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Original Article

Risk factors for pneumonia complication in Neuromyelitis optica spectrum disorders

Bingjun Zhang[1*], Yi Zhong[2, 3*], Yanqiang Wang[4], Zhengqi Lu[1]

Departments of [1]Neurology, [2]Rheumatology and Immunology, The Third Affiliated Hospital of Sun Yat-sen University,Guangzhou, Guangdong, China; [3]Department of Dermatology, Guangzhou Women and Children's Medical Center,Guangzhou, Guangdong, China; [4]Department of Neurology, Affiliated Hospital of Weifang Medical University, Weifang, China. [*]Equal contirbutors.

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Abstract: Although pneumonia complication is inevitable in many patients with a progressive clinical course of idiopathic demyelinating diseases, few studies have focused on the incidence and risk factors of pneumonia complication in neuromyelitis optica spectrum disorders (NMOSD). The aim of this study was to investigate the incidence and risk factors of pneumonia complication in NMOSD. One hundred and fifty two NMOSD patients with pneumonia (n = 20) and without pneumonia (n = 132) were enrolled. The clinical, laboratory and magnetic resonance imaging features between two groups were assessed. The correlation between pneumonia and the severity of NMOSD was determined by using spearman correlation analysis. Logistic regression analysis was used to determine independent risk predictors for pneumonia complication in NMOSD. 13.2% NMOSD patients had pneumonia complication. Pneumonia was positively correlated with the severity of NMOSD ($r = 0.390$, $p < 0.001$). Pneumonia complication occurred more frequently in NMOSD patients with Expanded Disability Status Scale (EDSS) > 3 than in NMOSD patients with EDSS ≤ 3 (40.5% vs 4.3%, $p < 0.001$). Smoking history (odds ratio [OR] 44.34, 95% confidence interval [CI] 2.67-736.65), midbrain lesion (OR 76.70, 95% CI 2.46-2390.37), and high EDSS (OR 1.45, 95% CI 1.02-2.07) were independently risk factors of pneumonia complication in NMOSD. Pneumonia is not rare in NMOSD patients. Pneumonia is associated with the severity of NMOSD. Smoking history, midbrain lesion, and high EDSS are independently risk factors of pneumonia complication in NMOSD.

Keywords: Neuromyelitis optica spectrum disorders, pneumonia, risk factors

Introduction

Neuromyelitis optica (NMO) is an idiopathic demyelinating disease of the central nervous system distinct from multiple sclerosis (MS) [1-3]. Most patients with NMO have detectable serum antibodies that target the water channel aquaporin-4 (AQP4-immunoglobulin G [IgG]), which are highly specific for clinically diagnosed NMO, and have pathogenic potential [4]. The broadened array of disorders associated with AQP4-IgG has been termed 'NMO spectrum disorders' (NMOSD) [1]. The International Panel for NMO diagnosis was convened to develop revised diagnostic criteria for NMOSD in 2015 [5]. Several groups have recognized pneumonia complication is inevitable in many patients with a progressive clinical course of idiopathic demyelinating diseases and can be treated [6]. Researchers have previously concentrated on prediction of respiratory complications in MS patients. However, few studies have focused on the incidence and risk factors of pneumonia complication in NMOSD. In this study, we investigated the incidence and risk factors of pneumonia complication in NMOSD.

Methods

Patients

This study was approved by the local Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University. All patients included provided written informed for research studies.

Our database comprised 170 Chinese patients with NMOSD who were diagnosed and admitted from Dec 1, 2005 to Dec 31, 2015 in the MS

Table 1. Demographic and clinical characteristics

	Pneumonia group	Non-pneumonia group	P
Gender, F:M	16:4	109:23	0.779
Age, years	40.20 ± 15.94	38.00 ± 14.10	0.524
Smoking history	4 (20.0%)	5 (3.8%)	0.004*
Age at onset, years	35.26 ± 14.88	34.85 ± 13.67	0.903
Disease duration, years	3.00 (0.17, 22.00)	1.50 (0.08, 31.08)	0.194
Annualized relapse rate	1.00 (0, 4.80)	0.74 (0, 12.00)	0.076
EDSS at last visit	8.5 (0, 10.0)	2.0 (0, 9.0)	0.000**
Clinical features, n (%)			
Headache	5 (25.0%)	22 (16.7%)	0.364
Nystagmus	2 (10.0%)	8 (6.1%)	0.508
Bulbar paralysis	4 (20.0%)	8 (6.1%)	0.031*
Bowel or bladder dysfunction	13 (65.0%)	53 (40.2%)	0.037*
Visual impairment	17 (85.0%)	113 (85.6%)	0.943
Movement deficit	16 (80.0%)	72 (54.5%)	0.032*
Sensory deficit	15 (75.0%)	91 (68.9%)	0.582
Consciousness disturbance	2 (10.0%)	0	0.000**
Urinary tract infections	10 (50.0%)	18 (13.6%)	0.000**
Leukopenia or leukocytosis	6 (30.0%)	33 (25.0%)	0.633
Neutrophilic leukocytosis	14 (70.0%)	51 (38.6%)	0.008*
Anemia	12 (60.0%)	38 (28.8%)	0.006*
Hyperglycemia	5 (25.0%)	15 (11.4%)	0.093
Mechanical ventilation	6 (30.0%)	0	0.000**
Gastric tube	7 (35.0%)	0	0.000**
High-dose steroid	13 (65%)	95 (72.0%)	0.522
Immunosuppressant drugs	11 (55.0%)	75 (56.5%)	0.878
IVIG/PE	6 (30.0%)	22 (16.7%)	0.152
PPI	19 (95.0%)	102 (77.3%)	0.067
Hospital stays (days > 21)	12 (60.0%)	22 (16.7%)	0.000
AQP4-IgG	12 (60.0%)	94 (71.2%)	0.309
OCB CSF	1 (5.0%)	8 (6.1%)	0.851
Brain lesions, n (%)			
Brain lobes	8 (40.0%)	64 (48.5%)	0.479
Basal ganglia	5 (25.0%)	18 (13.6%)	0.186
Hypothalamic and thalamic	2 (10.0%)	12 (9.1%)	0.896
Ventricle and aqueduct	3 (15.0%)	27 (20.5%)	0.568
Midbrain	4 (20.0%)	4 (3.0%)	0.002*
Pons	8 (40.0%)	16 (12.1%)	0.001*
Medulla oblongata	13 (65.0%)	29 (22.0%)	0.000**
Cerebellum	3 (15.0%)	7 (5.3%)	0.103
Spinal cord lesions, n (%)			
LETM	16 (80.0%)	92 (69.7%)	0.344
Cervical cord	16 (80.0%)	84 (63.6%)	0.151
Thoracic cord	15 (75.0%)	72 (54.5%)	0.085

Abbreviations: AQP4-IgG = aquaporin-4 immunoglobulin G; CSF = cerebrospinal fluid; EDSS = Expanded Disability Status Scale; F:M = female:male; IVIG = intravenous immunoglobulin; LETM = longitudinally extensive transverse myelitis; OCB = oligoclonal bands; PE = plasma exchange; PPI = proton-pump inhibitor. *$p < 0.05$, **$p < 0.001$.

Center of the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China. NMOSD was diagnosed according to the 2015 international consensus diagnostic criteria [5]. Pneu-

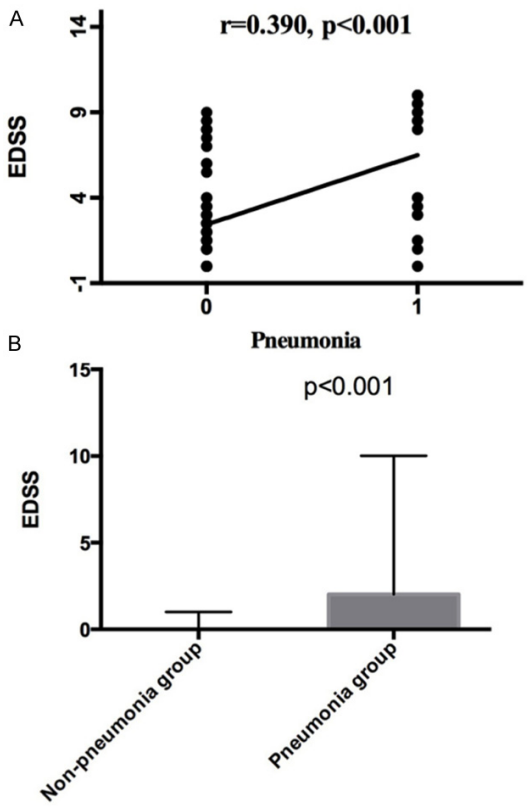

Figure 1. EDSS and pneumonia complication in NMOSD. A. Pneumonia was positively correlated with the severity of the NMOSD (r = 0.390, p < 0.001). B. The EDSS score was significantly higher in NMOSD patients with pneumonia than in NMOSD patients without pneumonia (p < 0.001). Abbreviations: EDSS = Expanded Disability Status Scale; NMOSD = neuromyelitis optica spectrum disorders.

monia was diagnosed by treating physician according to the criteria for community-acquired pneumonia [7], or hospital-acquired pneumonia [8], on a basis of clinical and laboratory indices of respiratory tract infection (fever, cough, auscultatory respiratory crackles, new purulent sputum, or positive sputum culture), and supported by typical chest X-ray findings [9].

For the present study, the following clinical data and magnetic resonance imaging (MRI) scans were collected from these individuals: (1) Demographics (age and sex); (2) Clinical characteristics and traditional risk factors for pneumonia: smoking history, age at onset, disease duration, annualized relapse rate, Expanded Disability Status Scale (EDSS) at last visit, clinical features (Headache, Nystagmus, Bulbar paralysis, Bowel or bladder dysfunction, Visual impairment, Movement deficit, Sensory deficit, Consciousness disturbance), urinary tract infections, leukopenia or leukocytosis, neutrophilic leukocytosis, anemia, hyperglycemia, mechanical ventilation, gastric tube, high-dose steroid, immunosuppressant drugs, intravenous immunoglobulin (IVIG) or plasma exchange (PE), proton-pump inhibitor (PPI), hospital stays (days > 21), AQP4-IgG, oligoclonal bands (OCB) cerebrospinal fluid (CSF); (3) Brain lesions in MRI: brain lobes, basal ganglia, hypothalamic and thalamic, ventricle and aqueduct, midbrain, pons, medulla oblongata, cerebellum; (4) Spinal cord lesions in MRI: longitudinally extensive transverse myelitis (LETM), cervical cord, thoracic cord.

Statistical analysis

Statistical analysis was performed by SPSS version 19.0. Values of $p = 0.05$ were considered statistically significant. Quantitative data were processed using the Mann-Whitney U-test or Student's t-test. All quantitative data in this study are presented as mean ± standard deviation or median ± range. Qualitative data were analyzed with the χ^2 test or Fisher's exact test. The correlation between pneumonia and EDSS was determined by using spearman correlation analysis. All tests in two groups with a *P* value < 0.05 were entered into Logistic regression analyses, which were used to determine independent risk factors for pneumonia complication in NMOSD. Meanwhile, the odds ratio (OR) and 95% confidence interval (CI) were obtained from the analysis.

Results

The data of 170 patients with NMOSD were reviewed between 2005 and 2015. A total of 152 patients satisfied the diagnostic criteria for inclusion in this study. The mean age was 38.29 ± 14.31, and 82.2% were female. The median EDSS score was 2 (0-10), and a total of 20 (13.2%) patients had pneumonia complication.

The demographic, clinical features and MRI features of the patients are summarized in **Table 1**. Smoking history, EDSS, bulbar paralysis, bowel or bladder dysfunction, movement deficit, consciousness disturbance, urinary tract infections, neutrophilic leukocytosis, anemia, mechanical ventilation, gastric tube, hospital stays (days > 21), midbrain lesion, pons lesion, medulla oblongata lesion were signifi-

Table 2. Logistic regression analysis on risk factors of pneumonia complication in NMOSD

	P	OR	95% CI
Smoking history	0.008*	44.34	2.67-736.65
EDSS at last visit	0.038*	1.45	1.02-2.07
Bulbar paralysis	0.593	0.26	0.00-35.43
Bowel or bladder dysfunction	0.519	1.87	0.28-12.64
Movement deficit	0.849	0.82	0.11-6.40
Consciousness disturbance	1	1.63	-
Urinary tract infections	0.264	3.65	0.38-35.33
Neutrophilic leukocytosis	0.481	2.12	0.26-17.22
Anemia	0.398	2.39	0.32-17.94
Mechanical ventilation	1	14.65	-
Gastric tube	1	7.39	-
Hospital stays (days > 21)	0.25	3.75	0.39-35.70
Midbrain	0.013*	76.70	2.46-2390.37
Pons	0.120	0.07	0.00-1.98
Medulla oblongata	0.089	7.42	0.74-74.62

Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale; NMOSD = neuromyelitis optica spectrum disorders. OR = odds ratio. *$p < 0.05$.

cantly predictive of pneumonia complication in NMOSD. Meanwhile, we found no significant differences between the two groups in sex, age, age at onset, disease duration, annualized relapse rate, clinical features (headache, nystagmus, visual impairment, sensory deficit), leukopenia or leukocytosis, hyperglycemia, high-dose steroid, immunosuppressant drugs, IVIG/PE, PPI, AQP4-IgG, OCB CSF, brain lesions in MRI (brain lobes, basal ganglia, hypothalamic and thalamic, ventricle and aqueduct, cerebellum), and spinal cord lesions in MRI (LETM, cervical cord, thoracic cord).

Next, we examined the correlation between pneumonia complication and severity of the NMOSD (**Figure 1**). Our data showed that pneumonia was positively correlated with the severity ($r = 0.390$, $p < 0.001$). Pneumonia complication occurred more frequently in NMOSD patients with EDSS > 3 than in NMOSD patients with EDSS ≤ 3 (40.5% vs 4.3%, $p < 0.001$).

Logistic regression analyses were performed to identify risk factors of pneumonia complication in NMOSD (**Table 2**), based on the parameters that differed significantly between two groups. Adjusted logistic regression analyses showed that smoking history (OR 44.34, 95% CI 2.67-736.65), midbrain lesion (OR 76.70, 95% CI 2.46-2390.37), and high EDSS (OR 1.45, 95% CI 1.02-2.07) were independently risk factors of pneumonia complication.

Discussion

To the best of our knowledge, this is the first research to analyze the incidence and risk factors of pneumonia complication in NMOSD. In the present study, 13.2% NMOSD patients have pneumonia complication. Pneumonia is associated with the severity of NMOSD. Smoking, midbrain lesion, and high EDSS are independently risk factors of pneumonia complication in NMOSD.

Pneumonia is not rare in NMOSD patients, while over 10% patients have pneumonia in our study. Pneumonia complication is common in the terminal stages of MS and contributes to mortality in these patients. Subsequently, in addition to bulbar dysfunction, respiratory muscle weakness may contribute to ineffective coughing, pneumonia, and sometimes even acute ventilatory failure may ensue [10]. However, there is only a small study focusing on pneumonia complication in NMOSD. Pittock et al described 4 patients with NMO who had predominantly mechanical respiratory failure, 2 of whom had aspiration pneumonia complication [6]. The frequency of pneumonia complication in NMOSD is consistent with other spinal cord diseases. Chen et al found that respiratory complications in upper cervical spinal injured occurred in 16 patients (17.4%), 12 had pneumonia (13.0%), 8 had respiratory failure (8.7%) [11]. Respiratory complications are a major cause of illness and death in persons with spinal cord injuries and dysfunction [12]. We should pay more attention on the pneumonia complication in NMOSD in the future.

Risk factors for pneumonia complication in patients with NMOSD have been not studied previously. We identified risk factors include smoking history, midbrain lesion, and high EDSS.

There are only a few NMOSD patients having smoking history, though it is not surprising that smoking history is the risk factor for pneumonia complication. There is a considerable amount of information concerning the association of

smoking with increased risk and mortality for pneumonia [13]. Tobacco inhibits some key innate immune response components, such as Toll-like receptor 2, nuclear factor-kB, dendritic cell maturation, and decreases opsonization and phagocytosis [14, 15]. Cigarette smoke is a strong inflammatory stimulus that induces cytokines, such as interleukin (IL)-5, IL-6, and IL-7, as well as tumor necrosis factor [16]. In vitro experimental models have shown impaired lung bacterial clearance and phagocytosis of S pneumonia [17]. In fact, the risk of bacterial (mainly pneumococcal) pneumonia is reduced to the level of nonsmokers after 1 year of smoking abstinence, and smoking cessation reduces the risk of hospitalization for pneumonia [18, 19]. Smoking is not a good inhibit for NMOSD.

Our previous study had focus on the brainstem lesions on NMO [20]. Brainstem lesions on MRI were reported in 23.0% to 78.3% of patients with NMO [20-22]. Lesions in the brainstem were relatively characteristic of NMO, showing involvement of the brainstem corresponds to sites of high AQP4 expression. The medulla oblongata is the most common lesion location in NMO, and lesions are usually located in the dorsal part with poorly defined shapes [20]. NMOSD patients with pneumonia had a significantly higher frequency of midbrain, pons, and medulla oblongata lesions than those without pneumonia did. It was interesting that only midbrain lesion was independently risk factors of pneumonia complication in NMOSD after multivariate analysis.

The EDSS score of patients with pneumonia was also higher than that of patients without pneumonia. Furthermore, EDSS score was independently risk factors of pneumonia complication in NMOSD. In the present study, over 40% NMOSD patients with high EDSS had suffered pneumonia. Pneumonia complication was common in the serious NMOSD patients. Respiratory complications should be paid more attention in the serious NMOSD patients. However, further study is necessary to determine whether prophylactic antibiotics in serious NMOSD patients.

Our study has some limitations. First, the imbalanced data (132:20) had an effect on multivariate analysis. Second, pneumonia was not divided in community-acquired pneumonia and nosocomial pneumonia in the present study. Third, this was a single-center research involving a modest sample size of Chinese NMOSD patients. We were not able to validate our findings by applying them to a subset of patients. Multicenter studies with large and diverse cohorts as well as ethnicities need to be done. Furthermore, as a retrospective study, bias is inevitable.

In conclusion, pneumonia is not rare in NMOSD patients. Pneumonia is associated with the severity of NMOSD. Smoking history, midbrain lesion, and high EDSS are independently risk factors of pneumonia complication in NMOSD.

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Disclosure of conflict of interest

None.

Address correspondence to: Zhengqi Lu, Department of Neurology, The Third Affiliated Hospital of Sun Yat-sen University, No 600 Tianhe Road, Guangzhou 510630, Guangdong, China. Tel: +86-2085252238; Fax: +86-2087567133; E-mail: lzqzssy@gmail.com

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