

Risk factors for pneumonia in patients with anti-NMDA receptor encephalitis

A single-center retrospective study

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Abstract

To identify the risk factors of pneumonia in patients with Anti-N-methyl-D-aspartate (Anti-NMDA) receptor encephalitis.

This is a retrospective study.

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Patients with a definitive diagnosis of anti-NMDA receptor encephalitis.

Risk factors associated with pneumonia were examined by bivariate analysis and multivariate logistic regression model.

A total of 104 patients were included in this study, of which 41% patients (n = 43) were diagnosed with pneumonia at 7 days (range: 4–40 days) after admission. The occurrence of pneumonia was associated with prolonged hospital stays, a higher rate of poor outcome, and extra healthcare costs. Risk factors associated with pneumonia included Glasgow coma scale score (GCS), abnormal movements and hypokalemia.

Pneumonia is a common complication in anti-NMDA receptor encephalitis. In the present study, we found that disorders of consciousness, abnormal movements, and hypokalemia were independent risk factors for pneumonia in inpatients with anti-NMDA receptor encephalitis. Pneumonia prolongs the patients' hospital stay, hospitalization expenditures, and affects the patients' prognosis.

Abbreviations: anti-GABABR = anti-gamma-aminobutyric-acid B receptor, Anti-NMDA = anti-N-methyl-D-aspartate, CSF = cerebrospinal fluid, GCS = Glasgow Coma Scale, mRS = modified Rankin scale, SD = standard deviation.

Keywords: anti-N-methyl-D-aspartate receptor, autoimmune encephalitis, pneumonia, risk factors

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1. Introduction

Anti-N-methyl-D-aspartate (Anti-NMDA) receptor encephalitis is a newly recognized autoimmune disorder in the central nervous system, associated with abnormal production of autoantibodies to the NR1 subunit of NMDA receptor.^[1] First described in young women with ovarian teratomas in 2007, is characterized by a progressive clinical course with the potential for effective management and improved outcome.^[2] Anti-NMDA receptor encephalitis accounts for about 4% of all encephalitis cases,^[3] of which typical symptoms are psychiatric features, seizure, speech dysfunction, movement disorder, decreased consciousness level and autonomic imbalance.^[1] The diagnosis of anti-NMDA receptor encephalitis is based on serum and cerebrospinal fluid (CSF) results. Furthermore, symptoms can be alleviated by first-line treatment (corticosteroid, plasma exchange, and immunoglobulin), and second-line treatment (cyclophosphamide and rituximab).^[4] The mortality of anti-NMDA receptor encephalitis is 8% to 10%,^[5] which was similar to that among acute encephalitis (8%)^[6] but much higher than encephalitis or meningitis (2.9%).^[7] Severe pneumonia has been reported to be the main cause of death in anti-NMDA receptor encephalitis.^[8] The incidence rate of pneumonia in anti-NMDA receptor encephalitis ranges from 55% to 65%,^[8,9] which was similar to that among patients with anti-gamma-aminobutyric-acid B receptor (anti-GABABR) encephalitis^[10] but higher than general

surgical procedures and stroke patients.^[11,12] However, the cause of pneumonia in patients with anti-NMDA receptor encephalitis is unclear. To investigate pneumonia among patients with anti-NMDA receptor encephalitis, we conducted this retrospective study to explore the risk factors for pneumonia and to describe the burden and prognosis of pneumonia in patients with anti-NMDA receptor encephalitis.

2. Methods

2.1. Study design and setting

This is a single-center retrospective study. Patients with a definitive diagnosis of anti-NMDA receptor encephalitis^[13] in the West China Hospital of Sichuan University between October 2012 and June 2017 were enrolled.

2.2. Participants

Patients who met the diagnostic criteria of anti-NMDA receptor encephalitis were included.^[13] Anti-NMDA receptor encephalitis diagnostic criteria were met if:

Anti-NMDA receptor antibody IgG was positive in the cerebrospinal fluid (All samples of each patient were sent to Oumeng Biotechnology Corporation, or Peking Union Medical College Hospital, Beijing, China, to detect the anti-NMDA receptor immunoglobulin G antibodies by indirect immunofluorescence using EU 90 cells as previously described^[14]).

Anti-NMDA receptor antibody IgG was positive in the serum. This is not essential.

One or more of the following major symptoms: seizures, abnormal behavior dysfunction, disturbance of consciousness, language impairment, movement disorder or dyskinesia, memory deficit, autonomic dysfunction or central hypoventilation was present.

The exclusion criteria were:

diagnosis of other diseases according to the clinical data, such as patients diagnosed with infectious encephalitis or etiology unknown encephalitis and

patients with pneumonia prior to admission.

The diagnosis criteria for pneumonia was based on the presence of new or progressive lung infiltrates on chest radiographs and patients had at least 2 of the following clinical signs: fever ($>38^{\circ}\text{C}$), cough, purulent sputum, leukocytosis ($>12,000$ WBC/mm³) or leucopenia (<4000 WBC/mm³), shortness of breath, and chest pain.^[15]

2.3. Data collection

Data extraction was performed by 2 researchers (PY and LZ) from the medical records system, including incidence of pneumonia (timing of diagnosis, etiological agents, signs/symptoms/laboratory/radiologic), demographic data (age, sex), imaging and blood tests (abnormal EEG, abnormal MRI, hyponatremia, gastrointestinal hemorrhage, hypo-albuminemia, liver dysfunction), 8 major clinical manifestations (psychiatric disorders, seizures, movement disorders, decreased level of consciousness, autonomic dysfunction, speech difficulties, memory deficit, and central hypoventilation), tumor, treatment (methylprednisolone, intravenous immunoglobulin), admission to ICU (Yes/No), nasogastric feeding or not, length of hospital stay and healthcare costs. And participants were regularly followed up by telephone and were evaluated using the modified

Rankin scale (mRS) after discharge from hospital in a 3-month interval. A poor outcome was defined by mRS score of 4–6 (severe disability or death)^[16] at the last follow up. The levels of consciousness of patients were evaluated by Glasgow Coma Scale (GCS) score.^[17]

2.4. Ethical considerations

The study was approved by the West China Hospital Institutional Review Board and Ethics Committee. Informed consent was obtained from each participant.

2.5. Data analysis

Statistical analysis was performed using IBM SPSS Statistics, version 22.0. Continuous variables with a normal and non-normal distribution were described as means \pm standard deviation (SD) and medians, respectively. Continuous variables were analyzed using the Student's *t* test or the Mann–Whitney test. Count data were expressed as the number of cases (%). The significance levels of the differences in gender, clinical presentations and ancillary examination between the 2 groups were analyzed using the chi-square test. Binary logistic regression models were developed to identify independent risk factors associated with pneumonia. Then factors associated with pneumonia by univariate analysis ($P < .05$) were entered into a multivariate logistic regression model using a stepwise selection procedure. *P* values of less than .05 (two-sided) were considered statistically significant.

3. Results

3.1. Study population

Finally, 104 patients were included in this study. The demographic information, clinical information, ancillary examination and treatment were summarized in Table 1. Patients had a median age of 28 (11–79) years and 62 (60%) of them were female.

Eighty patients (77%) exhibited seizures, of whom 31 experienced status epilepticus. Ninety-four (90%) presented with psychiatric symptoms, including abnormal behavior, anxiety, paranoia, catatonia, and hallucinations. Twelve (12%) patients were diagnosed with the tumor, 6 of them were with teratoma. The ancillary examination found all patients having anti-NMDA receptor antibody positive in the CSF, and 49 (47%) patients with anti-NMDA receptor antibody positive in the serum. Patients were mainly treated with methylprednisolone and intravenous immunoglobulin. Patients were discovered with other clinical information were summarized in Table 1.

Forty-three (41%) patients were diagnosed with pneumonia 7 (4–40) days after admission (Fig. 1). Altogether, 7 bacteria and 1 yeast were isolated from sputum samples of 9 patients out of the 40 pneumonia cases (22.50%), 5 patients (12.5%) had a single pathogen and other 4 (10%) had 2 pathogens, Gram-negative bacilli were the most common organisms Table 2. The signs/symptoms/laboratory/ radiologic for pneumonia were list in Table 3.

3.2. Burden of patients with pneumonia in anti-NMDA receptor encephalitis

The length of hospital stay was 28 (3–104) days in patients with pneumonia, longer than patients without pneumonia with

Table 1**Clinical information and univariable analysis of patients with anti-NMDA receptor encephalitis.**

Variables	Total (n=104,%)	Patients with Pneumonia (n=43, %)	Patients without Pneumonia (n=61, %)	Statistical Value	P value
Demographic data					
Sex(female)	62 (60)	27 (63)	35 (57)	0.307	.580
Age medium, Range(year)	28 (11–79)	28 (11–74)	27 (15–79)	–1.110	.267
Clinical presentations					
Prodromal symptoms	39 (38)	19 (44)	20 (33)	1.398	.237
Seizures	80 (77)	38 (88)	42 (69)	5.413	.020*
Psychiatric symptoms	94 (90)	40 (93)	54 (89)	0.184	.668
Disorders of consciousness (GCS score)	14 (3–15)	10 (3–15)	15 (4–15)	–5.427	<.001*
Abnormal movements	45 (43)	27 (63)	18 (30)	11.381	.001*
Memory dysfunction	59 (57)	23 (53)	36 (59)	0.314	.575
Speech dysfunction	36 (35)	15 (35)	21 (34)	0.002	.961
Autonomic dysfunctions	23 (22)	12 (28)	11 (18)	2.218	.136
Central hypoventilation	11 (11)	7 (16)	4 (7)	1.597	.206
Tumor	12 (12)	4 (9)	8 (13)	0.083	.774
Ancillary examination					
Abnormal EEG	70 (67)	29 (67)	41 (67)	0.882	.348
Abnormal MRI	35 (34)	17 (40)	18 (30)	1.442	.230
Antibody in serum (positive)	49 (47)	20 (47)	29 (48)	0.001	.971
Hyponatremia	6 (6)	5 (12)	1 (2)	2.974	.085
Hypo-albuminemia	15 (14)	13 (30)	2 (3)	14.845	<.001*
Liver dysfunction	22 (21)	11 (26)	11 (18)	0.862	.353
Hypokalemia	14 (13)	11 (26)	3 (5)	9.244	.002*
Gastrointestinal hemorrhage	11 (11)	9 (21)	2 (3)	6.547	.011*
Treatment					
MTP	58 (56)	31 (72)	27 (44)	7.919	.005*
IVIG					
Mechanical ventilation	11 (11)	10 (23)	1 (2)	10.280	.001*
Nasogastric tube	33 (32)	26 (60)	7 (11)	28.491	<.001*
Admission to ICU	8 (8)	7 (16)	1 (2)	5.690	.017*
First visit department					
Neurology	61 (59)	27 (63)	34 (56)		
Psychiatry	21 (20)	10 (23)	11 (18)	2.351	.309
Others	22 (21)	6 (14)	12 (20)		

CSF = cerebrospinal fluid, EEG = electroencephalography, GCS score = Glasgow coma scale score, ICU = intensive care unit, IVIG = intravenous immunoglobulin, MRI = magnetic resonance imaging, MTP = methylprednisolone.

* Significant difference.

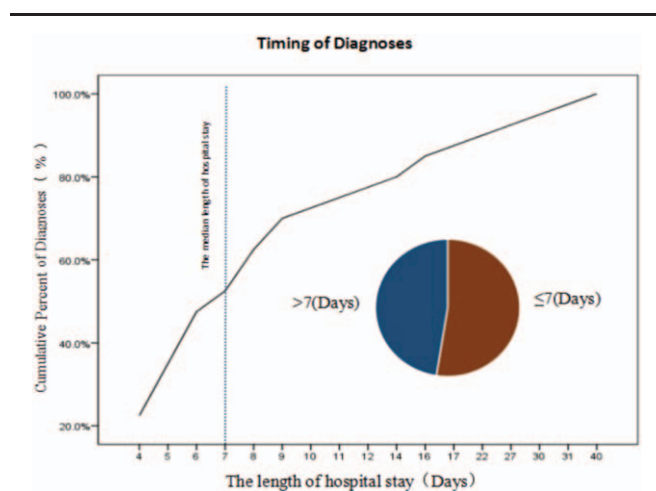


Figure 1. Timing of diagnoses. The median length of hospital stay on which pneumonia was diagnosed was day 7. The 52.5% of cases were diagnosed less than or equal to 7 days and 47.5% more than 7 days.

18 (4–69) days ($P < .001$). The healthcare cost of patients with pneumonia was $(28,792 \pm 13,943)$, higher than $18,092 \pm 13,995$ (¥, RMB) among those without ($P = .003$). Patients were with a median follow-up duration of 14 (3–48) months after discharge from the hospital. Patients with pneumonia were prone to have a

Table 2**Pathogen for pneumonia.**

Pathogen	N (% of total pneumonias)
Gram-negative bacilli	
Acinetobacter baumannii	3 (7.5%)
Acinetobacter calcoaceticus	3 (7.5%)
Klebsiella pneumoniae	2 (5%)
Pseudomonas aeruginosa	1 (2.5%)
Escherichia coli	1 (2.5%)
Enterobacter aerogenes	1 (2.5%)
Stenotrophomonas maltophilia	1 (2.5%)
Fungus	
Candida albicans	1 (2.5%)

Table 3
Signs/symptoms/laboratory/radiologic for pneumonia.

Item	N (% of total pneumonias)
Chest radiologic examination (new or progressive lung infiltrates)	43 (100%)
Cough	29 (67)
Fever (>38°C)	25 (58)
Purulent sputum	21 (49)
Leukocytosis (>12,000 WBC/mm ³)	19 (44)
Leucopenia (<4000 WBC/mm ³)	6 (14)
Shortness of breath	5 (12)
Chest pain	3 (7)

poorer outcome (mRS=4–6) compared to those without pneumonia (20% vs 3%, $P=.013$).

3.3. Univariable analysis of predictors of pneumonia

Univariate analysis of predictors of pneumonia was reported in Table 1. The demographic information, clinical information, ancillary examination and treatment of the patients were compared according to pneumonia.

Compared with patients without pneumonia, patients with pneumonia had higher frequency of seizures (88% vs 69%, $P=.020$), disorders of consciousness ($P<.001$), abnormal movements (63% vs 30%, $P=.001$), mechanical ventilation (23% vs 2%, $P=.001$), hypo-albuminemia (30% vs 3%, $P<.001$), hypokalemia (26% vs 5%, $P=.002$), gastrointestinal hemorrhage (21% vs 3%, $P=.011$), methylprednisolone (72% vs 44%, $P=.005$), nasogastric tube (60% vs 11%, $P<.001$) and admission to ICU (16% vs 2%, $P=.017$). No significant difference was found in others clinical information.

3.4. Multivariable analysis of risk factors for pneumonia

Multivariable analysis of predictors for pneumonia was shown in Table 4. Variables entered in the multivariate model were: seizures, disorders of consciousness, abnormal movements, hypokalemia, mechanical ventilation, hypo-albuminemia, gastrointestinal hemorrhage, methylprednisolone, nasogastric tube and admission to ICU. In multivariate analysis, factors associated with pneumonia included levels of consciousness (GCS score) (Odds Ratio 0.764, 95% CI: 0.620–0.942, $P=.012$), abnormal movements (Odds Ratio 3.716, 95% CI: 1.149–12.015,

Table 4
Variables associated with pneumonia in multivariate analysis.

Variable	Odds ratio (95%CI)	P value
Seizures	6.026 (0.896–40.523)	.065
Disorders of consciousness (GCS score)	0.764 (0.620–0.942)	.012*
Abnormal movements	3.716 (1.149–12.015)	.028*
Mechanical ventilation	2.059 (0.043–97.541)	.714
Hypo-albuminemia	4.699 (0.627–35.211)	.132
Hypokalemia	13.473 (1.974–91.967)	.008*
Gastrointestinal hemorrhage	0.970 (0.095–9.946)	.979
MTP	1.021 (0.295–3.538)	.973
Nasogastric tube	2.478 (0.522–11.751)	.253
Admission to ICU	1.099 (0.043–27.762)	.954

GCS score=Glasgow coma scale score, ICU=intensive care unit, MTP=methylprednisolone.
*Significant difference.

$P=.028$) and hypokalemia (Odds Ratio 13.473, 95% CI: 1.974–91.967, $P=.008$) (Table 4).

4. Discussion

In this study, the incidence of pneumonia in 104 in-patients with anti-NMDA receptor encephalitis was 41%. Pneumonia is associated with longer hospital stays, poorer outcome, and more healthcare costs. Disorders of consciousness, abnormal movements, and hypokalemia were identified to be risk factors for pneumonia in patients with anti-NMDA receptor encephalitis.

In our present study, a lower GCS was found to be associated with the occurrence of pneumonia in patients with anti-NMDA receptor encephalitis. This is consistent with previous studies^[18–20]. Caterina et al^[21] reported a high incidence of pneumonia (76.79%) in patients with disorders of consciousness.^[18–20] A lower GCS score was strongly related to the reduced gag and cough reflexes, indicating that patients with decreased consciousness maybe unable to protect their own airway and were at risk for aspiration.^[22] It was recommended that patients with a GCS of ≤ 8 should undergo tracheal intubation to prevent possible airway obstruction, aspiration, or respiratory compromise.^[19] However, a considerable proportion of those with a GCS ≤ 8 not intubated had no respiratory complications developed. This indicated that airway management in anti-NMDA receptor encephalitis should be paid more attention and decided by the clinical situation.^[20,23]

In the present retrospective study, movement disorder was also proving to be associated with the occurrence of pneumonia in patients with anti-NMDA receptor encephalitis. Movement disorders are typical symptoms in patients with anti-NMDA receptor encephalitis. Orofacial and tongue dyskinesia are the most frequent characteristic movement disorder.^[24,25] Orofacial and tongue dyskinesia can affect the oral phase of normal swallowing process,^[26] which may lead to dysphagia and increase the risk of aspiration.^[27] This maybe the best explanation that abnormal movement increases the incidence of pneumonia in patients with anti-NMDA receptor encephalitis.

Hypokalemia (serum potassium less than 3.5 mmol/L)^[28] is one of the most common electrolyte disturbances, which was often caused by steroid treatment. Hypokalemia may affect the muscles of respiration, which can lead to reduced protective cough function,^[29] difficulty in breathing, fast breathing or respiratory failure. Affected gastrointestinal muscles could cause intestinal obstruction with related symptoms of abdominal distension, nausea, and vomiting.^[21,30] Symptoms of respiration and gastrointestinal muscles weakness due to hypokalemia may be the cause for aspiration and increase the risk of pneumonia.

In our study, treatment with methylprednisolone (glucocorticoid) is associated with pneumonia, though did not enter the multivariate analysis result. Previous studies have shown long-term use of inhaled corticosteroids increases the risk of pneumonia in COPD,^[31] and glucocorticoid may be a risk factor for *Pneumocystis jirovecii* pneumonia infection in patients with autoimmune diseases.^[32] However, Glucocorticoids is recommended as first-line treatments in patients with anti-NMDA receptor encephalitis. This may be one of the reasons for the high rate of pneumonia in patients with anti-NMDA receptor encephalitis.

There were some limitations in our study. First, this is a retrospective study. Second, the sample size was small as our data were collected from a single center. We will strive for the

opportunity to collect data in multicenter and validate these variables in different data-set. Third, we were unable to classify the specific types of pneumonia for all patients due to restrictions on the information we obtained. Furthermore, we did not have the same follow-up time after patient discharge, which may affect the evaluation of prognosis.

5. Conclusion

In the present study, we found that disorders of consciousness, abnormal movements and hypokalemia were independent risk factors for pneumonia in inpatients with anti-NMDA receptor encephalitis. Pneumonia prolongs the patients' hospital stay, hospitalization expenditures, and affects the patients' prognosis.

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