四川大学学报（医学版） 2026，57（2）：376－382
J Sichuan Univ（Med Sci） doi: 10.12182/20260360605

在线全文

T淋巴细胞线粒体功能与抗NMDAR脑炎疾病进程的相关性研究*

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【摘要】 **目的** 探讨抗NMDAR脑炎（anti-N-methyl-D-aspartate receptor encephalitis, NMDAR-E）患者T淋巴细胞线粒体功能变化特征及其与免疫耗竭状态的相关性。**方法** 本研究纳入2025年1–3月在四川大学华西医院神经内科确诊的抗NMDAR脑炎患者25例（轻症14例，重症11例）及健康对照16名，采用流式细胞术检测患者外周血与脑脊液中免疫细胞分布，评估低线粒体膜电位细胞比例（low mitochondrial membrane potential, MMP-Low%）、线粒体质量（mitochondrial mass, MM）及PD-1表达水平。**结果** 重症患者脑脊液中$CD3^+$和$CD4^+$ T细胞占比、$CD3^+$、$CD4^+$和$CD8^+$ T细胞的MMP-Low%以及CD3和$CD8^+$ T细胞的MM均高于配对外周血（均$P<0.05$）。相比于健康对照，患者外周血$CD4^+$和$CD8^+$初始T细胞和中央记忆T细胞亚群MMP-Low%下降（$P<0.05$），同时$CD4^+$初始T细胞和中央记忆T细胞亚群的PD-1阳性细胞比例上升（$P<0.01$）。**结论** 抗NMDAR脑炎患者脑脊液T细胞处于功能障碍性线粒体积聚状态，提示中枢炎症环境下T细胞线粒体质量稳态调控机制失衡。外周T细胞线粒体状态提示存在系统性免疫耗竭。脑脊液$CD8^+$ T细胞MMP-Low%和外周血淋巴细胞占比可作为区分抗NMDAR-E脑炎患者病情轻重的潜在免疫代谢标志物。

【关键词】 抗NMDAR脑炎 T淋巴细胞 线粒体 PD-1

Association Between T Lymphocyte Mitochondrial Function and Disease Activity in Anti-NMDAR Encephalitis

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This study was supported by the 1·3·5 Project for Disciplines of Excellence–Clinical Research Incubation Project of West China Hospital, Sichuan University (Top Talent Support Program, No. ZYGD23036) and the "Qimingxing" Young Scientist Research Start-up Fund (No. HXQMX0089).

[**Abstract**] **Objective** To investigate mitochondrial functional alterations in T lymphocytes of patients with anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDAR encephalitis, NMDAR-E) and their association with immune exhaustion. **Methods** Twenty-five patients with NMDAR-E diagnosed in the Department of Neurology, West China Hospital, Sichuan University, between January and March 2025 (14 mild cases and 11 severe cases) and 16 healthy controls were enrolled. Flow cytometry was performed to characterize immune-cell distributions in paired peripheral blood and cerebrospinal fluid (CSF), and to evaluate the percentage of cells with low mitochondrial membrane potential (MMP-Low%), mitochondrial mass (MM), and PD-1 expression. **Results** In severe patients, the proportions of $CD3^+$ and $CD4^+$ T cells in CSF, the MMP-Low% of $CD3^+$, $CD4^+$, and $CD8^+$ T cells ($P < 0.01$), and the MM of $CD3^+$ ($P < 0.01$) and $CD8^+$ T cells ($P < 0.05$) were all significantly higher than those in matched peripheral blood. Compared with healthy controls, the MMP-Low% of naïve and central memory $CD4^+$ and $CD8^+$ T-cell subsets in peripheral blood was

* 四川大学华西医院学科卓越发展1·3·5工程项目（高端人才支持计划，No. ZYGD23036）和"启明星"青年人才科研启动基金（No. HXQMX0089）资助
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出版日期：2026-03-20

significantly decreased ($P < 0.05$), whereas the proportion of PD-1-positive cells was significantly increased in $CD4^+$naïve and central memory T-cell subsets ($P < 0.01$). **Conclusion** CSF T cells in patients with anti-NMDAR encephalitis display a state of dysfunctional mitochondrial accumulation, suggesting a possible dysregulation of mitochondrial mass homeostasis under the central inflammatory milieu. Mitochondrial features of peripheral T cells indicate the presence of systemic immune exhaustion. The MMP-Low% of CSF $CD8^+$ T cells and the peripheral blood lymphocyte percentage may serve as potential immunometabolic biomarkers for distinguishing disease severity in NMDAR-E.

[Key words] Anti-NMDAR encephalitis　T-lymphocytes　Mitochondria　PD-1

自身免疫性脑炎(autoimmune encephalitis, AE)是一类以免疫介导的中枢神经系统损伤为特征的疾病,主要累及灰质和神经元[1]。抗NMDAR脑炎(anti-N-methyl-D-aspartate receptor encephalitis, NMDAR-E)为最常见亚型,约占AE的54%～80%[2],多见于年轻女性,急性起病,临床表现包括精神行为异常、癫痫、认知障碍等,重症者可危及生命[3]。既往研究普遍认为,该疾病的致病机制以体液免疫介导为主:浆细胞产生的抗NMDAR抗体在血脑屏障受损后进入中枢,与NMDAR结合并促进受体内化,导致突触功能障碍[4]。早期免疫治疗、B细胞靶向治疗及抗体清除治疗(如激素、丙种球蛋白、血浆置换、利妥昔单抗等)可显著改善预后[1]。然而,抗体介导的核心致病机制并不能完全解释所有临床现象。一方面,部分患者在抗体滴度下降或初次免疫治疗后仍可出现症状迁延或复发,提示仍存在持续的免疫驱动因素[1, 3, 5]。另一方面,多项组织学及脑脊液分析发现,除B细胞外,活化的$CD4^+$和$CD8^+$ T细胞在中枢神经系统内显著浸润,说明细胞免疫在局部炎症放大中发挥作用[4, 6-7]。此外,外周T细胞亚群活化及其代谢异常与疾病严重程度、血脑屏障破坏程度存在相关性,提示T细胞相关的外周–中枢免疫轴可能是影响病程的重要环节[8-10]。

近年来的研究提示,T细胞是NMDAR-E免疫病理过程中的关键调节者。T细胞为B细胞分化与亲和成熟提供辅助信号,包括促进生发中心反应和免疫记忆形成,从而支持高亲和力致病性抗体的持续产生[11-12]。来自患者脑脊液和脑组织的分析发现,$CD4^+$和$CD8^+$ T细胞在中枢神经系统显著富集,伴随活化与克隆扩增,并呈现组织驻留样或耗竭样表型,提示这些T细胞经历了抗原持续刺激并在局部微环境中长期存留[10]。更重要的是,活化和克隆扩增的$CD8^+$ T细胞被证实与疾病严重程度和神经元损伤标志物升高相关,提示它们可能直接参与靶组织损伤[8, 10]。

T细胞的持续活化和组织浸润与其线粒体代谢状态密切相关。线粒体是T细胞能量代谢与效应功能的关键枢纽,调控T细胞的激活、增殖、分化、细胞毒性以及免疫耗竭过程[13-14]。线粒体膜电位(mitochondrial membrane potential, MMP)反映当前代谢水平,线粒体质量(mitochondrial mass, MM)代表代谢能力上限。低线粒体膜电位细胞占比(low mitochondrial membrane potential, MMP-Low%)升高提示线粒体功能障碍[15]。线粒体损伤机制已在类风湿性关节炎等自身免疫疾病中得到证实[16]。本研究拟从T细胞线粒体功能角度,探讨其在NMDAR-E患者中的代谢变化及其与病情进展的关系,为识别重症风险及早期干预提供线索。

1　资料与方法

1.1　研究对象

本研究纳入2025年1–3月在四川大学华西医院神经内科确诊的NMDAR-E患者25例。所有患者均符合《中国自身免疫性脑炎诊治专家共识(2022年版)》中抗NMDAR脑炎的诊断标准:急性或亚急性起病,出现精神行为异常、癫痫发作、言语障碍、运动障碍、意识障碍或自主神经功能障碍等症状,脑脊液抗NMDAR抗体检测阳性,并排除其他病因[1]。纳入标准包括:①首次发病,年龄≥18岁;②临床资料及流式细胞术数据完整;③发病至采样时间≤30 d,且未接受超过3 d的大剂量免疫治疗。排除标准为:①抗体滴度不明确;②合并其他神经系统疾病或其他类型自身免疫性脑炎;③ 妊娠或哺乳期;④ 样本不合格。

根据改良Rankin评分(mRS)[1]将患者分为轻症组(0～2分,14例)与重症组(3～6分,11例)(0～2分,14例)与重症组(3～6分,11例)。同期选取16名健康志愿者作为正常对照,排除存在炎症、肝功能或血常规异常者。所有受试者均采集EDTA抗凝外周血,患者另采集脑脊液。本研究经四川大学华西医院临床试验与生物医学伦理委员会批准,审批号:2018年审(495),所有受试者均签署知情同意书。

1.2　流式细胞术检测及线粒体功能评估

1.2.1　外周血TBNK检测与线粒体功能测定

采集2 mL外周血,混匀后取100 μL与20 μL TBNK抗体(CD8 FITC、CD19 FITC、CD3 PE、CD56 PE、CD45 PerCP-Cy5.5、CD4 PE-Cyanine7)室温避光孵育15 min,加入2 mL 1∶1纯水稀释的溶血素,室温避光孵育15 min。

700×*g*离心5 min后弃上清,加180 μL PBS重悬,取200 μL与线粒体探针MitoDye($C_{34}H_{36}Cl_2N_2$,专利号CN202110570964,泛肽生物科技(浙江)有限公司,宁波,中国)共孵育30 min(37 ℃避光),最后转入绝对计数管,使用BD FACSCanto™流式细胞分析仪(BD Biosciences, San Jose, CA, USA)进行检测。

1.2.2 脑脊液TBNK检测与线粒体功能测定

取1 mL脑脊液700×*g*离心5 min,富集沉淀细胞后加入20 μL TBNK抗体,补加100 μL PBS,室温避光孵育15 min。补加PBS至200 μL后与MitoDye共孵育30 min(37 ℃避光),转入绝对计数管上机检测。

1.2.3 外周血T细胞功能亚群(TFUN)线粒体功能检测

取100 μL外周血样本,与TFUN抗体混合物(含20 μL TFUN多色抗体、5 μL CD28抗体和5 μL PD-1抗体:CD4 FITC、CD45RA PerCP-Cy5.5、CD62L PECyanine7、CD8 APC-Cyanine7、CD28 mF540、PD-1 PE)室温避光孵育15 min。溶血并离心清洗(方法同1.2.1)后,加180 μL PBS重悬,取200 μL与MitoDye共孵育30 min(37 ℃避光),转入绝对计数管上机检测。

1.2.4 流式细胞图像设门分析

采用NovoExpress软件(版本1.4.1, Agilent Technologies, San Diego, CA, USA)进行流式数据设门与分析,TBNK与TFUN的设门策略如附图1所示。通过CD45与侧向散射(SSC)设门选取淋巴细胞群后,采用CD3/CD56与CD8/CD19双参数设门策略区分主要淋巴细胞亚群:T细胞定义为$CD3^+CD56^-$,B细胞定义为$CD3^-CD56^-CD19^+$,NK细胞定义为$CD3^-CD56^+$。在T细胞群中,根据CD4与CD8信号强度定义$CD4^+$ T细胞($CD4^+CD8^-$)和$CD8^+$ T细胞($CD4^-CD8^+$)。此外,依据CD45RA与CD62L信号强度将T细胞进一步分为以下功能性亚群:初始T细胞(Tn, $CD45RA^+CD62L^+$)、中央记忆T细胞(Tcm, $CD45RA^-CD62L^+$)、效应记忆T细胞(Tem, $CD45RA^-CD62L^-$)以及效应T细胞(Teff, $CD45RA^+CD62L^-$)。MM由荧光探针在37 ℃避光孵育30 min后,通过流式细胞仪APC通道检测,以线粒体探针中位荧光强度(median fluorescence index, MFI)表示[17-20];探针染色后,根据荧光强度分布将细胞分为阴性和阳性两群,对阴性分群进行设门,标记为低线粒体膜电位细胞(MMP-Low),其占靶细胞群的比例即为MMP-Low%。流式细胞检测数据(.fcs格式)经人淋巴细胞线粒体功能分析系统(软件,专利号CN202210495602.3)校正后输出。

1.3 统计学方法

采用GraphPad Prism(版本10.1.1)进行数据整理、统计分析与绘图。计量资料首先进行正态性与方差齐性检验。符合正态分布的数据以$\bar{x} \pm s$表示。两组间比较采用独立样本*t*检验或配对*t*检验。三组及以上组间比较:若满足方差齐性,采用单因素方差分析(one-way ANOVA),并在总体检验有统计学差异时使用Tukey事后多重比较法进行两两比较;若不满足方差齐性,采用Brown-Forsythe或Welch检验,并在总体检验差异有统计学意义时使用Dunnett T3法进行事后多重比较。对于不符合正态分布的数据,以中位数(四分位距)表示。两组比较采用Mann-Whitney *U*检验,多组间比较采用Kruskal-Wallis *H*检验,并在需要时采用Dunn法进行多重比较。多重比较均报告调整后的*P*值。检验水准$\alpha_{双侧}=0.05$。

2 结果

2.1 研究对象临床资料

共纳入NMDAR-E患者25例(轻症14例,重症11例)及健康对照16名。部分患者未留取脑脊液,导致外周血与脑脊液样本数量不一致,见表1。

2.2 淋巴细胞亚群占比分析

在外周血中,重症组淋巴细胞比例低于轻症组与健康对照组,轻症组$CD8^+$ T细胞比例高于健康对照组,B细胞比例则低于健康对照组(图1A, $P<0.05$或$P<0.01$)。脑脊液中,重症组淋巴细胞占比高于轻症组(图1B, $P=0.088$),也高于其配对外周血(图1C, $P<0.05$)。重症组$CD3^+$和$CD4^+$ T细胞比例亦高于其配对外周血(图1D、1E, $P<0.01$);轻症组呈相同趋势,但差异无统计学意义。所有患者脑脊液B细胞比例均低于其配对外周血(图1G, $P<0.05$或$P<0.01$);重症组脑脊液NK细胞比例亦低于其配对外周血(图1H, $P<0.01$)。

表 1 外周血及脑脊液标本临床资料

Table 1 Clinical characteristics of peripheral blood (PB) and cerebrospinal fluid (CSF) samples

Clinical characteristic	Mild cases (PB, *n* = 14)	Severe cases (PB, *n* = 11)	Healthy controls (PB, *n* = 16)	Mild cases (CSF, *n* = 10)	Severe cases (CSF, *n* = 11)
Age/yr.	35.71 ± 15.27	28.36 ± 13.26	36.50 ± 12.42	38.80 ± 14.00	29.27 ± 13.57
Sex (male/female)	6/8	10/1	7/9	7/3	9/2
Admission mRS score	2.64 ± 0.50	4.55 ± 0.52	/	2.63 ± 0.62	4.36 ± 0.50
Discharge mRS score	2.62 ± 0.51	4.27 ± 0.47	/	2.53 ± 0.64	4.10 ± 0.57

mRS: modified Rankin scale.

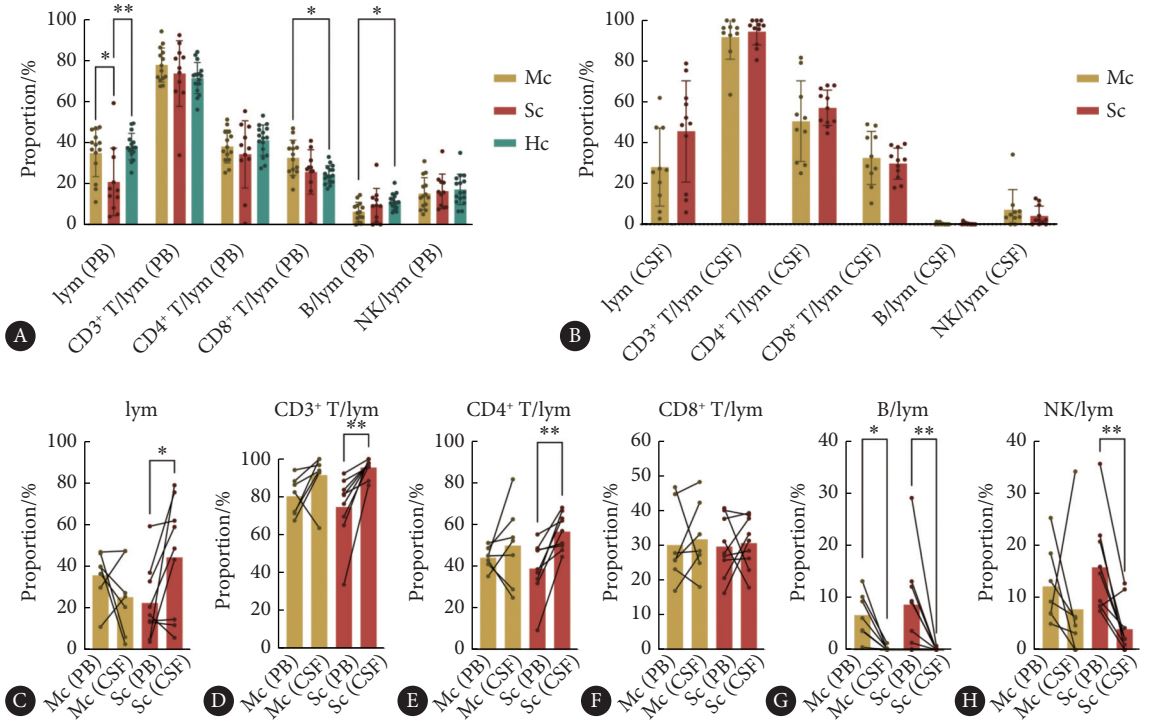

图 1 轻、重症患者外周血（A）、脑脊液（B）及配对样本（C ~ H）T、B、NK细胞占比

Fig 1 Proportions of T, B, and NK cells in peripheral blood (A), cerebrospinal fluid (B), and paired PB-CSF samples (C-H) comparing mild and severe cases

Mc, Sc, and Hc denote mild cases, severe cases, and healthy controls, respectively. Statistical significance is indicated by asterisks: * $P < 0.05$, ** $P < 0.01$ (two-sided tests; adjusted P values are reported when multiple comparisons were performed).

2.3 淋巴细胞亚群MMP-Low%与MM分析

重症组脑脊液CD3⁺、CD4⁺及CD8⁺ T细胞MMP-Low%高于轻症组(图2A, $P < 0.05$)。在配对样本中, 重症组T细胞与NK细胞MMP-Low%均高于外周血(图2F, $P < 0.05$; 图2B ~ 2D, $P < 0.01$)。线粒体质量方面, 重症组脑脊液CD3⁺ T、CD8⁺ T、B及NK细胞MM均高于配对外周血(图2I, $P < 0.05$; 图2G、2J、2K, $P < 0.01$)。轻症组MMP-Low%和MM亦有相同趋势, 但未达统计学意义。

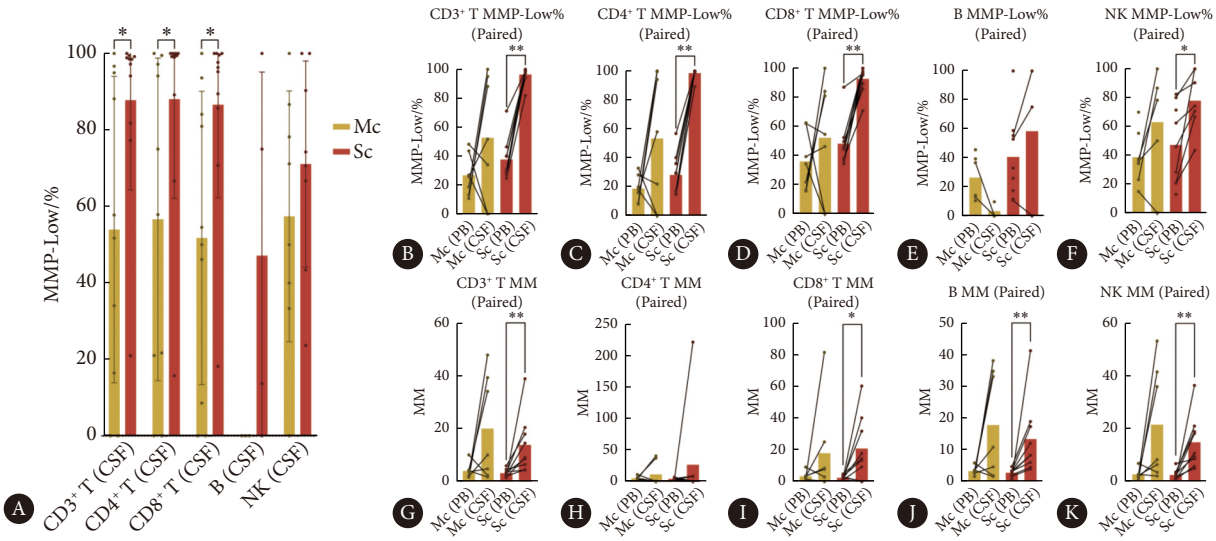

图 2 轻、重症患者脑脊液T、B、NK细胞MMP-Low%（A），配对样本T、B、NK细胞MMP-Low%（B ~ F）及MM（G ~ K）

Fig 2 MMP-Low% of T, B, and NK cells in CSF of mild and severe patients (A); paired sample comparison of MMP-Low% (B-F) and mitochondrial mass (MM) (G-K)

Mc, Sc, and Hc denote mild cases, severe cases, and healthy controls, respectively. Statistical significance is indicated by asterisks: * $P < 0.05$, ** $P < 0.01$ (two-sided tests; adjusted P values are reported when multiple comparisons were performed).

2.4 外周血T细胞精细亚群占比及MMP-Low%、MM差异分析

进一步分析外周血T细胞精细亚群(T4/T8-Tn, -Tcm, -Tem, -Teff)分布及MMP-Low%。结果显示部分亚群MMP-Low%存在组间差异。轻症组T4-Tn、T4-Tcm、T8-Tn和T8-Tcm亚群MMP-Low%均低于健康对照组(图3, $P<0.05$, <0.01或<0.001)。重症组T4-Tn MMP-Low%低于健康对照组(图3),但差异无统计学意义($P=0.050\,3$)。

2.5 外周血T细胞精细分群PD-1差异表达分析

检测T细胞精细亚群PD-1及CD28表达,结果显示PD-1阳性细胞比例存在组间差异。轻症组及重症组外周血$CD4^+$ T、T4-Tn、T4-Tcm及T4-Tem的PD-1阳性细胞比例均高于健康对照组(图4, $P<0.01$)。

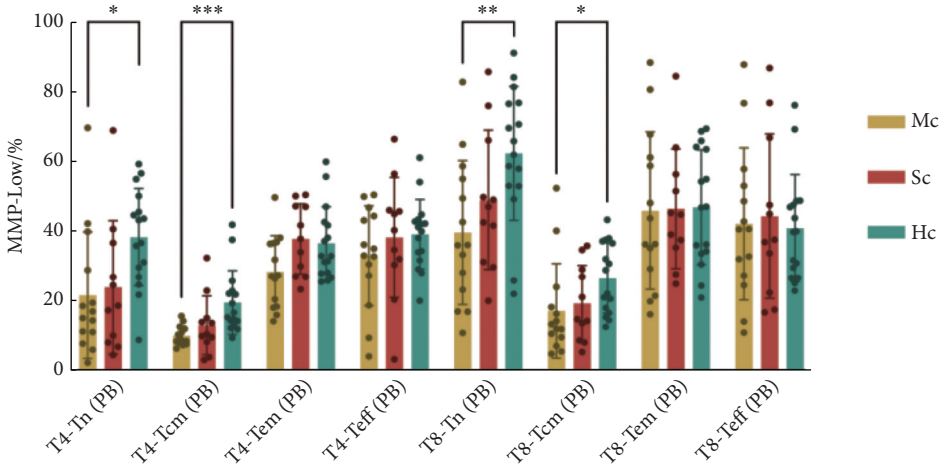

图 3 不同病情阶段外周血T细胞精细亚群MMP-Low%

Fig 3 MMP-Low% of refined peripheral T cell subsets across disease severity groups

Mc, Sc, and Hc denote mild cases, severe cases, and healthy controls, respectively. Statistical significance is indicated by asterisks: ** $P<0.01$ (two-sided tests; adjusted P values are reported when multiple comparisons were performed).

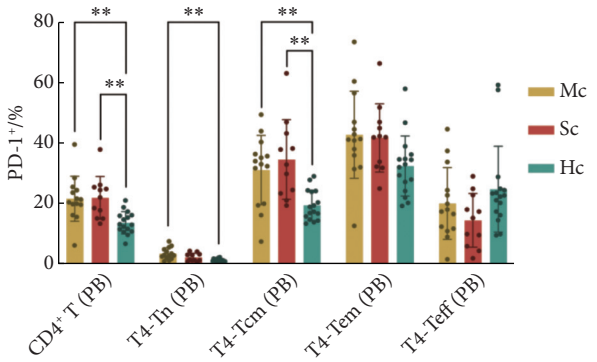

图 4 不同病情阶段外周血$CD4^+$ T细胞精细分群 PD-1阳性细胞比例

Fig 4 PD-1-positive cell proportions in peripheral blood $CD4^+$ T-cell subsets across disease stages

Mc, Sc, and Hc denote mild cases, severe cases, and healthy controls, respectively. Statistical significance is indicated by asterisks: ** $P<0.01$ (two-sided tests; adjusted P values are reported when multiple comparisons were performed).

2.6 免疫代谢指标的诊断效能评估

为评估免疫代谢指标的诊断价值,采用受试者工作特征(receiver operating characteristic, ROC)曲线分析其对轻症组与重症组间的区分能力。结果显示,脑脊液$CD8^+$ T MMP-Low%和外周血淋巴细胞占比在区分轻重症方面具有潜力,曲线下面积(area under the curve, AUC)分别为0.818 2(95%置信区间:0.626 1 ~ 1.000 0)和0.852 9(95%置信区间:0.710 6 ~ 0.995 3),见图5。

3 讨论

本研究结合淋巴细胞亚群分布与线粒体功能评估,初步描绘了NMDAR-E患者外周血与脑脊液中T细胞分化亚群与功能变化特征,重点揭示其代谢改变与免疫耗竭的可能关联。结果提示,患者在不同病情阶段外周与中枢T细胞亚群构成存在显著差异,T细胞在由外周向中枢迁移过程中呈现出"激活、效应、耗竭"的动态演变。尤其在重症患者中,脑脊液T细胞线粒体膜电位显著下降存在,质量升高,呈现典型耗竭代谢特征[21]。同时,外周$CD4^+$ T细胞PD-1表达水平上调,提示存在系统性免疫耗竭[22]。此外,多项代谢指标与疾病严重程度呈现相关性。

本研究观察到外周T细胞不同分化阶段的代谢差异。Tn与Tcm亚群MMP-Low%下降,提示其可能处于激活状态;而Tem与Teff亚群则未见明显代谢改变。该特征与其他中枢自身免疫性疾病相似[8, 23],表现为外周分化早期T细胞显著激活、代谢活化,提示外周T细胞可能在NMDAR-E发病中发挥的重要作用。

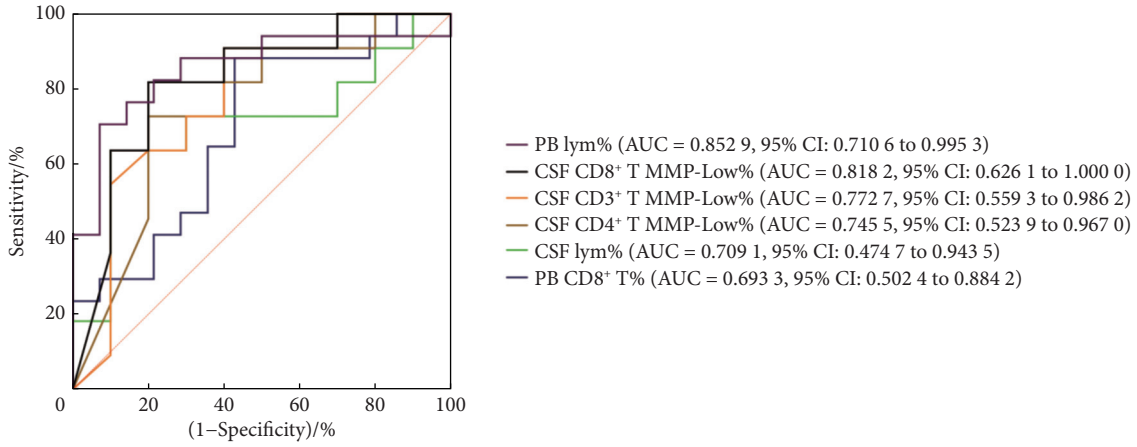

图 5　用于区分重症组与轻症组的免疫代谢指标及其ROC曲线

Fig 5　Immune-metabolic indicators distinguishing severe from mild cases and their corresponding ROC curves

PB: peripheral blood; CSF: cerebrospinal fluid; AUC: area under the curve.

在炎症驱动下，激活的外周T细胞可穿越血脑屏障进入中枢。研究证实，T细胞在多发性硬化、缺血性脑卒中及多种自身免疫性脑炎中广泛浸润中枢，参与炎症扩展及神经元损伤[9, 24-25]。在NMDAR-E中，患者脑脊液白细胞升高与病情严重程度和不良预后密切相关，且T细胞为主要浸润成分之一[10, 26]。本研究亦发现，NMDAR-E重症患者外周淋巴细胞比例显著下降而脑脊液中比例升高。这反映出淋巴细胞，特别是T细胞的中枢迁移不仅是炎症发生的重要前提，也可能在重症NMDAR-E中发挥重要作用，是值得关注的致病环节和干预靶点。

中枢浸润T细胞可能在慢性抗原刺激下趋于耗竭。本研究发现，NMDAR-E患者脑脊液T、B、NK细胞的MMP-Low%和MM均显著高于配对外周血，重症患者的T细胞代谢异常更加突出，提示其可能处于耗竭状态。SCHURICH等[27]在耗竭型乙型肝炎病毒特异性T细胞中观察到相同线粒体模式，并认为可能是由“无功能性巨型线粒体”(non-functional giant mitochondria)积聚所致。近年的研究进一步证实，在线粒体裂变及清除通路受损(如FIS1下调)时，细胞会形成过度延长、体积增大的线粒体，这些线粒体表现为膜电位下降、氧化磷酸化受限但仍难以被及时清除，呈现出数量表观升高但功能衰竭的特征[13, 21]。同时，慢性抗原持续刺激下，损伤线粒体的堆积被认为是T细胞由可逆耗竭向终末耗竭转化的关键驱动因素[28]。

PD-1是耗竭形成的核心调控因子，通过TCR-CD28、PI3K-AKT-mTOR与PGC1α等通路抑制T细胞增殖与线粒体新生，导致功能障碍和代谢异常。在系统性红斑狼疮和类风湿性关节炎患者中均观察到PD-1高表达与T细胞耗竭密切相关[29]，而我们也发现NMDAR-E患者外周CD4+ T细胞PD-1表达水平显著升高，提示其在NMDAR-E中可能发挥类似作用。

由于技术限制，本研究未能直接检测脑脊液T细胞PD-1表达，但其线粒体代谢特征与PD-1介导的耗竭机制高度一致。未来课题组将扩大样本量，结合单细胞功能验证与代谢追踪技术，进一步明确T细胞代谢耗竭在NMDAR-E中的作用。

综上，本研究揭示了NMDAR-E患者T细胞在分化迁移与代谢功能上的关键改变，支持其可能经历了由外周激活、中枢效应至功能耗竭的演变过程。这一发现不仅深化了对T细胞在NMDAR-E中作用的理解，也为未来靶向免疫代谢干预提供了理论基础。

*　　*　　*

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Author Contribution　MA Yuwen is responsible for conceptualization, data curation, formal analysis, methodology, validation, visualization, writing--original draft, and writing--review and editing. ZHANG Erdi is responsible for conceptualization, data curation, methodology, and writing--original draft. CAO Lin and WANG Zhiyin are responsible for data curation, methodology, and writing--original draft. WANG Minjin is responsible for project administration and resources. LI Feng is responsible for supervision. YING Binwu is responsible for conceptualization, funding acquisition, and resources. YAN Lin is responsible for conceptualization, funding acquisition, project administration, and resources. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

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Declaration of Conflicting Interests YING Binwu is a member of the Editorial Board of the journal. All processes involved in the editing and reviewing of this article were carried out in strict compliance with the journal's policies and there was no inappropriate personal involvement by the author. Other than this, all authors declare no competing interests.

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(2025 – 08 – 10收稿, 2026 – 01 – 28修回)

编辑 刘 华

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