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CASE REPORT

Difficulty in managing nephrotic syndrome-associated cerebral venous thrombosis

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Abstract

Thromboembolism is one of the most serious complications of nephrotic syndrome (NS). Although the occurrence of renal vein thrombosis or deep vein thrombosis is well recognized in NS patients, they rarely develop cerebral venous thrombosis (CVT). The mortality rate of CVT patients is still approximately 10%, and 6–10% of patients who survive have a severe and permanent disability. Herein, we report the case of a 26-year-old woman with multiple thrombotic risk factors, including the presence of NS, use of oral contraceptives, smoking, and alcohol consumption who developed wide-range CVT. Undetermined fraction heparin, albumin and AT-III transfusion, and direct mechanical catheter thrombectomy were insufficient for the improvement of CVT. However, CVT eventually improved along with the remission of NS by prednisolone administration. This process indicates that in the management of CVT associated with NS, it is crucial to control the activity of NS. Currently, knowledge on the treatment for NS associated with CVT is limited, and this is a subject of urgent investigation.

Keywords Cerebral venous thrombosis · Thromboembolism · Nephrotic syndrome · Corticosteroid

Introduction

Cerebral venous thrombosis (CVT) is an uncommon form of cerebral vascular insult, accounting for 0.5–1.0% of all stroke cases [1]. Approximately, 85% of these patients have an inherited or acquired prothrombotic risk factor, and approximately 45% of them have more than one risk factor [2]. The major predisposing causes include hereditary deficiency of anticoagulant proteins, cancer, inflammatory bowel disease, Bechet disease (BD), antiphospholipid syndrome, obesity, use of oral contraceptives, pregnancy, anemia, infection of the head or neck and dehydration, smoking, or alcohol consumption [3, 4]. The mortality rate of CVT is approximately 10%, generally resulting from cerebral herniation in acute phase and underlying condition in chronic phase [5, 6]. Additionally, 6–10% of patients who survive have severe and permanent disability [2].

Thromboembolism is common among patients with nephrotic syndrome (NS), and its incidence in adult patients is approximately 25% [7]. Although potential mechanisms are not completely clarified, it seems to include urinary loss of anticoagulant, high fibrinogen levels, synthesis of procoagulant proteins, platelet hyperaggregability, and low circulating plasma volume [8]. The occurrence of renal vein thrombosis, inferior vena cava thrombosis, or pulmonary infraction is frequent, whereas that of CVT is infrequent [9].

Herein, we report the case of a 26-year-old woman with multiple thrombotic predispositions, including the presence of NS, use of oral contraceptives, smoking, and alcohol consumption who developed severe CVT and had severe residual neurological sequelae despite therapeutic intervention.

Case report

A 26-year-old woman presented with occipital headache upon waking up on the day after she had consumed too much alcohol. Moreover, she presented with mild edema of the eyelids and legs lasting for a few weeks. Her previous medical history and family history were unremarkable. She only took oral contraceptives and smoked one pack of

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cigarette per day. The height and ordinal weight according to the self-report was 155 cm and 50 kg, respectively. The following examination results were obtained: blood pressure, 97/70 mm Hg; pulse rate, 90 beats/min; and temperature, 36.8 °C. Meanwhile, neurological examination revealed symmetry, and there were no other pathologic findings except for mild edema of the eyelids and legs. Laboratory examination revealed the presence of NS (serum total protein level, 4.0 g/dL; serum albumin level, 0.7 g/dL; low-density lipoprotein cholesterol level, 327 mg/dL; 24-h urinary total protein, 24.3 g/day; and SI (selectivity index), 0.21) with mild acute kidney injury (serum creatinine level, 0.83 mg/dL) and abnormalities in the coagulation–fibrinolysis system (D-dimer level, 27.2 μg/mL and fibrinogen degradation product level, 48.1 μg/mL). Except for the antithrombin activity (AT-III activity, 22%), which normally decreases due to NS, the thrombophilia screening test for protein S deficiency, protein C deficiency, hyperhomocysteinemia, antiphospholipid syndrome, systemic lupus erythematosus, or thyroid disease was normal (Table 1). Brain magnetic resonance imaging revealed acute cerebral infraction in the left occipital lobe (Fig. 1a-1), and magnetic resonance venography showed thrombosis in the superior sagittal sinus, bilateral transverse sinus, bilateral sigmoid sinus, and deep venous sinus (Fig. 1a-2). Whole-body contrast-enhanced CT revealed the absence of other thromboses.

After admission, anticoagulation therapy with adjusted-dose undetermined fraction heparin (UFH) with an activated partial thromboplastin time (APTT) of 1.5–2.0 times (approximately 50–70 s) was initiated (Fig. 2). Moreover, hypertonic albumin preparation and extracellular fluid were administered to correct intravascular volume depletion based on ultrasound evaluation of the inferior vena cava. Considering the possibility prednisolone-induced hypercoagulability could exacerbate CVT, leading to a fatal outcome, the administration was postponed for NS. On day 2 of hospitalization, her consciousness level rapidly decreased along with the expansion of the infarct lesion besides trivial hemorrhage from the lesion. Accordingly, we performed direct mechanical catheter thrombectomy without chemical thrombolysis.

Table 1 Laboratory data on admission

Blood count		Immunologic test	
White blood cells /μL	13,400	Immunoglobulin G (mg/dl)	562
Hemoglobin (g/dL)	15.5	Immunoglobulin M (mg/dl)	379
Platelets (μL)	27.2×10^4	Immunoglobulin A (mg/dl)	260
Coagulation		κ/λ ratio	1.48 (0.25–1.80)
Activated partial thromboplastin time (s)	28.1	Complement C3 (mg/dL)	138 (80–140)
Prothrombin time-international normalizd ratio	0.93	Complement C4 (mg/dL)	26 (11–34)
Fibrinogen (mg/dL)	512	50% hemolytic complement activity (U/mL)	50.4 (30–45)
Fibrin/fibrinogen degradation products (μg/mL)	48.1	C-reactive protein (mg/dL)	0.76
D-dimer (μg/mL)	27.2	Anticardiolipin antibody (RU/mL)	< 8.0
Antithromin III (%)	22 (80–130)	Anti-beta 2 glycoprotein I antibody (RU/mL)	< 1.2
Protein C (%)	127 (75–150)	Lupus anticoagulant raito	1.2 (<1.3)
Protein S (%)	79 (60–150)	Anti-nulear antibody	< 1:40
Blood chemistry		Perinuclear anti-neutrophil cytoplasmic antibody	Negative
Total protein (mg/dL)	4.0	Cytoplasmic anti-neutrophil cytoplasmic antibody	Negative
Serum albumin (g/dL)	0.7	Cryogloburin	Negative
Sodium (mEq/L)	133.7	HBs antigen	Negative
Calcium (mg/dL)	7.6	HCV antibody	Negative
Potassium (mEq/L)	4.0	HIV antibody	Negative
Chloride (mEq/L)	100	Endocine test	
Aspartate aminotrasferase (IU/L)	18	Thyroid stimulating hormone (μIU/ml)	5.06
Alanine aminotransferase (IU/L)	14	Free thyroxine (ng/dL)	0.8
Lactate dehydrogenase (IU/L)	246	Free triiodothyronine (ng/mL)	1.3
Creatine kinase (IU/L)	35	Urine test	
Blood urea nitrogen (mg/dL)	14.4	Occult blood	Above 1
Serum creatinine (mg/dL)	0.83	Red blood cell (/high power field)	3–5
Total cholesterol (mg/dL)	553	Protein (g/day)	24.3
Low density lipoprotein (mg/dL)	327	Casts (/high power field)	1
Homocysteine (μmol/l)	3.9 (3.7–13.5)	Selectivity index	0.21

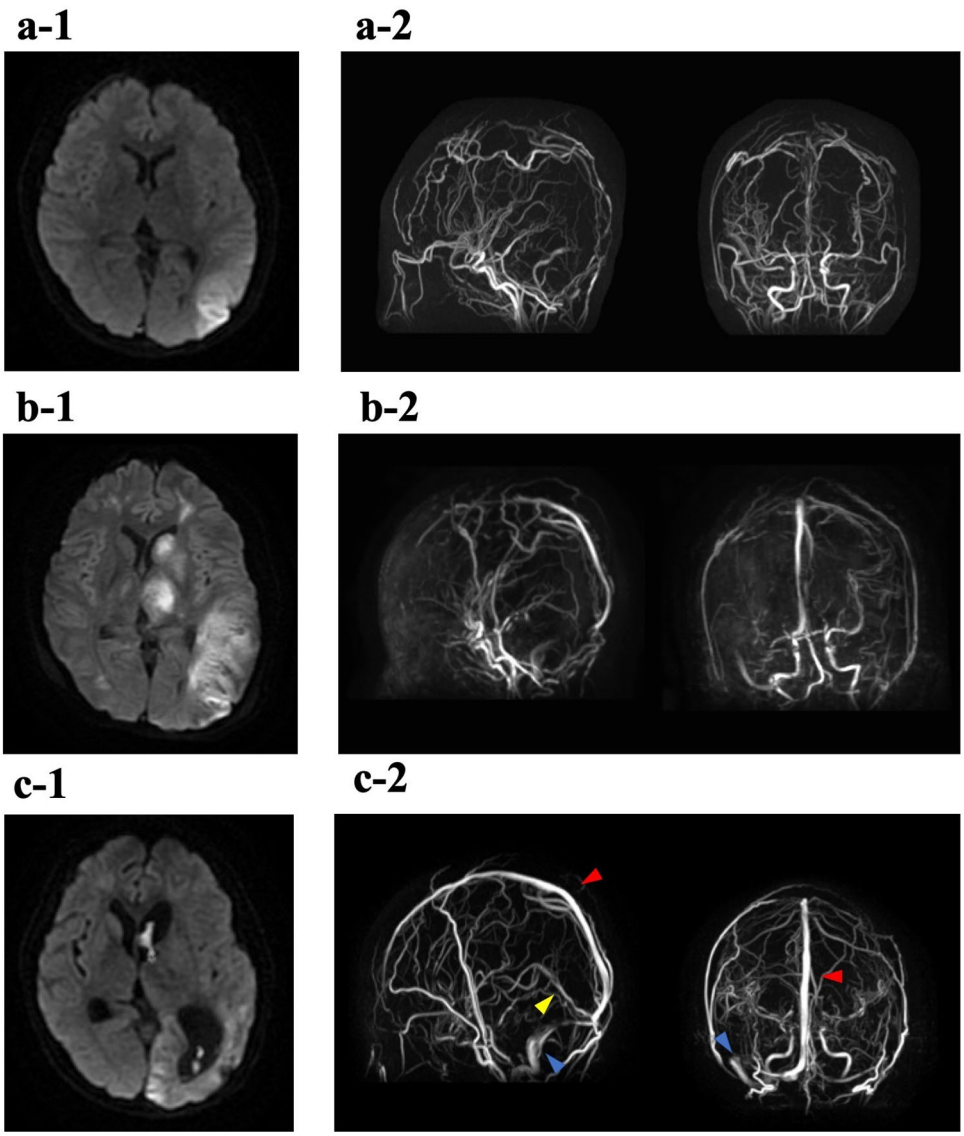

Fig. 1 Magnetic resonance imaging (MRI) and magnetic resonance venography (MRV). **a** First day of hospitalization. **a-1** Diffusion-weighted imaging (DWI) MRI revealed acute cerebral infraction in the left occipital lobe. **a-2** MRV revealed extensive thrombosis in the superior sagittal sinus, bilateral transverse sinus, bilateral sigmoid sinus, and deep venous sinus. **b** Fifth day of hospitalization. **b-1** DWI MRI revealed the expansion of infarction in the left occipital lobe and the presence of hemorrhage and new infractions in the bilateral thalamus and left basal ganglia. **b-2** MRV revealed partial reperfusion in the superior sagittal sinus and the right transverse sinus, and continuous obstruction in the other structures. **c** Forty-first day of hospitalization. **c-1** DWI MRI revealed reduced edema around the infarct in the left occipital lobe. **c-2** MRV revealed reperfusion in the deep venous sinus including straight sinus (yellow arrow) and further blood flow improvement in the superior sagittal sinus (red arrow) and the right transverse sinus (blue arrow)

The right transverse sinus and part of superior sagittal sinus were reperfused though other venous sinuses could not be reperfused as the structures were difficult to penetrate with a guidewire (Fig. 3), leading to her partially improved level of consciousness. On day 3 of hospitalization, the amount of UFH required to maintain an APTT of 1.5–2.0 times was modestly increased from 500 to 700 units/h probably due to the decreased AT-III activity; also, congenital AT-III deficiency could not be ruled out. Hence, approximately 1000 units/day of AT-III transfusion was initiated. However, on day 5 of hospitalization, she fell into coma again, with further exacerbation of infraction and no improvement in thromboses (Fig. 1b1–2). On day 6 of hospitalization, 60 mg of prednisolone was initiated for NS because CVT was resistant to the previous treatment. On day 23 of hospitalization, UFH administration was discontinued because the patient developed new massive hemorrhage in the left frontal lobe with ventricular perforation. After that, however, following the complete remission of NS on day 30, most of the CVT disappeared on day 41 even though anticoagulation was no longer provided (Fig. 1c1–2). After 3 months from the onset of NS and CVT, although her level of conscious remained severely impaired, she did not present with relapse as the dose of prednisolone was tapered to 10 mg, and was transferred to a rehabilitation facility.

Discussion

Herein, we present the case of a patient with NS who developed severe CVT. CVT reluctant to anticoagulant therapy, correction of intravascular volume depletion, and cessation of oral contraceptives improved along with decreased urinary protein exertion; hence, we concluded

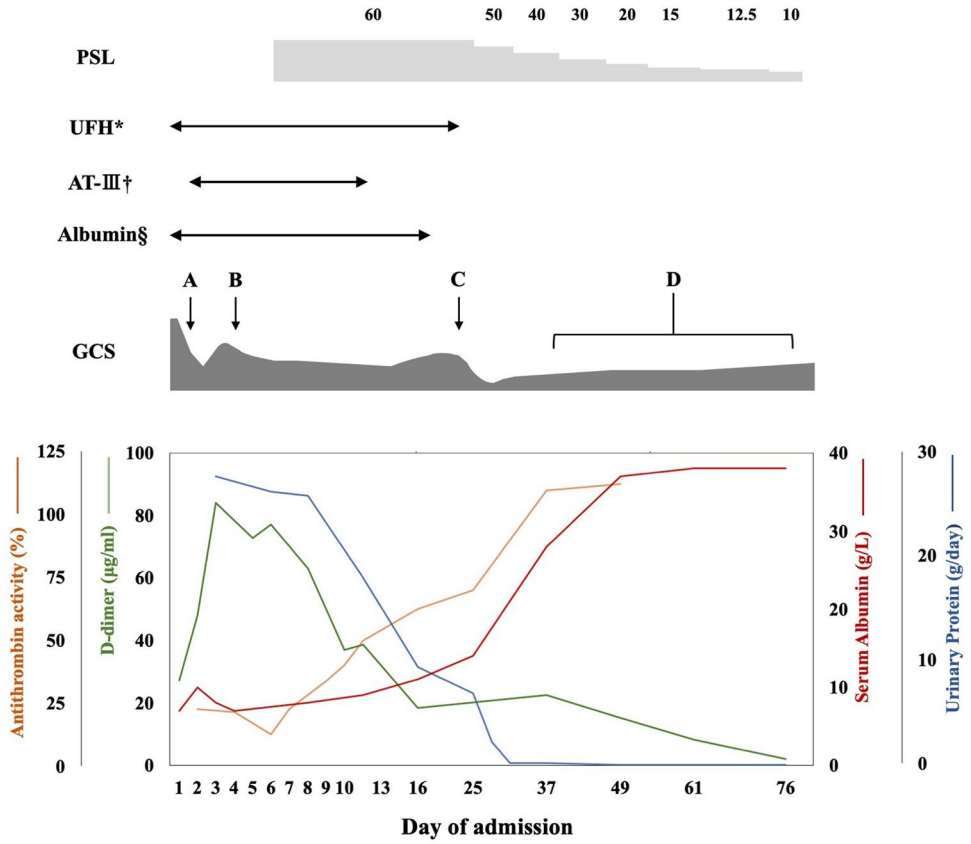

Fig. 2 Clinical course. Time course of the changes in the levels of the biochemical parameters (urinary protein, serum albumin, antithrombin, and D-dimer) and changes in the patient's level of consciousness after providing therapy for cerebral venous thrombosis (CVT). **a** Direct catheter thrombolysis was performed on the 2nd day of hospitalization because the patient's level of consciousness rapidly decreased with mild hemorrhage in the left occipital lobe. **b** Expansion of cerebral infraction in the left occipital lobe with no further improvement of CVT on the 5th day of hospitalization. **c** New massive hemorrhage with ventricular perforation in the left frontal lobe on the 23rd day of hospitalization. **d** Decreasing CVT and no expansion of cerebral infraction lesion. *The dose of UFH was adjusted with approximately double activated partial thromboplastin time. †The dose of albumin transfusion was approximately 12.5 g/day. §The dose of AT-III transfusion was approximately 1000 units/day. *PSL* prednisolone, *UFH* undetermined fraction heparin, *AT-III* antithrombin, *GCS* glasgow coma scale.

that the NS contributed to CVT (Fig. 2). On the other hand, it has been reported that about half of the patients with CVT have more than one prothrombotic risk factor [2]. Our patient also had multiple risk factors such as the use of oral contraceptives, smoking, and alcohol consumption besides NS, and their effects could not be neglected (Fig. 3).

The rate of mortality from CVT has been declining over the past few decades probably because the increased knowledge of CVT among clinicians, and the improvement in imaging modalities lead to early detection and treatment. In the present case, in addition to the coexistence of many risk factors, the remarkably high NS activity caused the broad thrombosis including deep venous sinus, known for the most important predictor of poor clinical outcome, and our patients ended up having severe disability despite early interventions after the onset of symptoms [2]. The prognosis of CVT seems to heavily depend on the underlying disease severity.

Histological diagnosis is essential in the management of NS. However, in the present case, renal biopsy could not be performed because CVT was out of control, and the patient's level of consciousness significantly decreased. Based on factors such as age in 20 s or subacute clinical course, minimal change in nephrotic syndrome (MCNS) was expected. However, nonselective proteinuria indicated other types of NS, including focal segmental sclerosis [10]. The results showed that the relatively good response to prednisolone monotherapy was in accordance with MCNS. In fact, in primary NS, MCNS is most commonly associated with CVT even though the incidence of pulmonary embolism or renal vein thrombosis is high in membranous nephropathy [11, 12].

Glucocorticoid therapy plays a key role in the treatment for NS, but it is also a significant risk factor for deep venous

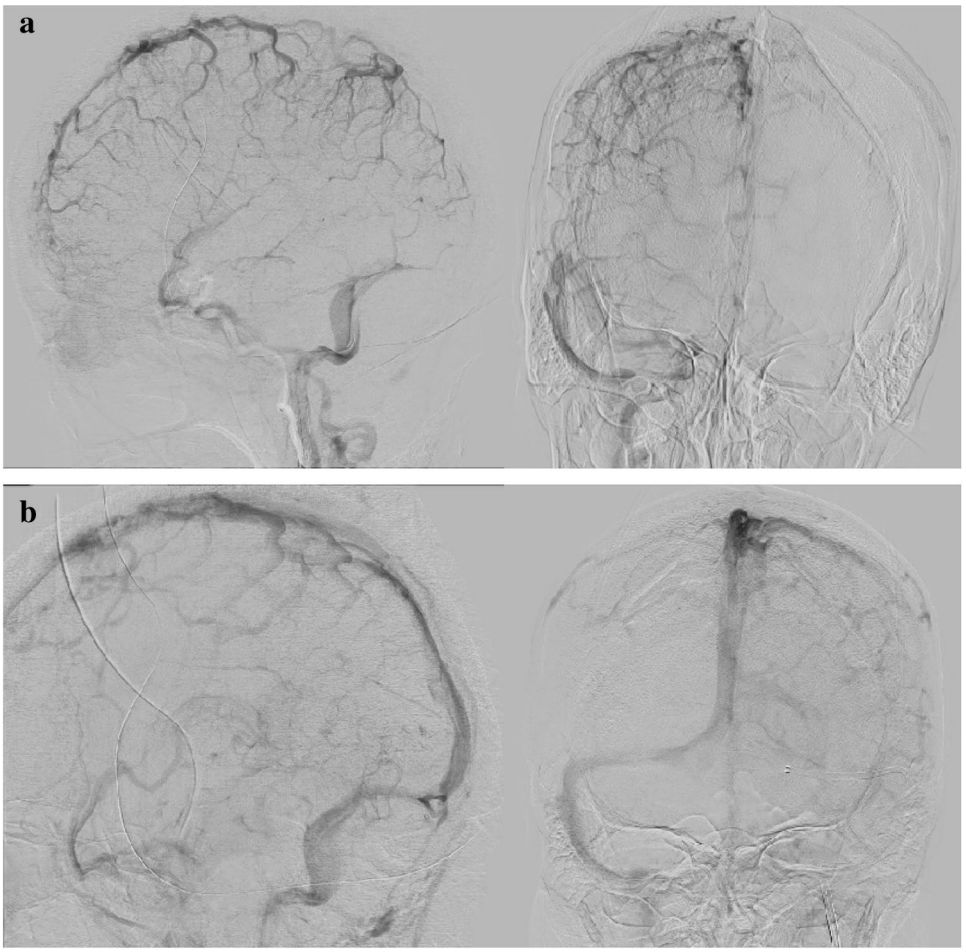

Fig. 3 Venous phase of direct carotid angiogram. **a** Before direct mechanical catheter thrombolysis, most of the cerebral sinus including the bilateral transverse sinus, sagittal superior sinus, left sigmoid sinus, and deep venous sinus were thrombosed. **b** After direct mechanical catheter thrombolysis, the recanalization of the right transverse sinus and part of the superior sagittal sinus was observed with improvement of the venous outflow, and the occlusion of others persisted

thrombosis (DVT), as increased levels of clotting factors and fibrinogen are believed to contribute. Johannesdottir et al. [13] have reported that compared with nonusers, corticosteroid users have a three-hold higher risk of developing DVT. In this context, there is no consensus on the timing of glucocorticoid therapy initiation for NS patients who develop severe thromboembolic events [14]. This is not mentioned in guidelines for NS, while in the treatment of CVT associated with BD, the European League Against Rheumatism recommends high-dose glucocorticoid to control the activity above anything else [15–17]. Considering the use of prednisolone further could promote thrombus formation, leading to a fatal course, we initially did not intend to administer prednisolone until CVT was partially under control by anticoagulant therapy, albumin and AT-III transfusion, and cessation of oral contraceptives. However, CVT resistant to these approaches improved along with the decreased urinary protein even after the cessation of anticoagulant therapy. This clinical course suggests that the essential CVT treatment associated with NS is to control NS activity with treatment including prednisolone administration, and we should have initiated it earlier. Furthermore, the combined therapy, such as calcineurin inhibitor, rituximab, or LDL apheresis can be useful to reduce total glucocorticoid dose or increase the possibility of remission within a short time, particularly when prednisolone monotherapy-resistant NS is expected [15]. Considering that the SI of our patient was not low enough to be indicative of MCNS, the early use of these treatments was worth considering.

Anticoagulant therapy with heparin is also an essential adjuvant therapy for CVT. This condition is commonly associated with intracerebral hemorrhage, but it is not a contraindication for heparin therapy [18–20]. It is still unclear whether low molecular weight heparin (LMWH) is more effective than dose-adjusted UFH. Based on the report that LMWH has fewer major hemorrhagic complications that UFH in the treatment of extracerebral thrombosis, the European Federation of Neurological Society recommends that LMWH should be preferred for CVT [19, 21]. On the other hand, there are few studies comparing the efficiency of UFH versus LMWH on CVT, and UFH also has an advantage that the effect can be rapidly adjusted when severe complications occur or surgical intervention is required. Considering the good controllability of UFH, we administered UFH with about double activated partial thromboplastin time, but this decision might have partially attribute to the development

of fatal cerebral bleeding. Therefore, future studies need to assess the appropriate type of anticoagulant or the optimal dose for the treatment.

AT-III, an important anticoagulant factor, has a molecular weight similar to albumin, and is thought to be pathologically excreted in the urine by the NS patients. There is a significant positive correlation between the serum levels of albumin and AT-III, and more than 80% of them have decreased AT-III levels [22, 23]. However, no unified view has been obtained to date whether AT-III deficiency is a risk factor for thrombosis in the NS patients [22–25]. Interestingly, in the present case, though the levels of D-dimer were only mildly reduced by anticoagulation therapy, correction of intravascular volume depletion, and cessation of oral contraceptives, those were remarkably decreasing along with the improvement of urinary protein and accompanying recovery of AT-III activity before the levels of serum albumin were increasing. This might suggest that AT-III has a crucial role in thrombus formation in NS patients and can be one of the sensitive serum markers to predict a therapeutic effect. Moreover, AT-III transfusion in NS associated with thrombosis might be effective. Although our patient did not show a good response to transfusion, this insufficient effect might be attributed to the inadequate administration dose. Whether AT-III transfusion is effective should be investigated in future studies.

NS patients rarely develop CVT, especially in the presence of other thromobogenic factors, which can lead to poor outcomes depending on the disease severity. However, knowledge on the treatment including the timing of glucocorticoid therapy initiation, appropriate anticoagulant type, or the usefulness of AT-III transfusion, is limited. In the future, these issues should be investigated in clinical trials.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interests exists.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent The authors declare that they have obtained consent from the patient's family discussed in the report.

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