Clinical Features of Nephrotic Syndrome with Cerebral Hemorrhage

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Background: Cerebral hemorrhage has been increasingly reported in patients with nephrotic syndrome (NS). However, the clinical features and pathogenesis of NS patients with cerebral hemorrhage remain unclear.

Material/Methods: From January 2007 to August 2017, continuous NS patients with cerebral hemorrhage at the First Affiliated Hospital of Guangxi Medical University were selected. The clinical manifestations, laboratory measurements, and neurological images of these patients were collected and analyzed.

Results: Acute cerebral hemorrhage was recorded in 15 of 10 461 NS patients. The average age of these 15 patients (9 males and 6 females) was 50.87±23.27 years old. Among these 15 patients, conventional vascular risk factors were identified in 8 patients, hypoalbuminemia and proteinuria were recorded in all 15 patients, coagulopathy was observed in 9 patients, increased D-dimer level was recorded in 13 patients, hyperlipidemia was recorded in 11 patients, and impaired renal function was recorded in 9 patients. The hemorrhage developed in the lobe (*n*=9), basal ganglia (*n*=3), cerebellum (*n*=2), and cerebral hemisphere (*n*=1). Eight patients were in a coma on the day the cerebral hemorrhage occurred, while 12 patients had a poor prognosis after 30 days of hemorrhage onset.

Conclusions: Poor prognosis was recorded in NS patients with cerebral hemorrhage. Although conventional vascular risk factors have only been identified in 8 patients, biochemical abnormalities (hypoalbuminemia, proteinuria, elevated D-dimer, and hyperlipidemia) were recorded in the majority of these 15 patients. Furthermore, most of the hemorrhages developed in the lobes. Coagulopathy might be the potential pathogenesis of cerebral hemorrhage in NS patients.

MeSH Keywords: Cerebral Hemorrhage • Disseminated Intravascular Coagulation • Nephrotic Syndrome • Pathology

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Background

Nephrotic syndrome (NS) is a common glomerular disease characterized by massive proteinuria, hypoalbuminemia, hyperlipidemia, and edema [1]. There is an increased risk of cardiovascular disease in NS patients due to hyperlipidemia, hypertension, and other multifactorial disorders [2]. In recent years, cerebral hemorrhage has been increasingly reported in NS patients [3–6]. It is noteworthy that in some cases, although no conventional vascular risk factor has been recorded, cerebral hemorrhage occurred months after the diagnosis of NS [3,4]. This indicates that NS itself can directly or indirectly affect the onset of cerebral hemorrhage (i.e., NS with cerebral hemorrhage). However, to the best of our knowledge, the availability of information on the clinical features of NS patients with cerebral hemorrhage is very limited in the literature. Furthermore, the underlying pathogenesis of NS with cerebral hemorrhage remains largely unknown. Thus, the clinical manifestations, laboratory measurements, and neurological images were collected and analyzed in the present study to illustrate the characteristics of NS patients with cerebral hemorrhage.

Material and Methods

Diagnostic criteria

From January 2007 to August 2017, consecutive NS patients with acute cerebral hemorrhage at the First Affiliated Hospital of Guangxi Medical University were recruited. The diagnostic criteria of NS were adapted from the 2014 Japanese Clinical Practice Guidelines for NS [7]. The diagnosis of cerebral hemorrhage was made based on the guidelines (2015) for the diagnosis and treatment of spontaneous intracerebral hemorrhage released by the American Heart Association [8]. The diagnostic criteria for hyperlipidemia in adults were obtained from the Adult Treatment Panel III of the National Cholesterol Education Program (NCEP) [9]. The diagnostic criteria for hyperlipidemia in children were obtained from the Expert Panel on blood cholesterol levels in children and adolescents of the 1992 NCEP [10]. According to the chronic kidney disease guidelines of the Kidney Disease Improving Global Outcomes (KDIGO) [11], the glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation: GFR (mL/min/1.73 m^2)=186×(serum creatinine)$^{1.154}$×(Age)$^{0.203}$×(0.742 if female)×(1.210 if Chinese) [12]. Renal function impairment was defined as a GFR of <90 mL/min/1.73 m^2 [11]. As previously reported [13], coagulopathy was diagnosed when any of the following situations occurred: platelet <100×10^9/L, prothrombin time (PT) >15 seconds, activated partial thromboplastin time (APTT) >45 seconds, international normalized ratio (INR) >1.5, disseminated intravascular coagulation (DIC), D-dimer >290 ng/dL, or fibrinogen <200 mg/dL.

Inclusion criteria

NS patients with cerebral hemorrhage were identified by a panel of nephrologists, neuroimaging experts, and neurologists. Briefly, patients in any of the following situations were included into the study: (1) patients who were admitted to the First Affiliated Hospital of Guangxi Medical University due to acute cerebral hemorrhage and had a history of NS, or patients initially diagnosed with NS after the development of hemorrhage; (2) patients who were admitted to the hospital due to NS and presentation of headache or local neurological deficiency (e.g., sudden limb weakness, unclear speech, and numbness), and the cerebral hemorrhage was confirmed by brain computed tomography (CT) or magnetic resonance imaging (MRI) scan; and (3) patients who underwent total brain digital subtraction angiography (DSA) or magnetic resonance venography (MRV), and intracranial venous sinus thrombosis (IVST) was not identified in the patient. The present study was approved by the Medical Ethics Committee at the First Affiliated Hospital of Guangxi Medical University (No. 2018 [KY-E-008]).

Exclusion criteria

Patients in any of the situations below were excluded from the study: (1) patients who had serious systemic diseases, such as hematologic disease or cancer; (2) patients with central nervous system complications such as intracranial venous system thrombosis, cerebral infarction, or traumatic brain injury; (3) cases with intracranial aneurysm or intracranial vascular malformation confirmed by brain DAS, magnetic resonance angiography (MRA), and computed tomography angiography (CTA) examinations; and (4) patients with incomplete medical records.

Collection of clinical data

General demographic characteristics such as gender and age were recorded. Conventional vascular risk factors such as hypertension, diabetes, coronary artery disease, hyperlipidemia, atrial fibrillation and smoking were collected. Pathological types and treatment methods of NS and the time interval between the onset of cerebral hemorrhage and the diagnosis of NS were documented. The main symptoms, signs, consciousness levels, hemorrhagic locations, and treatment methods of the cerebral hemorrhage were also collected.

The hematoma volume was calculated by the previously validated ABC/2 or ABC/3 methods for round and ellipsoid or irregularly and separately shaped hemorrhages, respectively [14,15]. The severity of neurological injury was evaluated based on the National Institutes of Health Stroke Scale (NIHSS). The level of consciousness was evaluated according to the Glasgow Coma Scale (GCS). The functional outcome of patients on the 30th day after cerebral hemorrhage onset was evaluated based on the

Table 1. General characteristics of patients*.

Characteristic	(n [%], or $\overline{\chi}$±S)	
Gender		
Male	9	(60.0)
Age (year)	50.9±23.3	
Coagulopathy	9	(60.0)
PLT <100×10⁹/L	1	(6.7)
INR >1.5	1	(6.7)
PT >15s	8	(53.3)
APTT >45 seconds	1	(6.7)
DIC	1	(6.7)
High D-dimer (>450 ng/ml)	13	(86.7)
Hyperlipidemia	11	(73.3)
High LDL-C	8	(53.3)
High TC	6	(40.0)
Low GFR (< 90 mL/min/1.73 m²)	9	(60.0)
24-h urine collection (mg/d)		
Proteinuria	15	(100.0)
≥3.5 g/d	10	(66.7)
>5.0 g/d	6	(40.0)
Hypoalbuminemia (≤30 g/L)	15	(100.0)

* Fifteen patients in total. PLT – platelets; INR – international normalized ratio; PT – prothrombin time; APTT – activated partial thromboplastin time; DIC – disseminated intravascular coagulation; LDL-C – low-density lipoprotein cholesterol; TC – total cholesterol; GFR – glomerular filtration rate.

modified Rankin Scale (mRS). A mRS score of ≥3 indicates poor outcome, while a mRS score of 6 indicates death. The laboratory analysis included the following: routine urine tests, routine blood and blood biochemistry examinations, proteinuria determination (using 24-hour urine), plasma D-dimer, coagulation indexes, electrocardiography (ECG), brain CT, CTA, brain MRI, MRA, MRV, and total brain DSA.

Results

NS with cerebral hemorrhage was identified in 15 of 10 461 (0.14%) patients. The average age of these 15 patients (9 males and 6 females) was 50.9±23.3 years old (range: 5–86 years old; Table 1). The etiology and pathology types of NS were unclear in most patients, and the course of NS ranged from months to years. Twenty percent (n=3) of these patients had a history of hemodialysis. In 7 (46.7%) patients, NS was diagnosed for

Table 2. Characteristics about cerebral hemorrhage*.

Characteristic	(n [%], or $\overline{\chi}$±S)	
With traditional vascular risk factors	8	(53.3)
Hypertension	6	(40.0)
Diabetes	2	(13.3)
Smoking	3	(20.0)
NS was first diagnosed after the onset of hemorrhage	7	(46.7)
History of hemodialysis	3	(20.0)
Location of the hemorrhage		
Lobe	9	(60.0)
Basal ganglia	3	(20.0)
Cerebellum	2	(13.3)
Cerebral hemisphere	1	(6.7)
Cerebral ventricular	6	(40.0)
Baseline hematoma volume (mL)	40.7±38.6	
Blend sign	1	(6.7)
Black hole sign	2	(13.3)
GCS score at the day of hemorrhage onset		
GCS 15	4	(26.7)
GCS 9 to 14	3	(20.0)
GCS 3 to 8	8	(53.3)
NIHSS score at the day of hemorrhage onset		
NIHSS 0	3	(20.0)
NIHSS 1 to 4	1	(6.7)
NIHSS 5 to 15	4	(26.7)
NIHSS 21 to 30	7	(46.7)
Surgery	3	(20.0)
mRS score at the 30th day after hemorrhage onset		
mRS 0 to 2	3	(20.0)
mRS 3 to 5	5	(33.3)
mRS 6	7	(46.7)

* Fifteen patients in total. NS – nephrotic syndrome; GCS – Glasgow coma scale; NIHSS – national institutes of health stroke scale; mRS – modified Rankin Scale.

the first time after the onset of cerebral hemorrhage (Table 2). According to the laboratory tests, coagulopathy was recorded in 9 (60.0%) patients (one patient developed disseminated
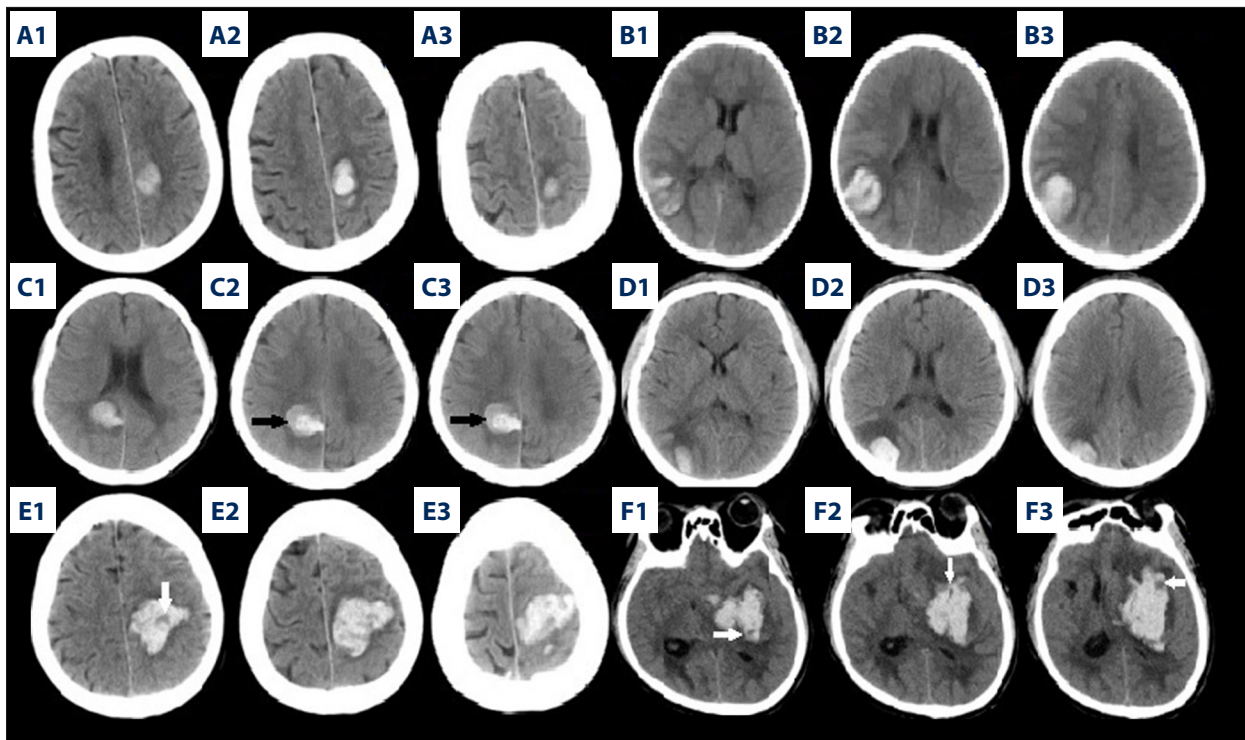
Figure 1. CT images of the cerebral hemorrhage. Images **A1–A3** were obtained from a 56-year-old male who had no traditional vascular risk factors, but developed cerebral hemorrhage (a lesion in the left parietal lobe) at 2 years after the diagnosis of NS. Images **B1–B3** were obtained from an 11-year-old boy who had no traditional vascular risk factors but developed cerebral hemorrhage (a lesion in the right parietal and occipital lobe) at 6 years after the diagnosis of NS. Images **C1–C3** were obtained from a 65-year-old female with a history of hypertension who developed cerebral hemorrhage (a lesion in the right parietal lobe) at 7 years after the diagnosis of NS. Images **D1–D3** were obtained from a 28-year-old male with a history of hypertension who was diagnosed with NS for the first time after the development of cerebral hemorrhage (a lesion in the right occipital lobe). Images **E1–E3** were obtained from a 56-year-old male with a history of hypertension who was diagnosed with NS for the first time after the development of cerebral hemorrhage (a lesion in the left parietal lobe). Images **F1–F3** were obtained from a 40-year-old male who was admitted to our hospital 4 hours after coma onset, and the CT revealed cerebral hemorrhage in the left basal ganglia. This patient died at 16 hours after admission. The black arrows indicate the blend sign and the white arrows indicate the black hole sign.

intravascular coagulation [DIC]), high plasma D-dimer level was detected in 13 (86.7%) patients, hyperlipidemia was identified in 11 (73.3%) patients, renal function impairment was recorded in 9 (60.0%) patients, hypoalbuminemia and proteinuria were observed in all 15 patients, and severe proteinuria (>5 g/day) was recorded in 6 (40.0%) patients (Table 1). As shown in Figure 1, during the acute onset of cerebral hemorrhage, hemorrhage developed in the lobe ($n=9$), basal ganglia ($n=3$), cerebellum ($n=2$), and cerebral hemisphere ($n=1$). One patient had poor outcome with a blend sign on CT. Two patients had a black hole sign on CT, among which, one patient died while the other patient had poor outcome. Furthermore, cerebral ventricular hemorrhage developed in 6 out of 15 (40.0%) patients. The baseline hematoma volume of these 15 patients was 40.7±38.6 mL (range: 5.1–150 mL; Table 2).

As shown in Table 2, 8 out of 15 (53.3%) patients had conventional vascular risk factors (hypertension, $n=6$; diabetes, $n=2$;

smoking, $n=3$). Focal neurological deficiency or headache was observed in all 15 patients. Furthermore, 8 (53.3%) patients were in a coma (the GCS score ranged within 3–8) on the day of cerebral hemorrhage onset. Among these patients, 4 (26.7%) patients had a NIHSS score within 0-4, while the remaining 11 (73.3%) patients had a NIHSS score within 5–30. On the 30th day after hemorrhage onset, 3 (20.0%) patients had a mRS score of 0–2, 5 (33.3%) patients had a mRS score of 3–5, and the remaining 7 (46.7%) patients died with a mRS score of 6.

Discussion

Clinical features of NS with cerebral hemorrhage

In the literature there is very limited information on the epidemiological profile of NS with cerebral hemorrhage. In the present study, in a population of 10 461 NS patients,

only 15 (0.14%) patients were identified as NS with cerebral hemorrhage, reflecting a low incidence rate. It has previously been reported that cerebral hemorrhage can occur in NS patients without conventional stroke risk factors [3,4]. Similarly, in the present study, 7 NS patients who had no conventional vascular risk factor records developed cerebral hemorrhage. Therefore, it would be reasonable to hypothesize that cerebral hemorrhage is associated with NS itself. It appears that some types of NS can be secondary to systemic amyloidosis [16–18]. Cerebral amyloidosis is a common cause of cerebral hemorrhage. Cerebral hemorrhage lesions are mainly located in the lobes and subcortical regions [19]. In previous studies, hemorrhage lesions were located at the occipital lobe in many cerebral hemorrhage patients who had NS [3,4,6,20]. Some researchers have speculated that the occipital lobe hemorrhage may have resulted from small blood vessel damage caused by the deposition of immune substances [20]. In the present study, lobe hemorrhage was observed in 9 patients, in which 5 had hemorrhages in the occipital lobe and parietal lobe (Figure 1). The cause of the lobe hemorrhage, which was possibly due to the cerebral amyloidosis, needs to be confirmed using techniques such as cerebrovascular biopsy in future studies. It is noteworthy that 7 patients were diagnosed with NS for the first time after the onset of cerebral hemorrhage. This means that in some cases cerebral hemorrhage is the first manifestation of NS. Thus, NS-related examinations may need to be conducted in patients with unknown causes of cerebral hemorrhage. Understanding the underlying pathogenesis of NS patients with cerebral hemorrhage as the initial manifestation may help in selecting proper therapeutic methods, and benefit patients and their family economically and physiologically.

According to previous publications [3–6], NS patients with cerebral hemorrhage have particular clinical features, such as low plasma albumin, proteinuria, and hyperlipidemia, when compared to traditional cerebral hemorrhage patients. In the present study, all NS patients with cerebral hemorrhage had hypoalbuminemia and proteinuria, and most of them had coagulopathy, elevated D-dimer levels, hyperlipidemia, and renal function impairment. Studies need to be conducted to confirm whether these results represent the clinical features of NS with cerebral hemorrhage. In addition, severe focal neurological deficit was observed in all NS patients with cerebral hemorrhage, and most of these patients were unconscious in the acute phase of cerebral hemorrhage. The poor therapeutic prognosis of patients NS who had cerebral hemorrhage was also supported by these results, in which 7 patients died within 30 days of hemorrhage onset. In 2015, Li et al. [21] studied 172 patients who underwent baseline CT scans within 6 hours after the onset of symptoms, and performed a follow-up CT scan after 24 hours. A blend sign was observed in 26 of the 172 (15.1%) patients, and 24 of 61 (39.3%) patients had hematoma growth. Multivariate logistic analysis revealed that

the CT blend sign was highly specific for predicting hematoma growth and could be used as an independent predictor. In 2017, Sporns et al. [22] retrospectively collected the medical data of 182 patients with cerebral hemorrhage. Multivariate logistic analysis revealed that the CT black hole sign and blend sign were reliable predictors for poor outcome in patients with cerebral hemorrhage. Similarly, in many recent studies on cerebral hemorrhage patients, the CT black hole sign and blend sign were proposed as reliable predictors [23–25]. In the present study, blend sign and black hole sign on CT were observed in 3 patients, among which 2 had poor outcome, while the remaining patient died (Figure 1). This indicates that the blend sign and black hole sign are associated with poor prognosis in NS patients with cerebral hemorrhage. According to a retrospective study on patients with acute intracerebral hemorrhage conducted by Morotti et al. [26], hospitalized patients with hypoalbuminemia had a higher frequency of intraventricular hemorrhage. Furthermore, low GCS at admission was more common in patients with a history of chronic kidney disease. In the same study, it was reported that low plasma albumin level was independently correlated with high mortality at 90 days after the onset of cerebral hemorrhage (odds ratio [OR]: 1.78; 95% confidence interval [CI]: 1.30–2.44; P<0.001), indicating that early hypoalbuminemia could be used to predict unfavorable outcome in patients with intracerebral hemorrhage. In the study conducted by Nagata et al. [27], during a follow-up period of 10.1 years, 1927 of 39 405 patients died from cardiovascular disease. They used the Cox proportional hazards regression model to evaluate the associations among proteinuria, glomerular filtration rate (GFR), and cardiovascular disease mortality. The results revealed that participants with proteinuria had a 1.75-fold higher risk of cardiovascular disease mortality compared to participants without proteinuria, participants with a GFR of <45 mL/minute/1.73 m^2 had a 2.22-fold higher risk of cardiovascular disease mortality compared to participants with a GFR of ≥90 mL/minute/1.73 m^2, and participants with both proteinuria and a GFR of <45 mL/minute/1.73 m^2 had a 4.05-fold higher risk of cardiovascular disease mortality compared to participants without proteinuria and had a GFR of ≥45 mL/minute/1.73 m^2. These findings clearly suggest that proteinuria and lower GFR are independent risk factors for cardiovascular disease mortality. In the present study, all 15 patients had hypoalbuminemia and proteinuria, and 9 of these patients had renal function impairment. These factors may be associated with the poor prognosis of NS with cerebral hemorrhage.

Potential pathogenesis of NS with cerebral hemorrhage

It is of great scientific and clinical value to explore the pathogenesis of cerebral hemorrhage in NS patients. In 2013, Kitamura et al. [4] reported a case that had a history of membranous nephropathy but had no hypertension. The patient

consulted a doctor due to cerebral hemorrhage. Increased APTT and PT were recorded in coagulation tests during the hospital stay. In addition, FV activity severely decreased, and the FV inhibitor was obviously elevated in this patient. Furthermore, the coagulation tests were normal, and the NS symptoms of the patient improved after steroid treatment. These results suggest that membranous nephropathy (or NS) may involve an acquired FV inhibitor. Furthermore, these coagulation disorders may be responsible for the patient's cerebral hemorrhage. In 2015, Gebregeorgis et al. [28] reported a patient with coagulopathy and recurrent spontaneous hemorrhage in association with NS. In addition, NS patients complicated with coagulopathy have been repeatedly mentioned in the literature [29–32]. These results indicate that NS can lead to coagulopathy and subsequently promote the occurrence of cerebral hemorrhage. In the present study, the majority of NS patients with cerebral hemorrhage (8 patients, 53.33%) were diagnosed with coagulopathy. Since cerebral hemorrhage developed in some patients with no conventional stroke risk factor, the above-mentioned observations indicate that coagulopathy might be a major factor in NS patients with cerebral hemorrhage.

In the present study, conventional stroke risk factors such as diabetes, hypertension, hyperlipidemia, and smoking were recorded in some of the NS patients with cerebral hemorrhage. For those patients, it is possible that the occurrence of cerebral hemorrhage shares the same pathogenesis as in traditional cerebral hemorrhage patients, which is caused by stroke traditional risk factors. In 2015, Li et al. [33] conducted a prospective study that included a Chinese general population 92 013 subjects. During the 4-year follow-up period, 406 subjects developed intracerebral hemorrhage. After adjusting for confounding variables, proteinuria subjects were found to have increased hazard ratios (HRs) for hemorrhagic stroke (HR: 1.90; 95% CI: 1.35–2.67). In other words, proteinuria may increase the risk of hemorrhagic stroke in the Chinese general population. In the study conducted by Yoshida et al. [34], the following measurements were performed for NS patients (n=33), chronic glomerulonephritis patients (n=30), and healthy volunteers (n=30): (1) serum and urinal levels of plasminogen activator inhibitor type I (PAI-1), tissue-type plasminogen activator (tPA), and fibrinogen degradation products (FDP); and (2) serum D-dimer levels. As a result,

serum FDP and D-dimer levels and urinary levels of FDP and tPA markedly increased in NS patients, when compared to chronic glomerulonephritis patients and healthy volunteers. In addition, plasma tPA levels are higher in NS patients compared to healthy subjects. These results clearly suggest that fibrinolytic activity is elevated in NS patients. In the present study, in some of the NS patients with cerebral hemorrhage, neither conventional risk factors nor coagulopathy were recorded. Instead, these patients had NS associated with biochemical abnormalities, such as severe proteinuria, high plasma D-dimer level, hyperlipidemia, and renal function impairment. Studies need to be conducted to determine whether these factors are correlated with the occurrence of cerebral hemorrhage in patients with both NS and cerebral hemorrhage.

Some limitations in the present study need to be mentioned. First, this is a single-center, retrospective study with information collected from a very limited number of subjects (n=15). A larger sample-size cohort should be conducted to confirm these findings and detail the clinical features and pathogenesis of NS patients with cerebral hemorrhage. Second, the clinical features of NS patients and non-NS patients could not be compared in the present study. Inclusion of control subjects should be seriously considered in future studies to illustrate the differences between NS and non-NS patients in terms of characteristics including, but not limited to, age, gender, baseline hematoma volume, coagulopathy, high D-dimer, hyperlipidemia, high LDL-C, high TC, low GFR, proteinuria, hypoalbuminemia, and the location of the hemorrhage.

Conclusions

The present study describes the potential pathogenesis and clinical features of patients who have NS complicated with cerebral hemorrhage. Coagulopathy might be the pathogenesis of cerebral hemorrhage in NS patients, and their prognosis is generally poor.

Conflicts of interest

None.

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