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# Acute ischemic stroke associated with nephrotic syndrome: Incidence and significance — Retrospective cohort study

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ABSTRACT

We report 10 cases with arterial ischemic stroke (AIS) with nephrotic syndrome (NS), and clarified its incidence and clinical characteristics. The patients having albumin less than 3.0 g/dl and serum cholesterol greater than 250 mg/dl at the same time were retrospectively screened from 11,161 cases of stroke. Furthermore, the patients of AIS showing heavy proteinuria were selected. The 10 cases were diagnosed as AIS with NS. Its incidence was 0.09% of all kinds of stroke and 0.12% of AIS. Their subtypes were 6 large-artery atherosclerosis, 3 small-vessel occlusion, and 1 cardioembolism. We carried out a retrospective cohort study to assess the association between NS and atherosclerosis progression in AIS patients. Seven AIS patients with NS due to diabetic nephropathy (cases; NS group) were compared with patients with AIS and diabetes mellitus (DM) without NS (control group). Control group subjects were matched in a 2:1 ratio to cases by age, sex, use of medications for DM, and hemoglobin A1c (HbA1c) level. The NS group had high cerebral artery atherosclerosis scores, especially in the anterior circulation. The NS group demonstrated atherosclerosis of the internal carotid and lower extremity arteries, although there were no statistical differences between the two groups. Study subjects had high serum fibrinogen and D-dimer levels, suggesting that AIS patients with NS have a greater degree of hypercoagulability than AIS patients without NS.



## 1. Introduction

Nephrotic syndrome (NS) is defined by the presence of heavy proteinuria (protein excretion greater than 3.5 g/24 h), hypoalbuminemia (less than 3.0 g/dl), hyperlipidemia and peripheral edema [1]. Thrombotic diseases are also frequently observed. Arterial and venous thromboses are potential complications of NS. Arterial thromboses are less frequent than venous thromboses and the most common locations are femoral arteries, although other arteries may be involved [1–3]. Stroke associated with NS has rarely been reported in several case reports [4–10]. We report 10 cases of acute ischemic stroke (AIS) associated with NS and the results of a retrospective cohort study comparing AIS patients with and without NS. The study's purpose is to define the incidence of AIS with NS and assess whether NS is associated with atherosclerosis progression.

## 2. Subjects and methods

### 2.1. Subjects

This retrospective study analyzed hospitalized patients enrolled in our stroke registry. First, the patients having albumin less than 3.0 g/dl and serum cholesterol higher than 250 mg/dl at the same time were screened from 11,161 cases of stroke for 9 years from April 2004 to August 2013. From these patients, furthermore, the cases associated with AIS showing heavy proteinuria were selected. The proteinuria was estimated quantitatively by measuring the protein in a urine/24 h or qualitatively by using paper kit (Eiken Chemical Co. Japan). Stroke subtypes were determined according to the classification of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) [11]. In the retrospective cohort study, AIS patients with NS due to diabetic nephropathy (DN) were compared with AIS patients without NS who were matched to cases in a 2:1 ratio by age, sex, use of medication for diabetes mellitus (DM), and hemoglobin A1c (HbA1c) level. Cases were compared with controls in terms of body mass index (BMI), morbidity of hypertension, and laboratory findings, including serum albumin, total cholesterol, low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol,

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triglycerides, creatinine, estimated glomerular filtration rate (eGFR) [12], hematocrit, platelet counts, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, and D-dimer.

### 2.2. Evaluation of cerebral arterial stenosis

In this retrospective study, the exact percentage of arterial stenosis could not be determined, because the enhanced MRA could not be available. Extent of atherosclerosis was evaluated by the simplified atherosclerosis score of intracranial and extracranial arteries on MRA, according to the scoring method by Uekita et al. [13]. All MRA and MRI findings were reviewed by two investigators (A.T. and H.K.) who were blind to the clinical data. There was 93% of interobserver agreement. In cases where there was disagreement, the investigators reviewed the findings, discussed them and reached a final diagnosis. Total 17 vessels including the common carotid arteries, the extracranial and intracranial portions of the internal carotid arteries and the vertebral arteries, the anterior, middle, and posterior cerebral arteries, and the basilar artery, were evaluated by the cervical and intracranial MRAs. The stenotic lesions were graded virtually from 0 to 2: 0 indicating less than 50% reduction compared to a normally appearing proximal arterial diameter; 1 indicating 50–99% reduction of the arterial diameter and/or unclearly depicted distal artery beyond the stenotic lesion, and 2 indicating an occluded artery. The individual total scores were divided into two scores: an anterior score and a posterior score related to the anterior circulation vessels (common carotid, internal carotid, anterior cerebral, and middle cerebral arteries) or posterior circulation vessels (vertebral, basilar, and posterior cerebral arteries), respectively.

### 2.3. Ultrasonography and ankle-brachial index

Ultrasonography of carotid artery and ultrasonic duplex Doppler scanning of the lower extremities arteries were performed by using the LOGIQE9, GE-Yokogawa Medical. The stenotic lesions of internal carotid artery were graded by the method of NASCET (North American Symptomatic Carotid Endaterectomy Trial) from 0 to 5: 0 indicating negative, 1 indicating 1–25%, 2 indicating 26–50%, 3 indicating 51–75%, 4 indicating 76–99%, 5 indicating an occluded artery. The stenotic lesions of lower extremities were graded from 0 to 3: 0 indicating negative, 1 indicating mild stenosis, 2 indicating moderate stenosis, 3 indicating severe stenosis. The atherosclerosis of lower extremity arteries were also evaluated by measurement of ankle-brachial index (ABI) by using Colin form BP-203 RPE III, OMRON, Kyoto. A total carotid ultrasonic score (T-CUS) and total extremities ultrasonic score (T-EUS) were estimated as the sum of the right and left ultrasound score grades for the carotid and extremity arteries, respectively. A total ABI (T-ABI) score was estimated as the sum of the right and left ABI.

## 3. Results

### 3.1. NS subjects selection

The patients having serum albumin less than 3.0 g/dl were 196 (1.9%) cases of 10,057 patients examined, and the patients having serum cholesterol higher than 250 mg/dl were 1201 (11.3%) cases of 10,619 patients examined. The patients fulfilled both two levels at the same time were only 21 cases. They included 2 cases with negative or equivocal (±) by the protein paper kit, 1 case with 1+ (30 mg/dl), 2 cases with 2+ (100 mg/dl), 5 cases with 3+ (300 mg/dl), and 11 cases with 4+ (1000 mg/dl). The 16 patients showed urinary protein 3+ or 4+, namely heavy proteinuria, and they consisted 10 AIS, 4 intracranial hemorrhage, and 2 cerebral venous thrombosis (CVT) (Table 1). Nine patients of these 16 patients showed protein excretion greater than 3.5 g/24 h. In the other 7 patients, the content of protein on urine/24 h was not measured. However, they all had moderate to severe peripheral edema and hyperlipidemia, and the diagnosis of NS was strongly suggested also in these 7 cases.

### 3.2. Incidence and subtypes of AIS with NS

The 10 cases, 8 males and 2 females, 64.4 ± 8.6 years (Mean ± SD), were diagnosed as AIS associated with NS. Its incidence rate was 0.09% of all kinds of stroke (total 11,161 patients) and 0.12% of AIS (total 8116 patients) in our hospital. And, its incidence was 5 folds of CVT during the same duration. Their subtypes were 6 large-artery atherosclerosis (LAA), 3 small-vessel occlusion (lacune, SVO), and 1 cardioembolism (CE) by the TOAST criteria [11] On MRI and MRA, middle cerebral arteries, anterior choroidal artery and internal carotid artery (occlusion) were involved in 6 cases, 1 case and 1 case, respectively. SVOs were located in the supra-tentorial basal ganglia in all 3 cases (Table 2).

### 3.3. Pathogenesis of NS

NS has not been diagnosed before the admission in any cases of 10 patients. Pathological diagnosis was decided by the histopathological examination of the renal biopsied samples in two cases; amyloid nephropathy due to primary amyloidosis in 1 case and membranoproliferative glomerulonephritis (MPGN) in 1 case. Eight cases were diagnosed as diabetic nephropathy (DN) based on the long history of DM and the exclusion of other pathogenetic diseases, although renal biopsy was not performed (Table 2).

### 3.4. Evaluation of atherosclerosis

Extent of atherosclerosis was evaluated by using the atherosclerosis score of intracranial and extracranial arteries on MRA. Two cases showed no or one vessel of stenosis, but 8 cases revealed more than two vessels of stenosis. There was no past history of coronary artery disease in all cases, except one case. The ultrasonography of carotid artery

**Table 1**
The patients of acute stroke.
Abbreviation: TC; total cholesterol, Alb; albumin, UP; urinary protein, TIA; transient ischemic attack, SVO; small-vessel occlusion, LAA; large-artery atherosclerosis, CE; cardioembolism, ICH; intracranial hemorrhage, SAH; subarachnoid hemorrhage, CVT; cerebral venous thrombosis.

| | TIA | SVO | LAA | CE | Other | ICH | SAH | Total |
|---|---|---|---|---|---|---|---|---|
| Patients n. | 660 | 2196 | 2547 | 2023 | 235 | 2200 | 733 | 10,619 |
| ①TC > 250 | 60 (9.1) | 299 (13.6) | 373 (14.6) | 133 (6.6) | 17 (7.2) | 242 (11.0) | 75 (10.2) | 1201(11.3) |
| Patients n. | 632 | 2070 | 2436 | 1958 | 202 | 2055 | 675 | 10,057 |
| ②Alb < 3.0 | 3 (0.5) | 16 (0.8) | 44 (1.8) | 66 (3.4) | 9 (4.5) | 48 (2.3) | 8 (1.2) | 196 (1.9) |
| Patients n. | 263 | 886 | 1123 | 917 | 99 | 1226 | 477 | 5002 |
| ③Massive UP | 8 (3.0) | 21(2.4) | 40 (3.6) | 45 (4.9) | 6 (6.1) | 118 (9.6) | 33 (7.0) | 272 (5.4) |
| ① + ② + ③ | 0 | 3 | 6 | 1 | 2 (CVT) | 4 | 0 | |

**Table 2**
The patients of acute ischemic stroke with nephrotic syndrome.
Abbreviation: TC; total cholesterol, Alb; albumin, UP; urinary protein, E; edema, SVO; small-vessel occlusion, LAA; large-artery atherosclerosis, CE; cardioembolism, L; left, R; right, MCA; middle cerebral artery, BAD; branched atheromatous disease, Ant; anterior, IC; internal carotid, NS; nephrotic syndrome, DN; diabetic nephropathy, MPGN; membranoproliferative glomerulonephritis.

| | | | | MRI | | | | | | DM | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Case | Age | Sex | Type | Location of infarction | Alb | TC | UP | Day | E | Duration | NS type |
| 1 | 50 | F | LAA | R. MCA (BAD) | 3 | 284 | 4 | 8.4 | ++ | 15 | DN s/p |
| 2 | 53 | F | LAA | R. MCA | 1.8 | 707 | 4 | 8.6 | ++ | – | Amyloidosis |
| 3 | 59 | M | LAA | R. ant. choroidal A | 2.1 | 336 | 3 | 9.5 | ++ | 5 | DN s/p |
| 4 | 62 | M | LAA | L. MCA | 2.8 | 407 | 4 | 6.4 | ++ | 30 | DN s/p |
| 5 | 79 | M | LAA | R. MCA (R. IC occlusion) | 2.8 | 315 | 4 | | ++ | 20 | DN s/p |
| 6 | 70 | M | LAA | R. MCA, | 1.9 | 326 | 3 | | + | 10 | DN s/p |
| 7 | 65 | M | SVO | L. basal ganglia | 2.7 | 264 | 4 | 6.5 | ++ | – | MPGN |
| 8 | 68 | M | SVO | R. basal ganglia | 3 | 285 | 3 | | ++ | 2 | DN s/p |
| 9 | 69 | M | SVO | R. basal ganglia | 3 | 299 | 3 | | ++ | 4 | DN s/p |
| 10 | 69 | M | CE | R. MCA | 3 | 264 | 4 | | ++ | 8 | DN s/p |

disclosed mild to severe stenosis of internal carotid artery in 5 cases of 8 patients examined. The atherosclerosis of lower extremity arteries was evaluated by measurement of ankle-brachial index or using the ultrasonic duplex Doppler scanning. Peripheral arterial disease (PAD) of lower extremities was suspected in 5 cases (more than moderate degree of PUS or <0.96 of ABI) [14].

### 3.5. Retrospective cohort study

We carried out a retrospective cohort study to assess the association between NS and atherosclerosis progression. Case 2 with amyloid nephropathy, case 7 with MPGN, and case 10 with CE, were excluded from this study. The remaining 7 patients with AIS and NS due to DN were selected as cases (NS group). Cases were compared with AIS patients with DM without NS (control group) who were matched to cases in a 2:1 ratio by age, sex, use of medications for DM, and HbA1c level. The control group included 11 cases with SVO and 3 cases with LAA, and had larger number of SVO than that of NS group. The NS group had statistically significantly higher cerebral artery atherosclerosis scores, especially in the anterior circulation. And the NS group also showed higher T-CUS, although there were no significant differences compared with the control group. T-EUS in the NS group were higher than those in the control group. However, there were no differences in T-ABI scores between the two groups. The NS group demonstrated hypoalbuminemia and hypercholesterolemia as well as anemia, increased creatinine level and low eGFR which were consistent with chronic kidney disease. They also had high fibrinogen and D-dimer levels, indicating a hypercoagulable state (Tables 3, 4).

**Table 3**
Comparison of clinical and atherosclerotic characteristics between patients with acute ischemic stroke and nephrotic syndrome due to diabetic nephropathy (NS group) and patients with acute ischemic stroke and diabetes mellitus without nephrotic syndrome (control group). The differences between the two groups were evaluated statistically by $\chi^2$ or Mann–Whitney's U tests.
Abbreviation: AIS acute ischemic stroke, SVO; small-vessel occlusion, LAA; large-artery atherosclerosis, AS; atherosclerosis score, anterior c; anterior circulation, posterior c; posterior circulation, T-CUS; total carotid ultrasonic score, T-EUS; total extremities ultrasonic score, T-ABI; total ankle-brachial index.

| | NS group | Control group | P |
|---|---|---|---|
| Patient (n) | 7 | 14 | |
| Age, year | 65.3 ± 9.3 | 66.0 ± 8.0 | – |
| Sex/male | 6 (85.7) | 12 (85.7) | – |
| DM | 7 (100) | 14 (100) | – |
| Duration | 12.3 ± 10.1 | 7.9 ± 6.2 | 0.397 |
| Hb A1c | 8.7 ± 3.3 | 8.1 ± 1.7 | – |
| On medication | 4 (57.1) | 7 (50.0) | – |
| Hypertension | 5 (71.4) | 10 (71.4) | 1 |
| BMI | 22.9 ± 2.4 | 22.9 ± 3.3 | 0.852 |
| AIS LAA | 5 (71.4) | 3 (21.4) | 0.056 |
| SVO | 2 (28.6) | 11 (78.6) | |
| AS score | 5.3 ± 3.7 | 2.1 ± 2.0 | 0.019 |
| Anterior c | 2.6 ± 1.8 | 0.9 ± 1.3 | 0.035 |
| Posterior c | 2.3 ± 2.9 | 1.1 ± 0.9 | 0.588 |
| T-CUS | 2.0 ± 2.3 | 0.6 ± 0.9 | 0.133 |
| T-EUS | 4.0 ± 1.0 | 1.8 ± 1.1 | 0.031 |
| T-ABI | 1.9 ± 0.4 | 2.1 ± 0.3 | 0.459 |

## 4. Discussion

Patients with NS have a high incidence (21 to 51% of patients) of venous thrombosis, particularly deep vein and renal vein thrombosis, and pulmonary emboli, especially in younger patients under 20 [15–20], and CVT has also been rarely reported [2]. On the other hand, the relative risk of arterial thrombosis was low (1.0 to 5.5%), compared to that of venous thrombosis [3,21,22]. In 2014, Sasaki et al. reported an additional case of ischemic stroke with NS, and reviewed 21 prior cases reported in 19 literatures [4]. However, the incidence and the clinical characteristics of AIS patients have still remained unclear [5–10].

We reported here 6 LAA patients, 3 SVO patients and 1 CE patient, and elucidated the followings. The incidence of AIS associated with NS was 0.09% of total stroke or 0.12% of AIS, and was 5 times of CVT in the adult patients with NS. The patients showed severe stenosis and/or occlusion of intracranial and extracranial arteries, and PDA. The pathogenesis of NS was from DN in 8 cases (80%), amyloid nephropathy in 1 case, and MPGN in 1 case. These results suggest that the AIS patients with NS, especially that from DN, had marked general arteriosclerosis of the body, which might be a clinical characteristic of the Japanese patients.

Mahmoodi et al. reported that annual incidences of venous and arterial thromboembolism in NS patients were 1.02% and 1.48%,

**Table 4**
The comparison of laboratory data between the patients of acute ischemic stroke with nephrotic syndrome due to diabetic nephropathy (NS group) and acute ischemic stroke with diabetes mellitus without nephrotic syndrome (control group).
The difference between two groups was statistically estimated by the method of $\chi^2$ test or Mann–Whitney's U-test. Abbreviation: LDL; low density lipoprotein, HDL; high density lipoprotein, eGFR; estimated glomerular filtration rate.

| | NS group | Control group | P |
|---|---|---|---|
| Albumin | 2.7 ± 0.5 | 4.2 ± 0.4 | <0.001 |
| Total cholesterol | 321.7 ± 42.5 | 211.7 ± 39.4 | 0.001 |
| LDL-cholesterol | 214.4 ± 40.5 | 132.6 ± 34.2 | 0.001 |
| HDL-cholesterol | 51.3 ± 17.4 | 49.4 ± 9.7 | 0.94 |
| Triglyceride | 229.0 ± 67.4 | 189.6 ± 203.1 | 0.037 |
| Creatinine | 2.1 ± 1.6 | 0.9 ± 0.3 | 0.009 |
| eGFR | 37.7 ± 23.3 | 71.5 ± 22.6 | 0.011 |
| Hematocrit | 35.7 ± 5.5 | 43.0 ± 5.1 | 0.006 |
| Platelet | 27.8 ± 2.7 | 22.4 ± 5.8 | 0.048 |
| PT | 0.9 ± 0.7 | 0.9 ± 0.0 | 0.55 |
| APTT | 28.9 ± 3.9 | 28.8 ± 3.1 | 0.933 |
| Fibrinogen | 385.4 ± 104.5 | 275.0 ± 57.9 | 0.019 |
| D-dimer | 1.8 ± 1.0 | 0.7 ± 0.4 | 0.01 |

respectively, which were 8 times higher than in general population from a retrospective cohort study. They also reported that multiple classic risk factors for atherosclerosis are associated with arterial thromboembolism in NS patients, including sex, age, hypertension, DM, smoking, prior arterial thromboembolism, and eGFR. And the annual incidence of DN patients was 7.43, which was the highest incidence among all types of nephropathy [3].

Hypercoagulability contributes to the predisposition to thromboembolism in NS. The low molecular weight coagulation factors (Factors IX, XI), antithrombin III, plasminogen, and free protein S excreted into the urine by the breakdown of permselectivity barrier of the glomerular capillary wall, and along with inverse increases in high molecular weight coagulation factors (Factors V, VII, VII, and X), fibrinogen, alpha 2-antiplasmin, alpha-2-macroglobulin and platelet aggregation have been reported [23–29]. These changes have been attributed to a hypercoagulable state in which an imbalance between procoagulant/prothrombotic factors and anticoagulant/antithrombotic factors promotes thromboses in veins and arteries. Hypoalbuminemia and secondary volume depletion, and hyperlipidemia also could play as risk factors for thromboembolism or atherosclerosis. NS may independently predispose individuals to arterial and venous thromboembolism, but the detailed mechanism of the hypercoagulability is not completely understood [1–4,23–29]. Study subjects had high serum fibrinogen and D-dimer levels, suggesting that AIS patients with NS have a greater degree of hypercoagulability than AIS patients without NS. The changes of PT and aPTT could not be recognized.

Histopathology of NS in the 22 AIS patients previously reported from several countries was membranous nephropathy in 5 cases (22.7%), minimal change in 4 cases (18.2%), MPGN in 3 cases (13.6%), focal segmental sclerosis in 2 cases (9.0%), Ig A nephropathy, undetermined pathology in 6 cases (27.2%), and DN in only 1 case (4.5%) [4]. In our study, DN was clinically apparent for the pathogenesis of NS in 80% of the patients, but could not be confirmed by the renal biopsy. The occurrence of non-diabetic renal disease (NDRD) in DN patients has been increasing recognized in recent years. Zhuo et al. reviewed the prior 13 literatures from 1983 to 2012, and reported the prevalence of DN complicating NDRD; the common histological diagnosis were tubule-interstitial nephritis (22.7%) and IgA nephropathy (14.1%) [30]. Although the complication of NDRD might exist, DN could be mainly responsible for the pathogenesis of NS in 80% of our patients. The patients with NS had the combined risks due to the basic disease induced NS as well as the hypercoagulation state due to NS. It has been well known that DM and hyperlipidemia are strong risk factors for AIS, however the existence of NS might be failed to notice as another risk among the risk factors of AIS. DM might be the most important strong risk factor for AIS associated with NS, especially in the Japanese patients.

## Conflict of interest

The authors declare that there are no conflicts of interest.

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