·专题综述·

抗N-甲基-D-天冬氨酸受体脑炎睡眠障碍研究进展

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【摘要】 抗N-甲基-D-天冬氨酸受体(NMDAR)脑炎患者睡眠障碍表现形式多样,易误诊,机制复杂,需早期鉴别诊断与治疗。本文从抗NMDAR脑炎睡眠障碍的临床表现、电生理学特征、发病机制及治疗原则等方面进行综述,以为临床医师识别和治疗抗NMDAR脑炎睡眠障碍提供帮助。

【关键词】 抗N-甲基-D-门冬氨酸受体脑炎; 睡眠障碍; 综述

Progress on sleep disorders in anti-N-methyl-D-aspartate receptor encephalitis

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【Abstract】 Sleep disorders in patients with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis present in a variety of forms, are easily misdiagnosed, have complex mechanisms, and require early recognition and treatment. This article reviews the clinical manifestations, electrophysiological characteristics, pathogenesis, diagnosis and treatment principles of sleep disorders in anti-NMDAR encephalitis, in order to provide some help for clinicians to identify and treat sleep disorders in anti-NMDAR encephalitis.

【Key words】 Anti-N-methyl-D-aspartate receptor encephalitis; Sleep disorders; Review

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抗N-甲基-D-天冬氨酸受体(NMDAR)脑炎是一种由抗体介导的罕见的中枢神经系统自身免疫性疾病,常见的临床症状包括运动障碍、癫痫发作、自主神经功能障碍或意识改变等神经系统症状以及幻觉、妄想、躁狂、激越等精神症状[1]。睡眠障碍亦为抗NMDAR脑炎较为常见的临床表现,其病理生理学机制复杂,表现形式多样,包括失眠、睡眠呼吸障碍、中枢性嗜睡症、异态睡眠、睡眠-觉醒昼夜节律障碍、睡眠相关运动障碍等。虽然目前暂未发现抗NMDAR脑炎睡眠障碍与发病后12个月神经功能状态不良[改良Rankin量表(mRS)评分≥3分][2-3]或死亡风险相关[4],但发现失眠症状与抗NMDAR脑炎患者的自杀倾向存在关联性[5],故早期识别和处理抗NMDAR脑炎睡眠障碍具有重要的临床意义。基于此,本文拟从抗NMDAR脑炎睡眠障碍的临床及电生理学特征、发病机制及诊疗原则等方面进行系统总结,以期辅助临床加深对疾病的认识,并为其治疗提供新的思路。

一、抗NMDAR脑炎睡眠障碍的影响因素

多项研究统计的抗NMDAR脑炎睡眠障碍的发生率为14%~96%[2,6-7],上述差异可能与研究人群的发病年龄、性别、抗体滴度以及是否伴随肿瘤等临床特征有关。与发病年龄<45岁患者相比,发病年龄≥45岁的抗NMDAR脑炎患者出现睡眠障碍的概率更低[8];但发病年龄<18岁与发病年龄>18岁

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的患者睡眠障碍发生率并无显著差异[9]。新加坡一项针对东南亚人群的单中心纵向研究显示，相较女性患者，男性抗NMDAR脑炎患者的失眠障碍更常见[10]。一般认为，睡眠障碍与伴随畸胎瘤无明显关联性[11]，但也有研究认为，伴肿瘤的抗NMDAR脑炎患者较不伴肿瘤者发生睡眠障碍的概率降低[12]。与脑脊液抗NMDAR抗体滴度＜1∶32的患者相比，抗体滴度≥1∶32的患者睡眠障碍发生率更高[13]；与上述研究矛盾的是，另一项研究发现，与抗体阴性的患者相比，脑脊液抗NMDAR抗体阳性患者出现睡眠障碍的概率降低[14]。上述研究之间存在差异，尚待进一步探究抗NMDAR脑炎睡眠障碍的影响因素。

二、抗NMDAR脑炎睡眠障碍的临床分类

抗NMDAR脑炎睡眠障碍的临床表现复杂，目前尚缺乏统一的分类标准，不同研究对抗NMDAR脑炎睡眠障碍的划分也存在差异。有研究将抗NMDAR脑炎睡眠障碍归为精神症状[1]、自主神经功能障碍[12]、神经症状[2]或行为障碍[15-16]，亦有研究将睡眠障碍单独列出，但是仅统计失眠症状[17]或仅统计急性期的睡眠障碍，而忽略缓解期或恢复期的睡眠障碍[18]。本文就相关文献所述分类将抗NMDAR脑炎睡眠障碍分述如下。

1.失眠　失眠是指在睡眠机会足够和睡眠环境理想的情况下，出现入睡困难、睡眠维持困难或非恢复性睡眠的体验，并伴随日间功能受损如注意力下降或注意力集中困难等[19]，是抗NMDAR脑炎最常见的睡眠障碍类型和最早出现的症状之一[17]。一般而言，发病时表现为失眠，在病程后期发展为嗜睡[20]，少数患者在发病初期即表现为嗜睡[21]，或在失眠与嗜睡之间波动[22]。抗NMDAR脑炎患者失眠的主要特征是睡眠时间显著减少而不伴日间过度思睡（EDS），并且予苯二氮䓬类药物治疗后失眠症状无改善。一项前瞻性临床试验发现，16/18的抗NMDAR脑炎患者急性期出现失眠症状，13/18的患者失眠症状先于其他临床症状数周出现[23]；也有病例报道显示，患者在恢复期出现失眠或持续性睡眠片段化和日间疲劳[24]。此外，抗NMDAR脑炎患者失眠症状的一些罕见表现为：Marques等[25]报告1例以完全性失眠（兴奋性失眠）为首发表现的抗NMDAR脑炎患者，该患者在接受免疫治疗后严重的失眠症状以及言语、运动、行为、自主神经功能障碍等其他症状出现了显著改善；Wiels等[26]报告1例慢性失眠长达25年的抗NMDAR脑炎患者，确诊前长期使用抗精神病药控制失眠，存在酒精依赖、抑郁等症状，确诊后予以连续5天大剂量（1 g）甲泼尼松龙冲击治疗后所有抗精神病药剂量逐渐减少，治疗3个月后复诊时自述每晚睡眠时间可达7小时，并戒断酒精和镇静催眠药。上述研究提示在诊治伴有神经系统和精神症状和体征的急性和慢性失眠患者时，应排除免疫介导的脑病之可能。

2.睡眠呼吸障碍　睡眠呼吸障碍主要包括中枢性睡眠呼吸暂停综合征（CSAS）、阻塞性睡眠呼吸暂停/低通气综合征（OSAHS）、中枢性低通气和睡眠相关低氧血症等。中枢性低通气是伴随畸胎瘤的年轻女性抗NMDAR脑炎患者的常见表现，通常需要数周或数月的机械通气支持[11,27]。抗NMDAR脑炎患者急性期往往存在肺部感染、呼吸衰竭等状况，与中枢性低通气鉴别困难，且相关研究较少。目前报道的抗NMDAR脑炎患者中枢性低通气多发生在恢复期。有研究发现，67.3%的抗NMDAR脑炎患者存在中枢性低通气，但是否仅发生于睡眠期并未提及[11]。中枢性低通气对预测患者预后有一定的临床价值：有研究发现，中枢性低通气与治疗12个月时神经功能预后不良（mRS≥3分）相关[3]。

3.中枢性嗜睡症　中枢性嗜睡症是中枢神经系统功能障碍引起的以日间过度思睡为特征的一类疾病，包括特发性嗜睡、发作性睡病、Kleine-Levin综合征等。研究显示，仅11%的抗NMDAR脑炎患者在急性期出现嗜睡，而78%的患者在恢复期出现嗜睡，一般程度较轻，可伴随食欲亢进、情感淡漠、体重增加、性欲亢进等，尽管镇静催眠药的使用可能是嗜睡的混杂因素[23]；但在停用镇静催眠药后嗜睡症状仍在持续，提示嗜睡不仅是治疗的不良反应，而是抗NMDAR脑炎自身症状之一[23-24]。发作性睡病、Kleine-Levin综合征属于抗NMDAR脑炎罕见的中枢性嗜睡症表现，在抗NMDAR脑炎患者中偶见报道[28-29]。

4.睡眠-觉醒昼夜节律障碍　睡眠-觉醒昼夜节律障碍是由生理节律改变，或环境因素导致的个人睡眠-觉醒周期失调的慢性或复发性睡眠障碍。27%的抗NMDAR脑炎患者在恢复期出现睡眠模式反转，表现为夜间失眠和日间过度思睡[30]。多项研究显示，抗NMDAR脑炎患者在病程中存在睡眠昼夜颠倒[21,24]，但仅为观察性研究，尚不能确定是否符合睡眠-觉醒昼夜节律障碍的诊断标准。

5.异态睡眠　异态睡眠是指入睡时、睡眠中或从睡眠中觉醒时出现的不良身体事件(复杂的动作、行为)或体验(情绪、感知、梦境)。Guasp等[7]的研究发现,在急性期后(发病后4个月左右),28例抗NMDAR脑炎患者中有7例表现为非快速眼动睡眠期(NREM)异态睡眠的觉醒混淆,其中3例患者的觉醒混淆症状持续至发病后1年;1例表现为快速眼动睡眠期(REM)异态睡眠的快速眼动睡眠期行为障碍(RBD)。

6.睡眠相关运动障碍　睡眠相关运动障碍指在睡眠期间发生的简单、无目的、刻板的口面部及肢体运动。这类睡眠障碍研究并不多见,有研究报道2例抗NMDAR脑炎患者在病程恢复期出现不宁腿综合征(RLS)和周期性肢体运动障碍(PLMD)[24];还可见睡眠期孤立性口面部运动障碍[22]。

三、抗NMDAR脑炎睡眠障碍的电生理学特征

连续脑电监测(cEEG)能动态、连续性评估清醒、嗜睡和睡眠等状态[31],在抗NMDAR脑炎的睡眠与脑功能评估中具有重要作用。抗NMDAR脑炎睡眠障碍cEEG表现为睡眠模式异常甚至缺失[25],如睡眠潜伏期异常、NREMⅡ期睡眠特征(K复合体和睡眠纺锤体)缺失[32]、NREMⅢ期或慢波睡眠减少、REM睡眠减少、REM骨骼肌失弛缓[33],以及睡眠始发的快速眼动睡眠(SOREM)等[34]。cEEG所示睡眠结构的缺失与抗NMDAR脑炎发病1年后的不良预后有关[35]。

视频多导睡眠监测(v-PSG)是诊断睡眠障碍的“金标准”。抗NMDAR脑炎患者v-PSG表现为睡眠潜伏期、睡眠效率异常,通过v-PSG可以区分睡眠呼吸障碍、异态睡眠、睡眠相关运动障碍等。多导睡眠图(PSG)的纺锤波是NREM睡眠特征性电生理标记之一。研究发现,抗NMDAR脑炎患者存在过度的纺锤体活动[36],但也有研究发现,抗NMDAR脑炎患者的睡眠纺锤波参数(睡眠纺锤波密度、最大振幅和σ波)与健康对照组并无显著差异,但这是在样本量较少(8例)的情况下得出的结果[37]。目前尚缺乏统一结论,未来需要进一步扩大样本量研究抗NMDAR脑炎的睡眠纺锤波改变。

v-PSG存在操作繁琐、存在首夜效应、患者难以配合等缺点,因而在器质性脑病中的应用受限。笔者团队将基于心电记录的睡眠评估方法——心肺耦合分析(CPC)用于自身免疫性脑炎患者睡眠的研究,该检查方法具有简易、方便、对患者睡眠干扰小的特点。并发现与健康对照组相比,自身免疫性脑炎患者睡眠效率下降,代表深睡眠的高频耦合下降,REM睡眠及觉醒比例偏高,呼吸紊乱指数偏高,伴有显著的自主神经功能障碍,并且发现心肺耦合分析参数中睡眠效率、高频耦合/低频耦合比值是自身免疫性脑炎患者匹兹堡睡眠质量指数(PSQI)评分的影响因素[38],提示心肺耦合分析在自身免疫性脑炎的睡眠评估中具有良好的应用前景。

四、抗NMDAR脑炎睡眠障碍的发病机制

NMDAR是一类配体门控兴奋性离子通道[39],NMDAR的NR1亚基是抗NMDAR抗体的作用靶点,而*NR1*基因几乎在大鼠所有神经元中均有表达[40]。NMDAR影响睡眠的机制可能在于皮质慢波振荡的产生以及皮质慢波振荡对丘脑慢δ波的诱导和同步化这两方面[41]。动物实验发现,抗NMDAR抗体可能通过影响睡眠起始和控制环路的不同部位从而产生临床表现迥异的睡眠症状[42]:通过向应激状态下新生雏鸡脑室系统注射NMDAR激动剂可以剂量依赖性产生睡眠诱导作用[43];另一研究发现,将NMDAR阻断剂MK-801注射入大鼠体内,大鼠在中毒阶段会产生运动增多和失眠症状,随后导致NREM睡眠期脑电图δ频段(1~4 Hz)振幅积分增加[44];向大鼠结节乳头核(TMN)脑区微量注射谷氨酸和N-甲基-D-天冬氨酸(NMDA)可以增加觉醒,减少NREM睡眠[45];选择性敲低小鼠下丘脑外侧视前区(LPO)神经元中NMDAR会减少NREM睡眠和REM睡眠时间并且导致睡眠片段化,还可导致REM期θ波显著减弱[46]。尽管越来越多的动物实验证实NMDAR在睡眠中的重要作用,但抗NMDAR抗体在自身免疫性脑炎患者睡眠障碍中的机制仍有待基础研究进一步阐明。

五、抗NMDAR脑炎睡眠障碍的治疗

抗NMDAR脑炎睡眠障碍的治疗目前尚缺乏统一的共识及指南。针对原发病的治疗是改善抗NMDAR脑炎睡眠障碍的基础。针对原发病的治疗包括一线免疫治疗(糖皮质激素、静脉注射免疫球蛋白和血浆置换)、二线免疫治疗(利妥昔单抗和环磷酰胺)和手术切除畸胎瘤[47]。抗NMDAR脑炎患者的失眠、梦境演绎行为等睡眠障碍可以在免疫治疗后得到改善[33]。

针对抗NMDAR脑炎临床表现迥异的睡眠障碍,其对症治疗仍以个体化经验性治疗为主。如前所述,单独使用抗精神病药喹硫平、镇静催眠药唑

吡坦等对抗NMDAR脑炎患者失眠症状往往无明显改善[1,23]；如患者出现昼夜节律倒错，可以通过使用药物（镇静催眠药或抗精神病药）和支持疗法如低刺激环境下定向性提示、熟悉物品、安慰和支持等进行纠正[48]；加巴喷丁和普拉克索联合治疗可以改善睡眠片段化[24]；夜间中枢性低通气可给予机械通气治疗[24]；曲唑酮和苯海拉明亦对睡眠障碍有益，但药物的有效剂量范围尚未完全确定[49]。

总的来说，抗NMDAR脑炎睡眠障碍具有较大的异质性，其发病机制尚未完全明确，其分类仍缺乏统一意见，治疗尚缺乏充分的循证医学依据。充分认识与理解抗NMDAR脑炎睡眠障碍的类型与特点，有助于临床诊断与治疗，从而改善疾病预后。此外，伴睡眠障碍的抗NMDAR脑炎易误诊或漏诊而延误治疗，因此应重视抗NMDAR脑炎患者的睡眠情况，并进行相关基础研究以进一步阐明其发生机制。

利益冲突 无

参 考 文 献

[1] Dalmau J, Armangué T, Planagumà J, Radosevic M, Mannara F, Leypoldt F, Geis C, Lancaster E, Titulaer MJ, Rosenfeld MR, Graus F. An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models[J]. Lancet Neurol, 2019, 18:1045-1057.

[2] Gong X, Chen C, Liu X, Lin J, Li A, Guo K, Zhou D, Hong Z. Long-term functional outcomes and relapse of anti-NMDA receptor encephalitis: a cohort study in Western China[J]. Neurol Neuroimmunol Neuroinflamm, 2021, 8:e958.

[3] Balu R, McCracken L, Lancaster E, Graus F, Dalmau J, Titulaer MJ. A score that predicts 1-year functional status in patients with anti-NMDA receptor encephalitis[J]. Neurology, 2019, 92:e244-e252.

[4] Zhong R, Chen Q, Zhang X, Zhang H, Lin W. Risk factors for mortality in anti-NMDAR, anti-LGI1, and anti-GABABR encephalitis[J]. Front Immunol, 2022, 13:845365.

[5] Zhang L, Sander JW, Zhang L, Jiang XY, Wang W, Shuang K, Abdulaziz ATA, Wu MQ, Chi XS, Li JM, Zhou D. Suicidality is a common and serious feature of anti-N-methyl-D-aspartate receptor encephalitis[J]. J Neurol, 2017, 264:2378-2386.

[6] Al-Diwani A, Handel A, Townsend L, Pollak T, Leite MI, Harrison PJ, Lennox BR, Okai D, Manohar SG, Irani SR. The psychopathology of NMDAR-antibody encephalitis in adults: a systematic review and phenotypic analysis of individual patient data[J]. Lancet Psychiatry, 2019, 6:235-246.

[7] Guasp M, Rosa-Justicia M, Muñoz-Lopetegi A, Martínez-Hernández E, Armangué T, Sugranyes G, Stein H, Borràs R, Prades L, Ariño H, Planagumà J, De-La-Serna E, Escudero D, Llufriu S, Sánchez-Valle R, Santamaria J, Compte A, Castro-Fornieles J, Dalmau J; Spanish anti-NMDAR Encephalitis Study Group. Clinical characterisation of patients in the post-acute stage of anti-NMDA receptor encephalitis: a prospective cohort study and comparison with patients with schizophrenia spectrum disorders[J]. Lancet Neurol, 2022, 21:899-910.

[8] Bastiaansen AEM, de Bruijn MAAM, Schuller SL, Martinez-Hernandez E, Brenner J, Paunovic M, Crijnen YS, Mulder MJHL, Schreurs MWJ, de Graaff E, Smitt PAE, Neuteboom RF, de Vries JM, Titulaer MJ. Anti-NMDAR encephalitis in the Netherlands, focusing on late-onset patients and antibody test accuracy[J]. Neurol Neuroimmunol Neuroinflamm, 2021, 9:e1127.

[9] Xu X, Lu Q, Huang Y, Fan S, Zhou L, Yuan J, Yang X, Ren H, Sun D, Dai Y, Zhu H, Jiang Y, Zhu Y, Peng B, Cui L, Guan H. Anti-NMDAR encephalitis: a single-center, longitudinal study in China[J]. Neurol Neuroimmunol Neuroinflamm, 2019, 7:e633.

[10] Tan YJ, Siow IE, Ong CS, Narasimhalu K, Yong KP. Anti-NMDAR encephalitis in Southeast Asia: a single-centre, longitudinal study[J]. Clin Neurol Neurosurg, 2023, 231:107845.

[11] Dai Y, Zhang J, Ren H, Zhou X, Chen J, Cui L, Lang J, Guan H, Sun D. Surgical outcomes in patients with anti-N-methyl D-aspartate receptor encephalitis with ovarian teratoma[J]. Am J Obstet Gynecol, 2019, 221:485.e1-485.e10.

[12] Giri YR, Parrill A, Damodar S, Fogel J, Ayed N, Syed M, Korie I, Ayyanar S, Typhair C, Hashmi S. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents: a systematic review and quantitative analysis of reported cases[J]. J Can Acad Child Adolesc Psychiatry, 2021, 30:236-248.

[13] Dou X, Li D, Wu F, Wang Z, Niu M, Wu Y, Deng T, Wang D, Li X. The clinical features, treatment and outcomes of 33 children from Northwestern China with anti-N-methyl-D-aspartate receptor encephalitis[J]. Neurol Res, 2022, 44:429-438.

[14] Blackman G, Lim MF, Pollak T, Al-Diwani A, Symmonds M, Mazumder A, Carter B, Irani S, David A. The clinical relevance of serum versus CSF NMDAR autoantibodies associated exclusively with psychiatric features: a systematic review and meta-analysis of individual patient data[J]. J Neurol, 2022, 269:5302-5311.

[15] Espinola-Nadurille M, Restrepo-Martínez M, Bayliss L, Flores-Montes E, Rivas-Alonso V, Vargas-Cañas S, Hernández L, Martínez-Juarez I, Gonzalez-Aguilar A, Solis-Vivanco R, Fricchione GL, Flores-Rivera J, Ramirez-Bermudez J. Neuropsychiatric phenotypes of anti-NMDAR encephalitis: a prospective study[J]. Psychol Med, 2023, 53:4266-4274.

[16] Brooks J, Yarbrough ML, Bucelli RC, Day GS. Testing for N-methyl-D-aspartate receptor autoantibodies in clinical practice[J]. Can J Neurol Sci, 2020, 47:69-76.

[17] Gurrera RJ. Recognizing psychiatric presentations of anti-NMDA receptor encephalitis in children and adolescents: a synthesis of published reports[J]. Psychiatry Clin Neurosci, 2019, 73:262-268.

[18] Heine J, Kopp UA, Klag J, Ploner CJ, Prüss H, Finke C. Long-term cognitive outcome in anti-N-methyl-D-aspartate receptor encephalitis[J]. Ann Neurol, 2021, 90:949-961.

[19] Perlis ML, Posner D, Riemann D, Bastien CH, Teel J, Thase M. Insomnia[J]. Lancet, 2022, 400:1047-1060.

[20] Pérez-Carbonell L, Iranzo A. Sleep disturbances in autoimmune neurological diseases[J]. Curr Neurol Neurosci Rep, 2023, 23:617-625.

[21] Barry H, Hardiman O, Healy DG, Keogan M, Moroney J, Molnar PP, Cotter DR, Murphy KC. Anti-NMDA receptor encephalitis: an important differential diagnosis in psychosis[J]. Br J Psychiatry, 2011, 199:508-509.

[22] Morales-Briceño H, Fung VSC. Isolated nocturnal occurrence of orofacial dyskinesias in N-methyl-D-aspartate receptor encephalitis: a new diagnostic clue[J]. Mov Disord Clin Pract,

2017, 4:884-886.
[23] Ariño H, Muñoz-Lopetegi A, Martinez-Hernandez E, Armangue T, Rosa-Justicia M, Escudero D, Matos N, Graus F, Sugranyes G, Castro-Fornieles J, Compte A, Dalmau J, Santamaria J. Sleep disorders in anti-NMDAR encephalitis[J]. Neurology, 2020, 95: e671-e684.
[24] Anderson KN, Kelly TP, Griffiths TD. Primary sleep disorders can cause long-term sleep disturbance in patients with autoimmune mediated limbic encephalitis [J]. Clin Neurol Neurosurg, 2013, 115:1079-1082.
[25] Marques IB, Teotónio R, Cunha C, Bento C, Sales F. Anti-NMDA receptor encephalitis presenting with total insomnia: a case report[J]. J Neurol Sci, 2014, 336(1/2):276-280.
[26] Wiels WA, Boudiba Y, Seynaeve L, Raedt S. Anti-NMDA-receptor encephalitis: an unusual treatable cause of chronic insomnia[J]. Sleep Sci, 2021, 14:296-298.
[27] Iranzo A. Sleep and neurological autoimmune diseases [J]. Neuropsychopharmacology, 2020, 45:129-140.
[28] Tsutsui K, Kanbayashi T, Tanaka K, Boku S, Ito W, Tokunaga J, Mori A, Hishikawa Y, Shimizu T, Nishino S. Anti-NMDA-receptor antibody detected in encephalitis, schizophrenia, and narcolepsy with psychotic features[J]. BMC Psychiatry, 2012, 12:37.
[29] Tani M, Konishi Y, Nishida T, Takahashi Y, Kusaka T. A case of Kleine-Levin syndrome with positive anti-NMDA-type glutamate receptor antibodies[J]. Pediatr Int, 2020, 62:409-410.
[30] Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis [J]. Lancet Neurol, 2011, 10:63-74.
[31] Freund B, Ritzl EK. A review of EEG in anti-NMDA receptor encephalitis[J]. J Neuroimmunol, 2019, 332:64-68.
[32] Jeannin-Mayer S, André-Obadia N, Rosenberg S, Boutet C, Honnorat J, Antoine JC, Mazzola L. EEG analysis in anti-NMDA receptor encephalitis: description of typical patterns[J]. Clin Neurophysiol, 2019, 130:289-296.
[33] Blattner MS, de Bruin GS, Bucelli RC, Day GS. Sleep disturbances are common in patients with autoimmune encephalitis[J]. J Neurol, 2019, 266:1007-1015.
[34] Kanbayashi T, Tsutsui K, Tanaka K, Imanishi A, Sagawa, Y, Omokawa M, Ohmori Y, Kusanagi H, Nishino S, Shimizu T. Anti-NMDA-receptor antibodies detected in limbic encephalitis, schizophrenia and narcolepsy with psychotic symptoms[J]. Early Interv Psychiatry, 2014, 8(Suppl 1):13.
[35] Lin J, Elkins K, Bhalla S, Gedela S, Kheder A, Zhang G, Loerinc L, Blackwell L, Howarth R, Gombolay G. Electroencephalography characteristics to predict one-year outcomes in pediatric anti-NMDA receptor encephalitis [J]. Epilepsy Res, 2021, 178:106787.
[36] Mohammad SS, Soe SM, Pillai SC, Nosadini M, Barnes EH, Gill D, Dale RC. Etiological associations and outcome predictors of acute electroencephalography in childhood encephalitis[J]. Clin Neurophysiol, 2016, 127:3217-3224.
[37] Dimitriades ME, Markovic A, Gefferie SR, Buckley A, Driver DI, Rapoport JL, Nosadini M, Rostasy K, Sartori S, Suppiej A, Kurth S, Franscini M, Walitza S, Huber R, Tarokh L, Bölsterli BK, Gerstenberg M. Sleep spindles across youth affected by schizophrenia or anti-N-methyl-D-aspartate-receptor encephalitis [J]. Front Psychiatry, 2023, 14:1055459.
[38] Liao J, Lu Y, Lu Y, Huang Y, Wang Y, Long L, Hu X, Lu Z, Qiu W, Shu Y. Cardiopulmonary coupling spectrogram as an ambulatory method for assessing sleep disorders in patients with autoimmune encephalitis[J]. Neurology, 2024, 102:e209302.
[39] Yin D, Chen S, Liu J. Sleep disturbances in autoimmune neurologic diseases: manifestation and pathophysiology [J]. Front Neurosci, 2021, 15:687536.
[40] Monyer H, Burnashev N, Laurie DJ, Sakmann B, Seeburg PH. Developmental and regional expression in the rat brain and functional properties of four NMDA receptors[J]. Neuron, 1994, 12:529-540.
[41] Gitiaux C, Simonnet H, Eisermann M, Leunen D, Dulac O, Nabbout R, Chevignard M, Honnorat J, Gataullina S, Musset L, Scalais E, Gauthier A, Hully M, Boddaert N, Kuchenbuch M, Desguerre I, Kaminska A. Early electro-clinical features may contribute to diagnosis of the anti-NMDA receptor encephalitis in children[J]. Clin Neurophysiol, 2013, 124:2354-2361.
[42] Song Q, Feng G, Zhang J, Xia X, Ji M, Lv L, Ping Y. NMDA receptor-mediated Ca^{2+} influx in the absence of Mg^{2+} block disrupts rest: activity rhythms in Drosophila[J]. Sleep, 2017, 40: ID29029290.
[43] Yamane H, Tsuneyoshi Y, Denbow DM, Furuse M. N-Methyl-D-aspartate and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptors involved in the induction of sedative effects under an acute stress in neonatal chicks [J]. Amino Acids, 2009, 37:733-739.
[44] Campbell IG, Feinberg I. Noncompetitive NMDA channel blockade during waking intensely stimulates NREM delta[J]. J Pharmacol Exp Ther, 1996, 276:737-742.
[45] Yin D, Dong H, Wang TX, Hu ZZ, Cheng NN, Qu WM, Huang ZL. Glutamate activates the histaminergic tuberomammillary nucleus and increases wakefulness in rats [J]. Neuroscience, 2019, 413:86-98.
[46] Miracca G, Anuncibay-Soto B, Tossell K, Yustos R, Vyssotski AL, Franks NP, Wisden W. NMDA receptors in the lateral preoptic hypothalamus are essential for sustaining NREM and REM sleep[J]. J Neurosci, 2022, 42:5389-5409.
[47] Nissen MS, Ørvik MS, Nilsson AC, Ryding M, Lydolph M, Blaabjerg M. NMDA-receptor encephalitis in Denmark from 2009 to 2019: a national cohort study[J]. J Neurol, 2022, 269: 1618-1630.
[48] Peery HE, Day GS, Dunn S, Fritzler MJ, Prüss H, De Souza C, Doja A, Mossman K, Resch L, Xia C, Sakic B, Belbeck L, Foster WG. Anti-NMDA receptor encephalitis: the disorder, the diagnosis and the immunobiology[J]. Autoimmun Rev, 2012, 11: 863-872.
[49] Varma A, Sapra M. Anti-NMDA receptor encephalitis: a need for increased awareness among psychiatrists [J]. Psychiatric Annals, 2015, 45:572-576.

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