ORIGINAL RESEARCH

Risk factors for nosocomial nontraumatic coma: sepsis and respiratory failure

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Background: Coma's are a major cause of clinical deterioration or death. Identification of risks that predispose to coma are important in managing patients; however, the risk factors for nosocomial nontraumatic coma (NNC) are not well known. Our aim was to investigate the risk factors in patients with NNC.

Methods: A retrospective case–control design was used to compare patients with NNC and a control group of patients without coma in a population-based cohort of 263 participants from the neurological intensive care unit in Shuyang County People's Hospital of Northern China. Coma was diagnosed by a Glasgow Coma Scale score ≤8. Adjusted odds ratios for patients with NNC were derived from multivariate logistic regression analyses.

Results: A total of 96 subjects had NNC. The prevalence of NNC was 36.5% among the subjects. Among these, 82% had acute cerebrovascular etiology. Most of the NNC usually occurred at day 3 after admission to the neurological intensive care unit. Patients with NNC had higher hospital mortality rates (67.7% vs 3%, $P<0.0001$) and were more likely to have a central herniation (47.9% vs 0%, $P<0.001$) or uncal herniation (11.5% vs 0%, $P<0.001$) than those without NNC. Multiple logistic regression showed that systemic inflammatory response syndrome-positive sepsis (odds ratio =4, 95% confidence interval =1.875–8.567, $P<0.001$) and acute respiratory failure (odds ratio =3.275, 95% confidence interval =1.014–10.573, $P<0.05$) were the factors independently associated with a higher risk of NNC.

Conclusion: Systemic inflammatory response syndrome-positive sepsis and acute respiratory failure are independently associated with an increased risk of NNC. This information may be important for patients with NNC.

Keywords: nosocomial nontraumatic coma, infection, sepsis, acute respiratory failure, GCS

Introduction

Nontraumatic coma is a common, life-threatening emergency disorder encountered by primary care physicians. Coma may result from direct cerebral injury; however, many cases develop as a complication of a systemic insult.[1] The prognosis for coma depends on the cause or the complication.[1–3] Nevertheless, patients with nontraumatic coma caused by nosocomial complications can easily be neglected. Previous studies have demonstrated that infection/inflammation may predispose to subsequent deterioration.[3–5] Therefore, identification of risk factors that predispose to nosocomial coma is important for managing this critical illness and improving its outcome. However, no studies have described the acute precipitants of nosocomial nontraumatic coma (NNC). The aim of this study was to investigate the risk factors in patients with NNC.

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Methods

Study design

From May 2007 to June 2010, a retrospective case–control study was performed in the neurological intensive care unit (NICU) in Shuyang County People's Hospital of Northern China. All consecutive patients with NNC matched with age and sex with a control group without coma were recruited into the study. This study was approved by the Medical Ethics Committee of the Shuyang County People's Hospital, People's Republic of China. The study was in full compliance with the Declaration of Helsinki and solely required deidentification of all personal information related to the already collected clinical data without requirement of informed consent.

Identification of study patients

A total of 263 patients with neurocritical illness were included in the study. Of these, 96 patients with nontraumatic coma caused by nosocomial complications were identified during the study period. The diagnostic criteria for patients with an NNC event were: 1) NNC referring to a coma that occurred inside the hospital (nosocomial-acquired coma) rather than before the hospital admission and 2) the threshold of coma with a Glasgow Coma Scale (GCS) score ≤8 and following a duration for >2 hours, usually prolonging for several days, or persistently longer. Exclusion criteria were: 1) patients with coma occurring in prehospitalization (community-acquired coma); 2) patients with a coma of traumatic cause; and 3) patients with the effects of sedatives and opioids.

Data collection

The cardinal indicators of the patients with NNC were recorded either from the admission notes or from the medical notes. We examined the duration before coma occurrence, before recording the values of GCS score, temperature, blood pressure, heart rate, respiratory rate, white cell count, hematocrit, levels of serum potassium, serum sodium, serum creatinine, blood glucose, and arterial blood gas values. We also performed neurological examination (including level of consciousness, pupillary responses, eye movements, respiratory patterns, and motor responses), bacteriology analysis, electrocardiogram, chest X-ray, and head computed tomography or magnetic resonance imaging. Other findings for coma were evaluated, including organ function, intracerebral hemorrhage growth, infarction growth, recurrent subarachnoid hemorrhage, hematoma volume, infarction volume, and distribution and source of infection, which was confirmed either by positive blood culture or by clinically

ruling out the noninfectious causes. In addition, mechanical ventilation, length of NICU stay, hospital stay, and outcome at 30 days after admission were also recorded.

Medical treatment

All patients were managed according to a standard protocol in the NICU, which included intensive resuscitation, fluid and electrolyte monitoring, 3 L/min of oxygen by nasal cannula, establishing a good airway, insertion of a large-bore intravenous catheter, and nutritional support (nasojejunal feeding or total parenteral nutrition and supportive care). All patients with brain herniation and increased intracranial pressure were treated with mannitol. All patients with infection were treated by giving pertinent antibiotics. Fluid replacement and vasopressors were given if there were any hypotensive episodes. Some patients with severe respiratory failure were administered mechanical ventilation. Rapid lowering of blood pressure was avoided unless the patients had critically high blood pressure.

Definitions of the risk of NNC

The risks of NNC were considered, including age, sex, primary diseases, acute complications, and preexisting conditions. Primary diseases, acute complications, and preexisting conditions of patients were identified by the International Classification of Diseases, 10th Revision, codes.

Systemic inflammatory response syndrome (SIRS) was diagnosed by more than one of the following criteria: 1) temperature >38°C or <36°C, 2) heart rate >90 beats/minute, 3) tachypnea (>20 respirations/minute or PCO_2 <32 mmHg), 4) white blood cell count >12.0×10^9 or <4.0×10^9/L, or 5) >10% band forms.[6]

Sepsis was defined as a life-threatening organ dysfunction due to dysregulated host response to infection,[7] which was published by the recent Third International Consensus Definitions Task Force. In this study, we followed Kaukonen et al,[8] the diagnostic criteria for sepsis classification: sepsis was classified as SIRS-positive sepsis (having infection associated with organ dysfunction and met 2–4 SIRS criteria) and SIRS-negative sepsis (having infection associated with organ dysfunction and only met 0–1 SIRS criteria).

Organ failure was defined as a Sequential Organ Failure Assessment (SOFA) score ≥2 for that organ. The following were considered to be organ dysfunctions: brain – GCS score <13; respiratory – bilateral infiltrates on chest thorax radiograph and arterial oxygen pressure/fraction of inspired oxygen ratio (PaO_2/FiO_2) ≤300 or the need for supplemental oxygen to maintain oxygen saturation >90% (excluding

the prior need for oxygen); circulation – hypotension (systolic blood pressure <90 mmHg or mean arterial pressure <65 mmHg or decrease >40 mmHg in the systolic pressure); liver – total serum bilirubin >2 mg/dL; renal – creatinine >171 mmol/L; and blood – platelet count ≤100×10^9/L.

Statistical analysis

Values are given as mean ± standard deviation or median (interquartile range) for continuous variables and as a number and percentage for categorical variables. Difference testing between groups was performed using the two-tailed t-test, X^2-test, and Fisher's exact test as appropriate. All variables with a P-value of <0.05 in univariate analysis were entered into multivariate forward stepwise logistic regression analysis. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were derived from forward stepwise logistic regression analysis, and statistical significance was set at $P<0.05$ after adjustment for risk factors for NNC. All statistical analyses were performed with SPSS version 17.0 software (SPSS Inc., Chicago, IL, USA).

Results

During the study period, 96 subjects had NNC, with a crude prevalence of NNC of 36.5%. The median period from admission to occurrence of NNC was 3 days (shortest, 2 hours; longest, 41 days). The clinical characteristics of patients with and without NNC are summarized in Table 1.

Among 96 patients with NNC, 82% had a diagnosis of primary cerebrovascular etiology, including intracerebral hemorrhage, infarction, and subarachnoid hemorrhage. Ten patients (9.6%) had a primary systemic disease (six had septic shock and four had other diseases). There was no differences in age, sex, acute stroke, and other primary diseases between the two groups ($P>0.05$). There were no significant differences in hypertension, diabetes, and atrial fibrillation between the two groups. Patients who presented with low initial GCS score (10.0±0.9 vs 13.9±8.2, $P<0.001$), midline shift (46.9% vs 16.2%, $P<0.001$), compressed basal cisterns (69.8% vs 13.8%, $P<0.001$), central herniation (47.9% vs 0%, $P<0.001$), or uncal herniation (11.5% vs 0%, $P<0.001$) were more likely to achieve an NNC than those who did not, and more patients with NNC had mechanical ventilation (28.1% vs 0.6%, $P<0.001$) than those without NNC. NICU length of stay was longer ($P<0.0001$) in patients with NNC than in patients without NNC. The mortality rate was significantly higher (67.7% vs 3%, $P<0.0001$) in patients with NNC than in patients without NNC. Few patients with NNC were more

Table 1 Characteristics of the patients with and without NNC

	With NNC (n=96)	Without NNC (n=167)	P-value
Age (years), mean ± SD	58.0±13.6	60.0±14.8	0.291
Female	36 (37.5)	66 (39.5)	0.702
Hypertension	58 (60.4)	91 (54.5)	0.351
Diabetics	11 (11.5)	15 (8.9)	0.517
Atrial fibrillation	2 (2.1)	11 (6.6)	0.105
Hyperlipidemia	61 (63.5)	89 (53.3)	0.106
Intracerebral hemorrhage	44 (43.8)	85 (50.9)	0.429
Cerebral infarction	27 (28.1)	42 (25.1)	0.597
Subarachnoid hemorrhage	11 (11.5)	13 (7.8)	0.319
Encephalitis/meningoencephalitis	4 (4.2)	13 (7.8)	0.251
Septic shock	6 (6.3)	3 (1.8)	0.077
Others	4 (4.2)	11 (6.6)	0.583
Midline shift	45 (46.9)	27 (16.2)	0.000
Basal cisterns compressed	52 (69.8)	23 (13.8)	0.000
Central herniation	46 (47.9)	0 (0)	0.000
Uncal herniation	11 (11.5)	0 (0)	0.000
Mechanical ventilation	27 (28.1)	1 (0.6)	0.000
Mortality in 30 days	65 (67.7)	5 (3)	0.000
Vegetative state	3 (3.1)	0 (0)	0.022
Minimally conscious state	2 (2.1)	0 (0)	0.061

Notes: Data presented as n (%) unless otherwise stated. P-values obtained using a two-tailed t-test.
Abbreviations: NNC, nosocomial nontraumatic coma; SD, standard deviation.

likely to experience a vegetative state (3.1% vs 0%, $P<0.05$) than those without NNC.

Univariate and multivariate analyses

The results of univariate analyses in patients with NNC and control patients are summarized in Table 2. There was no differences in age, sex, hypertension, SIRS-negative sepsis, hypoglycemia, severe hyponatremia, acute seizures, acute hepatic failure, atrial fibrillation, the mean volume of intracerebral hemorrhage, and the mean volume of cerebral infarction at onset of NNC between patients in the NNC group and the control group ($P>0.05$). The presence of NNC was significantly associated with frequent SIRS-positive sepsis (70% vs 13.2%, $P<0.0001$), acute respiratory failure (30.2% vs 2.4%, $P<0.001$), acute renal failure (26% vs 4.8%, $P<0.001$), hyperglycemia (16.7% vs 3%, $P<0.001$), hypernatremia (8.3% vs 0.6%, $P<0.001$), intracerebral hemorrhage growth (7.3% vs 1.2%, $P<0.01$), old focal lesions in brain (17.7% vs 8.9%, $P<0.05$), midline shift (46.9% vs 16.2%, $P<0.001$), and basal cisterns compressed (69.8% vs 13.8%, $P<0.001$).

In patients with NNC, primary infection was present in 19.4% (13/67) of patients and secondary infection was pres-

Table 2 The univariate analyses at coma onset in patients with NNC and control subjects

	NNC (N=96)	Control subjects (N=167)	P-value
SIRS-positive sepsis	67 (70.0)	22 (13.2)	0.000[a]
SIRS-negative sepsis	2 (2.1)	0 (0)	0.061
Acute respiratory failure	29 (30.2)	4 (2.4)	0.000[a]
Acute renal failure	25 (26.0)	8 (4.8)	0.000[a]
Hyperglycemia (>7.8 mmol/L)	16 (16.7)	5 (3.0)	0.000[a]
Hypoglycemia (<2.1 mmol/L)	2 (2.1)	0 (0)	0.061
Severe hyponatremia (<110 mmol/L)	2 (2.1)	1 (0.6)	0.275
Hypernatremia (>150 mmol/L)	8 (8.3)	1 (0.6)	0.001[a]
Acute seizures	8 (8.3)	8 (4.8)	0.247
Acute hepatic failure	1 (1.0)	0 (0)	0.186
Intracerebral hemorrhage growth	7 (7.3)	2 (1.2)	0.009[a]
Recurrent subarachnoid hemorrhage	3 (3.1)	1 (0.6)	0.107
Old focal lesion in brain	17 (17.7)	15 (8.9)	0.037[b]
Brain midline shift	45 (46.9)	27 (16.2)	0.000[a]
Basal cisterns compressed	52 (69.8)	23 (13.8)	0.000[a]

Notes: [a]$P<0.01$. [b]$P<0.05$. Data presented as n (%). P-values obtained using a two-tailed t-test.
Abbreviations: NNC, nosocomial nontraumatic coma; SD, standard deviation; SIRS, systemic inflammatory response syndrome.

ent in 80.6% (54/67). Hospital-acquired infection was present in 53.7% (36/67) of patients and community-acquired infection was present in 46.3% (31/67). Among those patients who had NNC with SIRS-positive sepsis, the mortality rate was 59.7% (40/67), and blood stream and respiratory infections were more common (Table 3).

Consequently, a total of eight variables from univariate analyses were considered for logistic regression analyses. Table 4 summarizes the results of multiple logistic regression with values of $P<0.05$. Two independent factors concerning coma onset were found. These early predictors included

Table 4 Multivariate odds ratios for nosocomial nontraumatic coma

	OR	P-value	95% CI for OR
SIRS-positive sepsis	4.008	0.000	1.875–8.567
Acute respiratory failure	3.275	0.047	1.014–10.573

Abbreviations: CI, confidence interval; OR, odds ratio; SIRS, systemic inflammatory response syndrome.

SIRS-positive sepsis (OR =4.008, 95% CI =1.875–8.567, $P<0.001$) and acute respiratory failure (OR =3.275, 95% CI =1.014–10.573, $P<0.05$).

Discussion

The present study indicated a high prevalence of severe infectious, which lead to almost fourfold of SIRS-positive sepsis in patients with NNC than those without NNC. This study suggests that SIRS-positive sepsis was associated with development of NNC.

In the present study, SIRS-positive sepsis was considered as an independent risk factor for NNC. Bone[9] indicated that a massive systemic inflammatory reaction might destroy the integrity of the capillary walls. Inflammatory responses play a crucial role in impairment of the microcirculation of the brain and development of cerebral edema.[10,11] This has been confirmed that both patient and rodent models of sepsis have the evidence of blood–brain barrier dysfunction.[12] In cases of sepsis, the mechanisms are more likely to be multifactorial, such as multiple organ dysfunction.[7,9,13] Moreover, the pathogenesis of brain dysfunction involves several mediators, including tumor necrosis factor alpha, interleukins, platelet-activating factor, leukotrienes, thromboxane A2, and activators of the complement cascade.[14,15] Therefore, these mediators due to infection can aggravate cerebral injury or cerebral edema and may lead to brain dysfunction or herniation, which is called a sepsis-associated encephalopathy.

Table 3 The distribution and source of infection in patients with SIRS-positive sepsis

SIRS-positive sepsis	ICH	CI	SAH	Other	N-AI	C-AI	Death
Primary infection (n=13)							8 (67.5%)
Systemic blood stream (n=6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (100.0%)	5 (83.3%)
Pneumonia (n=3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (100.0%)	2 (66.7%)
Encephalitis (n=4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (100.0%)	1 (25.0%)
Secondary infection (n=54)							32 (50.9%)
Systemic blood stream (n=15)	8 (53.3%)	6 (40.0%)	0 (0)	1 (6.7%)	10 (66.7%)	5 (33.3%)	12 (80.0%)
Pneumonia (n=23)	15 (65.2%)	5 (21.7%)	2 (8.7%)	1 (4.3%)	15 (65.2%)	8 (34.8%)	14 (60.9%)
Tracheobronchial (n=6)	3 (50.0%)	3 (50.0%)	0 (0)	0 (0)	4 (66.7%)	2 (33.3%)	4 (66.7%)
Others (n=10)	4 (40.0%)	4 (40.0%)	1 (10.0%)	1 (10.0%)	7 (70.0%)	3 (30.0%)	2 (20.0%)
All (N=67)	30 (44.8%)	18 (26.9%)	3 (4.5%)	3 (4.5%)	36 (53.7%)	31 (46.2%)	40 (59.7%)

Abbreviations: C-AI, community-acquired infection; CI, cerebral infarction; ICH, intracerebral hemorrhage; N-AI, nosocomial-acquired infection; SAH, subarachnoid hemorrhage; SIRS, systemic inflammatory response syndrome.

The present study showed that SIRS-positive sepsis from pneumonia accounted for 38.8% of the patients who had an NNC, and a high incidence of nosocomial-acquired pneumonia has been confirmed by previous studies.[16,17] In fact, in our study, those SIRS-positive sepsis from the hospital-acquired blood stream infection that was confirmed either by positive culture or by clinically ruling out the noninfectious causes and other infections such as tracheobronchial infections were also observed. A previous study has found that sepsis-associated encephalopathy accounts for 70% of septic patients.[18] Because currently the majority of SIRS-positive sepsis have been associated with NNC, we believe that those stroke patients who experienced secondary blood stream infection, pneumonia, or other severe infections had an sepsis-associated encephalopathy.[10]

In addition, our data showed that an incidence of respiratory failure was 30.2% of patients with NNC. Furthermore, several authors have reported that infection and inflammation responses may be associated with an increased risk of acute respiratory failure.[5,7,19] The frequent prevalence of systemic infection, as well as pulmonary and tracheobronchial infection, was also confirmed in our patients with NNC. Indeed, a previous study showed that NICU-acquired respiratory failure was more frequent in patients with NNC than in other patients and was one of the factors independently associated with a higher risk of death.[3] Our data confirm this finding and also suggest that the acute respiratory failure is independently associated with an increased risk of NNC.

The mechanisms of brain displacement and brain herniation in precipitating coma are the most important. This is confirmed by our current study. The brain herniation was caused by many reasons, including hemispheral mass effect,[20] increased intracranial pressure,[21] reduction in cerebral blood flow,[22] and interruption of synaptic or neurochemical functions in the ascending reticular activating system.[23] However, this study's findings suggest the SIRS-positive sepsis and acute respiratory failure are also associated with an increased risk of brain herniation. This may aid clinical diagnosis and treatment of NNC.

There are some limitations to this study. First, the sample size was relatively small, which may have added to the limitations of the analysis. Second, this study involved a various primary diseases that may have affected the incidence of complication, and emergence interventions required for these different diseases could also influence physiologic parameters. Furthermore, a recent study has confirmed that the SIRS-positive sepsis and SIRS-negative sepsis are two different sepsis modes.[8] However, the pathophysiology

change caused by the infection and inflammation responses is basically the same principle.[23] Not to mention the sepsis is also defined as a dysregulated host response to infection, causing a life-threatening organ dysfunction,[7] rather than other factors. Finally, although the fluid overload therapy may be a cause of high mortality for sepsis,[24] unfortunately, we did not obtain these data. However, infection is high in our NNC patients with sepsis, and thus we believe that the 59.7% of mortality in our NNC patients with sepsis is more likely to be due to infections without control in time causing the life-threatening organ dysfunction, because the guide for sepsis has indicated that the patient survival rate will reach 80%. If a correct diagnosis and antibiotic treatment may be done within 1 hour of infection, although antibiotic therapy can be given only during 1–6 hours after infection recognition, then the mortality rate of patients may be increased to 70%.[25] Therefore, we believe that the information of this study is valid.

Conclusion

This study identified two complications, including SIRS-positive sepsis and acute respiratory failure, which are associated with an increased risk of NNC. NNC is a common medical emergency event inside hospital, and most of the NNC usually occurred at day 3 after NICU admission. NICU/hospital mortality rates were higher among patients with NNC than among patients without NNC. Therefore, this information may be important for patients with NNC.

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Disclosure

The authors report no conflicts of interest in this work.

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