0.05$), and a higher KLK6 level ($t = 15.107$, $P < 0.05$). Compared with the mild-to-moderate group, the severe group had lower serum Klotho and NCAM levels ($t = 9.576$, 7.598, both $P < 0.05$), and higher NHS3 score and KLK6 level ($t = 14.546$, 6.183, both $P < 0.05$). Spearman's correlation analysis showed that the serum Klotho and the NCAM levels in the older patients with epilepsy were negatively correlated with the NHS3 score ($r = -0.429$, -0.401, both $P < 0.05$), and the KLK6 level was positively correlated with the NHS3 score ($r = 0.435$, $P < 0.05$). Logistic regression analysis showed that the serum Klotho level ($OR = 0.942$, 95%CI: 0.909–0.976) and the NCAM

基金项目：宁夏自然科学基金（2022AAC02167）
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收稿日期：2025-07-16
网络出版时间：2026-07-10 10:17:44

level (*OR* = 0.869, 95%*CI*: 0.773–0.977) were protective factors for the severity of epilepsy ($P < 0.05$), and the KLK6 level (*OR* = 1.264, 95%*CI*: 1.058–1.511) was a risk factor ($P < 0.05$). ROC curve analysis showed that the sensitivity and specificity of the combined diagnosis of severe epilepsy using the serum Klotho, KLK6, and NCAM levels were 91.43% and 81.93%, respectively, with an area under the curve of 0.902. The diagnostic efficacy was higher than that of the Klotho level ($Z = 2.080$, $P = 0.038$), KLK6 level ($Z = 2.634$, $P = 0.008$), and NCAM level ($Z = 2.373$, $P = 0.018$) alone. **Conclusion** The serum Klotho and NCAM levels are lower, and the KLK6 level is higher in older patients with epilepsy. They are closely related to the severity of disease, and have evaluation value.

Keywords epilepsy; disease severity; Klotho; kallikrein-releasing enzyme 6; neural cell adhesion molecule

癫痫是一种脑部神经元异常放电所致反复发作的神经系统疾病。癫痫在老年人群中的发病率高于其他年龄段，但由于老年癫痫往往症状不典型，如短暂性意识障碍、精神错乱、躯体感觉异常，极易被误诊为心脑血管疾病、代谢性脑病或正常衰老健忘[1-4]。脑电图是评估癫痫病情严重程度的客观手段，但只能反映脑电活动，具有局限性。目前尚无准确评估癫痫病情的生物标志物。研究[5-7]发现，Klotho、激肽释放酶6（kallikrein-releasing enzyme 6，KLK6）和神经细胞黏附因子（neural cell adhesion molecule，NCAM）参与介导神经损伤过程，但这三者与癫痫及病情严重程度的关系目前尚不明确。因此，本研究通过检测老年癫痫患者的血清Klotho、NCAM和KLK6水平，探讨其与老年癫痫患者病情严重程度的关系。

1　材料与方法

1.1　研究对象

选取2022年1月至2024年2月间我院收治的老年癫痫患者118例，设为癫痫组。纳入标准：符合癫痫诊断标准[8]；年龄≥60岁；首次发病，入院前未进行抗癫痫治疗。排除标准：伴有脑部器质性病变；合并恶性肿瘤；合并血液或免疫系统疾病；近半年手术史；肝脏等器官功能严重受损。另选取同期124例健康老年人，设为健康组。纳入标准：年龄≥60岁；既往无癫痫史或可能引起癫痫的疾病史。排除标准同癫痫组。2组患者性别、年龄等差异无统计学意义，具有可比性。本研究获得我院伦理委员会批准（GKY2021-1109-02）。所有研究对象知情同意。

1.2　研究方法

1.2.1　血清Klotho、KLK6及NCAM水平检测：抽取所有研究对象静脉血4 mL，1 500 *g*离心10 min，按照Klotho、KLK6及NCAM ELISA试剂盒（货号ZK-2819，上海臻科生物科技有限公司；货号ab287163，英国abcam公司；货号ZK-4381，上海臻科生物科技有限公司）说明书检测血清Klotho、KLK6及NCAM水平。

1.2.2　癫痫病情严重程度评估：采用脑电图仪（Nicolet EEG，美国内特斯神经系统公司）对癫痫组患者行脑电图检查，描记时间≥20 min。脑电图显示广泛弥漫性慢波或周期样放电即为重度癫痫[9]。根据脑电图结果，将癫痫组患者再分为轻中度组（$n = 83$）及重度组（$n = 35$）。采用国立医院癫痫发作严重程度量表（National Hospital Seizure Severity Scale，NHS3）评估癫痫组患者癫痫发作程度，总分27分。

1.3　统计学分析

采用PASS 15软件计算样本量，设双侧α=0.05，β=0.90，计算得出$n = 86$，因此，每组样本量至少为86例。采用SPSS 25.0软件进行统计学分析。计数资料用率（%）表示，组间比较采用χ^2检验。计量资料用$\bar{x} \pm s$表示，组间比较采用*t*检验。采用Spearman相关分析老年癫痫患者血清Klotho、KLK6及NCAM水平与NHS3评分的相关性。采用多因素logistic回归分析老年癫痫病情严重程度的影响因素。采用受试者操作特征（receiver operating characteristic，ROC）曲线分析血清Klotho、KLK6及NCAM诊断老年重度癫痫的效能。采用临床决策分析评估Klotho、KLK6及NCAM的临床应用价值。$P < 0.05$为差异有统计学意义。

2　结果

2.1　癫痫组与健康组血清Klotho、KLK6及NCAM水平比较

与健康组比较，癫痫组血清Klotho和NCAM水平降低[(301.17 ± 39.88) pg/mL vs. (362.09 ± 50.14) pg/mL，$t = 10.427$，$P < 0.001$；(95.42 ± 12.74) μg/mL vs. (119.83 ± 16.07) μg/mL，$t = 13.052$，$P < 0.001$]，KLK6

水平升高[(3.40 ± 0.77)μg/L vs.(2.21 ± 0.41)μg/L，t = 15.107，P < 0.001]。

2.2　轻中度组与重度组患者临床资料比较

重度组NHS3评分显著高于轻中度组(t = 14.546，P < 0.05)，2组基础疾病、发作类型等比较无统计学差异(P > 0.05)。见表1。

表1　轻中度组与重度组老年癫痫患者临床资料比较

Tab.1　Comparison of clinical data between mild-to-moderate group and severe group of older patients with epilepsy

Indicator	Mild-to-moderate group (n = 83)	Severe group (n = 35)	t/χ^2	P
Age (year)	69.63 ± 6.87	70.85 ± 7.12	0.872	0.385
Sex [n (%)]			0.158	0.691
Male	46 (55.42)	18 (51.43)		
Female	37 (44.58)	17 (48.57)		
Body mass index (kg/m^2)	23.71 ± 2.39	23.34 ± 2.36	0.771	0.442
Underlying disease [n (%)]				
Hypertension	22 (26.51)	12 (34.29)	0.726	0.394
Diabetes	17 (20.48)	6 (17.14)	0.175	0.676
Coronary heart disease	13 (15.66)	7 (20.00)	0.329	0.566
Type of attack [n (%)]			1.210	0.546
Generalized tonic clonic seizures	32 (38.55)	17 (48.57)		
Partial seizure	28 (33.73)	11 (31.43)		
Simple partial attack	23 (27.71)	7 (20.00)		
NHS3 score	7.37 ± 1.82	13.97 ± 3.05	14.546	<0.001

2.3　轻中度组与重度组患者血清Klotho、KLK6及NCAM水平比较

与轻中度组比较，重度组血清Klotho和NCAM水平显著降低[(246.57 ± 32.35) pg/mL vs.(324.19 ± 43.06) pg/mL，t = 9.576，P < 0.001；(81.63 ± 10.92) μg/mL vs.(101.24 ± 13.51) μg/mL，t = 7.598，P < 0.001]，KLK6水平显著升高[(4.08 ± 0.86) μg/L vs.(3.12 ± 0.73) μg/L，t = 6.183，P < 0.001]。

2.4　癫痫组患者血清Klotho、KLK6及NCAM水平与NHS3评分的相关性

癫痫组患者血清Klotho和NCAM水平与NHS3评分呈负相关(r = –0.429，P < 0.05；r = –0.401，P < 0.05)，KLK6水平与NHS3评分呈正相关(r = 0.435，P < 0.05)。

2.5　老年癫痫病情严重程度的影响因素

以癫痫病情严重程度为因变量(重度=1、轻中度=0)，以患者血清Klotho、KLK6及NCAM水平作自变量(均以实测值代入)，进行多因素logistic回归分析(逐步向前法)，结果如表2所示，血清Klotho和NCAM为癫痫病情严重程度的保护因素(P < 0.05)，KLK6为危险因素(P < 0.05)。

表2　老年癫痫病情严重程度的多因素logistic回归分析

Tab.2　Multivariate logistic regression analysis of the severity of epilepsy in older patients

Variable	β	SE	Wald χ^2	P	OR	95% CI
Klotho	–0.060	0.018	11.019	0.001	0.942	0.909–0.976
KLK6	0.234	0.091	6.628	0.010	1.264	1.058–1.511
NCAM	–0.140	0.060	5.477	0.019	0.869	0.773–0.977

2.6　血清Klotho、KLK6及NCAM对老年重度癫痫的诊断价值

ROC曲线显示，血清Klotho、KLK6及NCAM单独诊断重度癫痫的曲线下面积(area under the curve，AUC)分别为0.815、0.765和0.798，血清Klotho、KLK6及NCAM联合诊断的AUC达0.902，高于Klotho(Z = 2.080，P = 0.038)、KLK6(Z = 2.634，P = 0.008)及NCAM(Z = 2.373，P = 0.018)单独诊断。见表3、图1。

表3　血清Klotho、KLK6及NCAM检测对老年重度癫痫的诊断价值

Tab.3　Diagnostic value of serum Klotho，KLK6，and NCAM detection for severe epilepsy in older patients

Variable	AUC	Cutoff value	95%*CI* for AUC	Sensitivity (%)	Specificity (%)	Youden index
Klotho	0.815	293.78 pg/mL	0.733–0.880	68.57	84.34	0.529
KLK6	0.765	3.54 μg/L	0.678–0.838	65.71	85.54	0.513
NCAM	0.798	92.53 μg/mL	0.714–0.866	62.86	83.13	0.460
Combination	0.902	–	0.833–0.949	91.43	81.93	0.734

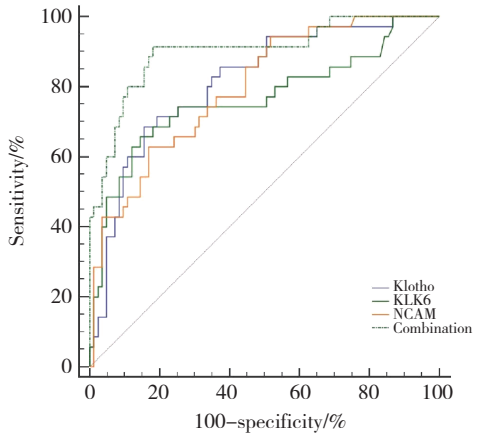


图1　血清Klotho、KLK6及NCAM诊断老年重度癫痫的ROC曲线

Fig.1　ROC curves of serum Klotho，KLK6，and NCAM for diagnosing severe epilepsy in older patients

2.7　血清Klotho、KLK6及NCAM评估老年癫痫患者病情严重程度的临床应用价值

临床决策分析曲线显示，联合诊断的净获益更大，临床价值更高。见图2。

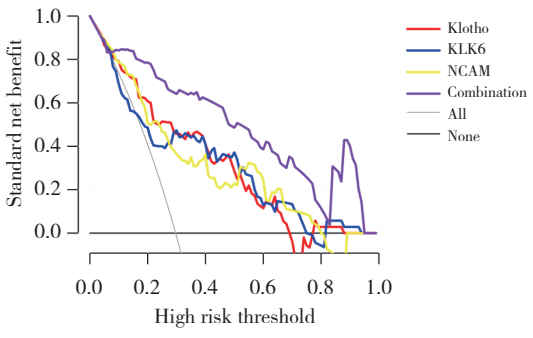


图2　临床决策分析曲线

Fig.2　Clinical decision analysis curve

3　讨论

脑电图在癫痫病情评估中发挥重要作用，但操作复杂，且有一定假阴性率[10]。因此，探讨血清标志物Klotho、NCAM和KLK6与癫痫病情严重程度的关系具有重要意义。

Klotho主要在前列腺、肾脏等多种组织中表达[11]。研究[12]发现，血清Klotho水平与65岁以下人群及男性的癫痫患病率呈负相关。本研究结果显示，癫痫组血清Klotho水平低于健康组。相比于轻中度组，重度组老年癫痫患者血清Klotho水平明显降低，推测Klotho水平可能与癫痫的发生及病情严重程度有关。多因素logistic回归显示，血清Klotho为癫痫病情严重程度的保护因素。本研究还发现，血清Klotho单独诊断重度癫痫的AUC为0.815，特异度为84.34%，但灵敏度(68.57%)较低。

KLK6在人脑干、下丘脑、脊髓等区域表达，介导神经元生长、死亡过程[13]。有研究[14-15]报道，KLK6可能通过促进脑组织β淀粉样蛋白聚集发挥神经毒性，促进神经元细胞凋亡，加剧血管性痴呆患者脑组织损伤。本研究中，癫痫组患者血清KLK6水平高于健康组，重度组患者血清KLK6水平显著高于轻中度组，且logistic回归结果也表明血清KLK6水平越高，发生重度癫痫的风险越高。朱洁楠等[16]报道，KLK6在帕金森病患者血清中水平较高，且能够预测其严重程度。本研究结果显示，血清KLK6单独诊断重度癫痫的灵敏度、特异度分别为65.71%、85.54%，AUC为0.765，可见血清KLK6对老年癫痫病情严重程度具有一定评估价值，但诊断效能不够高。

NCAM是一种主要在神经系统中表达的糖蛋白，其衍生肽P2能减轻皮质神经元损伤及氧化应激，减少神经细胞凋亡，发挥神经保护作用[17-18]。本研究结果显示，癫痫组患者血清NCAM水平低于健康组，重度组癫痫患者血清NCAM水平低于轻中度组，logistic回归也表明血清NCAM为癫痫病情严重程度的保护因素，推测可能与低水平NCAM不利于突触形成，加重神经元损伤等有关[19]。此外，血清NCAM单独诊断重度癫痫的AUC(0.798)一般，特异

度(83.13%)较佳,表明血清NCAM对老年癫痫病情严重程度具有一定的评估价值。

本研究还发现,癫痫组患者血清Klotho和NCAM水平与NHS3评分呈负相关,而KLK6水平与其呈正相关,说明Klotho、KLK6和NCAM与癫痫病情严重程度具有相关性。此外,血清Klotho、KLK6及NCAM联合检测诊断轻中度以及重度癫痫的灵敏度及特异度分别为91.43%和81.93%,AUC达0.902,诊断效能较高,临床决策分析曲线提示三者联合评估的临床应用价值更高,有望成为评估癫痫病情严重程度的生物标志物。

综上所述,Klotho、KLK6和NCAM与癫痫的发生、发展密切相关,血清Klotho、KLK6和NCAM水平对老年癫痫病情严重程度具有一定的评估价值。但Klotho、KLK6和NCAM在癫痫发生、发展中的具体作用机制尚不明确,有待进一步研究。

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(编辑　王又冬)