

抗 NMDA 受体脑炎患者临床表现、并发症及相关影响因素分析

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【摘要】 目的 分析抗 N-甲基-D-天冬氨酸(NMDA)受体脑炎患者临床表现及并发症情况,并探讨其相关影响因素。方法 回顾性收集确诊为抗 NMDA 受体脑炎患者的临床资料,根据患者临床症状复杂程度分为临床症状 ≥ 4 种组(96例,67.1%)和 < 4 种组(47例,32.9%),以及根据患者并发症发生情况分为有并发症组(109例)和无并发症组(34例),单因素及多因素分析其相关影响因素。结果 共纳入抗 NMDA 受体脑炎患者 143例,130例(90.9%)患者具有精神障碍,120例(83.9%)患者出现癫痫发作。并发症中,以肺部感染(84例,58.7%)和胃肠道功能紊乱(70例,49.0%)最为常见。单因素分析显示,患者临床症状复杂程度与脑电图异常、脑脊液(CSF)和血清中均出现抗 NMDA 受体抗体阳性有关。患者有并发症组与无并发症组在癫痫、意识障碍、入院时日常生活能力(ADL)评分和住院时间等的差异有统计学意义($P < 0.05$)。多因素分析显示,脑电图异常是影响患者临床症状复杂程度的预测因素[比值比($OR = 2.620, P < 0.05$);运动障碍和患者入院时的低 ADL 评分是影响患者并发症的独立危险因素(OR 值分别为 4.338、0.980, $P < 0.05$)。结论 脑电图结果显示异常的抗 NMDA 受体脑炎患者临床症状复杂程度高于脑电图正常的患者;抗 NMDA 受体脑炎患者并发症的发生率高,运动障碍和患者入院时较差的生活自理能力是患者出现并发症的独立危险因素。

【关键词】 抗 NMDA 受体 脑炎 并发症 因素分析

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【Abstract】 **Objective** To investigate the clinical manifestations and complications in the patients of anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis. **Methods** We retrospectively collected clinical data of 143 patients diagnosed with anti-NMDA receptor encephalitis. According to the complexity of clinical symptoms, the patients were divided into two groups: ≥ 4 clinical symptoms group (96 cases, 67.1%) and < 4 group (47 cases, 32.9%). There were 109 patients with complications and 34 patients without any complications. The related factors to symptom complexity and complications were analyzed by univariate and multivariate analysis method. **Results** In the 143 patients of anti-NMDA receptor encephalitis, 120 (83.9%) exhibited seizures, 130 (90.9%) presented with psychiatric symptoms. Pulmonary infections (58.7%) and gastrointestinal disorders (49.0%) were the most common complications. Univariate analysis showed that the complexity of clinical symptoms was related to abnormal electroencephalography (EEG), positive anti-NMDA receptor antibody in cerebrospinal fluid (CSF) and serum. There were more frequent seizures, disorders of consciousness, abnormal movements, central hypoventilation in the patients with complications than those in patients without complications, all the differences were significant ($P < 0.05$). Multivariate analysis showed that abnormal EEG was an independent risk factor for symptom complexity [odds ratio ($OR = 2.620, P < 0.05$)]. The abnormal movements and the activities of daily living (ADL) on admission were predictor factors for the incidence of complications ($OR = 4.338, 0.980$, respectively, $P < 0.05$). **Conclusion** In the patients of anti-NMDA receptor encephalitis, abnormal EEG may related to more complex clinical symptoms. Abnormal movements and low ADL on admission seems to be independent risk factors related to the incidence of complications.

【Key words】 Anti-NMDA receptor Encephalitis Complication Factor analysis

抗 N-甲基-D-天冬氨酸(NMDA)受体脑炎是一种由抗 NMDA 受体 NR1 介导的病情严重、症状复杂的自身免疫性

脑炎, DALMAU 等^[1]于 2007 年首次报道了该病。抗 NMDA 受体脑炎是自身免疫性脑炎的最常见类型, 临床表现常有精神症状、癫痫发作、意识状态改变、言语障碍、自主神经功能紊乱及运动障碍等, 不同患者出现的症状不同^[2], 临床表现复杂, 导致诊断较困难, 疾病初期误诊率高达 57%^[3]。抗 NMDA 受体脑炎患者病情严重, 致死率为 8%~10%^[4]。有报道^[5]显示, 抗 NMDA 受体脑炎的并发症如肺部感染是患者重要的死亡原因之一。近年来, 随着国内外抗 NMDA 受体脑炎的病例报道越来越多, 抗 NMDA 受体脑炎的诊断、治疗越来越受到重视^[6-7]。但是有关该病临床症状及并发症的相关影响因素报道少见。因此, 本研究回顾性分析抗 NMDA 受体脑炎患者临床表现和并发症存在的流行病学现状, 并分析其相关影响因素。

1 对象与方法

1.1 研究对象

本研究纳入 2012 年 10 月至 2017 年 6 月于四川大学华西医院确诊为抗 NMDA 受体脑炎的患者 143 例。抗 NMDA 受体脑炎的诊断标准^[8]: ①患者脑脊液(CSF)和(或)血清中抗 NMDA 受体抗体 IgG 检测结果为阳性; ②存在以下 8 种临床表现中的一个或多个: 精神症状、癫痫、意识障碍、运动障碍、记忆缺陷、言语障碍、自主神经功能紊乱、中枢性低通气。若患者反复多次入院, 则收集患者首次确诊为抗 NMDA 受体脑炎的入院相关资料。所有患者均知情同意。

1.2 研究方法

回顾性收集患者的一般人口学资料(年龄、性别), 临床表现(前驱症状、精神症状、癫痫、意识障碍等), 并发症(感染、电解质紊乱、胃肠道功能紊乱等), 辅助检查(磁共振成像(MRI)、脑电图(EEG)、CSF 和血清中抗 NMDA 受体抗体检测结果), 入院时日常生活能力(ADL)评分(根据 ADL 评分量表进行^[9], ADL 评分越高则表示患者生活自理能力越好), 住院时间等资料, 分析患者临床表现及并发症情况。

1.3 统计学方法

符合正态分布的计量资料(入院时 ADL 评分、住院时间)用 $\bar{x} \pm s$ 描述, 采用 t 检验分析; 偏态分布计量资料(年龄)用中位数描述, 组间比较采用秩和检验分析; 计数资料(性别、临床表现、辅助检查)用频数、构成比描述, 组间比较采用 χ^2 检验。多因素分析采用 logistic 回归模型分析。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 抗 NMDA 受体脑炎患者临床表现及并发症情况

共 143 例抗 NMDA 受体脑炎患者纳入研究。其中男性 59 例, 女性 84 例, 年龄中位数为 28(11~79)岁。患者临床表现及并发症情况见表 1、表 2。可见最常见的临床表现为精神障碍(90.9%)和癫痫发作(83.9%)。并发症中, 以肺部感染(58.7%)和胃肠道功能紊乱(49.0%)最为常见。存在

一种及以上并发症的患者数为 109 例, 占比高达 76.2%。

表 1 抗 NMDA 受体脑炎患者临床症状($n=143$)

Table 1 Clinical symptoms of anti-NMDA receptor encephalitis ($n=143$)

Clinical symptom	Case (%)
Prodromal symptoms	60 (42.0)
Seizures	120 (83.9)
Psychiatric symptoms	130 (90.9)
Disorders of consciousness	87 (60.8)
Abnormal movements	67 (46.9)
Memory dysfunction	73 (51.0)
Speech dysfunction	58 (40.6)
Autonomic dysfunctions	40 (28.0)
Central hypoventilation	36 (25.2)

表 2 抗 NMDA 受体脑炎患者的并发症情况

Table 2 Complications of anti-NMDA receptor encephalitis ($n=143$)

Complication	Case (%)
With complications	109 (76.2)
Pneumonia	84 (58.7)
Urinary tract infection	23 (16.1)
Electrolyte disorders	37 (25.9)
Gastrointestinal disorders	70 (49.0)
Gastrointestinal hemorrhage	21 (14.7)
Hypo-albuminemia	20 (14.0)
Rash	32 (22.4)

2.2 影响抗 NMDA 受体脑炎患者临床症状复杂程度的单因素分析

抗 NMDA 受体脑炎患者有 8 种主要的临床症状, 但是不同患者临床症状的复杂程度截然不同, 有些患者可 8 种临床症状均出现, 有些患者则只出现 1 种。为了探讨其影响患者临床症状复杂程度的相关因素, 将患者分为临床症状 ≥ 4 种组(96 例, 67.1%)和 < 4 种组(47 例, 32.9%), 单因素分析结果(表 3)显示, 脑电图异常、脑脊液和血清中均出现抗 NMDA 受体抗体阳性与患者临床症状的复杂程度有关。

表 3 抗 NMDA 受体脑炎患者临床症状复杂程度的单因素分析

Table 3 Univariate analysis of the complexity of clinical symptoms in patients with anti-NMDA receptor encephalitis

Variable	≥ 4 clinical symptoms ($n=96$)	< 4 clinical symptoms ($n=47$)	P
(Female : male)/case	54 : 44	30 : 17	0.387
Age/yr. [median (range)]	28.5 (14-74)	28 (11-79)	0.976
Prodromal symptoms/case (%)	39 (40.6)	21 (44.7)	0.644
Abnormal MRI/case (%)	38 (39.6)	14 (29.8)	0.285
Abnormal EEG/case (%)	62 (64.6)	24 (51.1)	0.019
Antibody in CSF and serum (positive)/case (%)	54 (56.3)	17 (36.2)	0.030

MRI: Magnetic resonance imaging; EEG: Electroencephalography; CSF: Cerebrospinal fluid

2.3 影响抗 NMDA 受体脑炎患者并发症的单因素分析

根据患者是否出现并发症将其分为有并发症组(109

例)和无并发症组(34 例),单因素分析结果显示,抗 NMDA 受体脑炎患者发生并发症与有癫痫、意识障碍、运动障碍、自主功能紊乱临床表现,有中枢性低通气、入院时 ADL 评分低和住院时间长有关($P < 0.05$)。见表 4。

表 4 抗 NMDA 受体脑炎患者并发症的单因素分析

Table 4 Univariate analysis of complications in patients with anti-NMDA receptor encephalitis

Variable	With complication (n=109)	Non-complication (n=34)	P
(Female : male)/case	62 : 47	22 : 12	0.418
Age/yr. [median (range)]	29 (11-79)	25 (15-56)	0.138
Prodromal symptoms/case (%)	49 (45.0)	11 (32.4)	0.194
Seizures/case (%)	96 (88.1)	24 (70.6)	0.015
Psychiatric symptoms/case (%)	102 (93.6)	28 (82.4)	0.100
Disorders of consciousness/ case (%)	80 (73.4)	7 (20.6)	0.000
Abnormal movements/case (%)	59 (54.1)	8 (23.5)	0.002
Memory dysfunction/case (%)	54 (49.5)	19 (55.9)	0.518
Speech dysfunction/case (%)	45 (41.3)	13 (38.2)	0.752
Autonomic dysfunctions/ case (%)	36 (33.0)	4 (11.8)	0.016
Central hypoventilation/ case (%)	35 (32.1)	1 (2.9)	0.001
Abnormal MRI/case (%)	40 (36.7)	12 (35.3)	0.832
Abnormal EEG/case (%)	67 (61.5)	19 (55.9)	0.108
Antibody in CSF and serum (positive)/case (%)	54 (49.5)	17 (50.0)	0.885
ADL score on admission/score	39.45±36.50	77.90±23.55	0.000
Hospital stay/d	31.93±22.57	17.88±12.30	0.001

MRI: Magnetic resonance imaging; EEG: Electroencephalography; CSF: Cerebrospinal fluid; ADL: Activities of daily living

表 5 影响患者临床症状复杂程度和并发症的多因素分析

Table 5 Multivariate analysis of complications and the complexity of clinical symptoms in patients with anti-NMDA receptor encephalitis

Variable	β	Wald	SE	P	OR	95%CI
Clinical symptoms						
Age	-0.019	1.370	0.016	0.242	0.981	(0.950,1.013)
Sex (female)	-0.656	2.400	0.424	0.121	0.519	(0.226,1.190)
Abnormal EEG (yes)	0.963	4.749	0.442	0.029	2.620	(1.102,6.231)
Anti-Antibody in CSF and serum (positive)	0.542	1.709	0.415	0.191	1.719	(0.763,3.874)
Complications						
Age	0.024	0.989	0.024	0.320	1.024	(0.977,1.074)
Sex (female)	-0.438	0.597	0.566	0.440	0.646	(0.213,1.959)
Seizures (yes)	0.523	0.590	0.681	0.443	1.687	(0.444,6.413)
Disorders of consciousness (yes)	0.958	2.414	0.617	0.120	2.607	(0.778,8.733)
Abnormal movements (yes)	1.468	5.206	0.643	0.023	4.338	(1.230,15.305)
Autonomic dysfunctions (yes)	0.644	0.539	0.877	0.463	1.904	(0.341,10.631)
Central hypoventilation (yes)	1.028	0.763	1.177	0.382	2.796	(0.278,28.078)
ADL score on admission	-0.020	3.991	0.010	0.046	0.980	(0.961,1.000)
Hospital stay	0.025	1.036	0.024	0.309	1.025	(0.977,1.076)

EEG: Electroencephalography; ADL: Activities of daily living; β : Partial regression coefficient; SE: Standard error; OR: Odds ratio; 95%CI: 95% confidence interval

患者的预后和病情复发具有相关性^[13]。本研究发现,与只有 CSF 中出现抗 NMDA 受体抗体阳性相比,CSF 与血清中均有抗体存在的患者临床表现种类数更多,症状更加复杂。另外,已有众多研究显示,抗 NMDA 受体脑炎患者脑电图异常的比例较高,脑电图结果或许有助于抗 NMDA 受体脑炎的鉴别诊断^[11,14-15]。在本研究中,我们发现脑电图异常是患者临床表现复杂程度的影响因素,脑电图异常的患者更有

2.4 影响抗 NMDA 受体脑炎患者临床症状复杂程度和并发症的多因素分析

将单因素分析中 $P < 0.1$ 的因素及患者的年龄、性别纳入多因素 logistic 回归模型分析。调整混杂因素后多因素分析显示,脑电图异常是影响患者临床症状(Y , 临床症状 ≥ 4 种 = 1, 临床症状 < 4 种 = 0)的独立危险因素($OR = 2.620$, $P < 0.05$);存在运动障碍和患者入院时的生活自理能力(ADL)评分低是影响患者并发症(Y , 有并发症 = 1, 无 = 0)的独立危险因素(OR 值分别为 4.338、0.980, $P < 0.05$)。见表 5。

3 讨论

3.1 抗 NMDA 受体脑炎患者临床表现情况及相关影响因素分析

本研究显示,90.9% 的患者具有精神障碍,83.9% 的患者出现癫痫发作,癫痫和精神障碍是抗 NMDA 受体脑炎患者的主要临床表现^[10]。另外,有 67.1% 的患者出现 4 种及以上的临床症状,提示抗 NMDA 受体脑炎患者临床表现相当复杂,症状具有非特异性。本研究报道的抗 NMDA 受体脑炎患者意识障碍、运动障碍、言语及记忆障碍等各种临床表现的出现比例情况与 ZHANG 等^[11]的报道相一致。明确患者临床表现情况,将有助于抗 NMDA 受体脑炎患者的辨别诊断,减少误诊率^[12]。

有研究显示,CSF 和血清中抗 NMDA 受体抗体滴度与

可能出现较多的临床症状。我们推测,脑电图异常及 CSF 和血清均显示抗体阳性或许有助于预测患者临床表现的复杂程度,间接预测患者病情的严重程度。

3.2 抗 NMDA 受体脑炎患者并发症情况及相关影响因素分析

本研究显示,抗 NMDA 受体脑炎患者并发症以肺部感染(58.7%)和胃肠道功能紊乱(49.0%)最为常见,此外还可

出现尿路感染、电解质紊乱、消化道出血、低蛋白血症和皮疹等并发症。患者并发症发生率较高,有 76.2% 的患者出现了一种及以上的并发症。有报道显示抗 NMDA 受体脑炎患者肺部感染率为 55%~65%^[5,16],与本研究相一致。本研究中有 22.4% 的患者出现了不明原因的皮疹,这可能与抗 NMDA 受体脑炎患者更易出现过敏有关^[17]。其他种类的并发症尚未见到相关报道,有待进一步研究。

抗 NMDA 受体脑炎患者并发症与多种临床表现(癫痫、意识障碍、运动障碍、自主功能紊乱、中枢性低通气)有关,我们推测,患者临床表现越复杂,则出现并发症的可能性越大。这可能与患者临床症状越多,患者相应的生理功能越差有关,也可能与相应的医疗干预越多有关。本研究显示患者入院时 ADL 评分是患者出现并发症的影响因素,患者自理能力越差则越容易出现并发症^[18];此外,运动障碍也是患者并发症发生的独立危险因素之一,口面部运动障碍是患者运动障碍的最常见类型^[19-20],可影响患者吞咽过程的口腔期,从而可能会导致误吸,增加吸入性肺炎的危险。这也许是运动障碍患者更容易出现并发症的原因之一。综上所述,抗 NMDA 受体脑炎患者的临床表现复杂,且具有非特异性,以精神症状和癫痫为主。脑电图异常的患者更有可能表现更复杂的临床症状。抗 NMDA 受体脑炎患者并发症的发生率高,以肺部感染和胃肠道功能紊乱最为常见。运动障碍和患者入院时的生活自理能力较差是患者出现并发症的独立危险因素。应加强对患者的观察,防止并发症发生,以改善患者预后。

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