Clinical characteristics of cerebral venous sinus thrombosis in childhood-onset systemic lupus erythematosus patients: a single-centre study from China

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Abstract

Objective

Cerebral venous sinus thrombosis (CVST) is a rare complication of childhood-onset SLE (cSLE) and is potentially fatal to the patient. In order to better define the characteristics of CVST in cSLE, we analysed a single-centre study of cSLE presenting with CVST.

Methods

Clinical characteristics and laboratory findings of cSLE patients complicated with CVST from January 2006 to December 2019 were analysed through this retrospective, single-centre study.

Results

A total of 1395 records of cSLE patients were reviewed. Five patients (0.36%) had CVST. Headache (80%) was the most frequent symptom. The transverse sinus (45%) was the most frequent location of thrombus, followed by the sigmoid sinus (27%). The SLE disease activity index (SLEDAI) at the time of CVST was 11±3. The D-dimer was elevated in all 5 cases, only one patient was positive for ACL and anti-β2GP-I IgM. All the patients underwent MRV screen to confirm the diagnosis. All the patients had a favourable outcome after receiving glucocorticoid and immunosuppressant treatment, as well as anticoagulant therapy.

Conclusion

CVST is relatively rare in cSLE and tends to occur in active lupus patients. Severe and persistent headache is an index of CVST. Early diagnosis and more intensive therapy for SLE, combined with anticoagulation therapy, could significantly improve the prognosis of CVST in cSLE.

Key words

cerebral venous sinus thrombosis, childhood-onset SLE, anticoagulation therapy

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Introduction

Systemic lupus erythematosus (SLE) is a chronic, heterogeneous, autoimmune inflammatory disease involving multiple systems. Childhood-onset SLE (cSLE) is associated with greater mortality and a higher rate of major organ involvement comparing to adult SLE (1). Thrombosis event is one of the severe complications of SLE and is an important reason for death (2). It has been widely reported that SLE itself is an independent risk factor for developing arterial and venous thrombotic events (3). Cerebral venous sinus thrombosis (CVST) is a rare complication of SLE and is potentially fatal to the patient if acute neurological deterioration occurs. The incidence of CVST ranges between 1 and 12 cases per 1,000,000 adults per year (4), while it occurs in 0.36% to 1.31% of SLE cases according to some studies (5, 6). The general incidence of childhood CVST is estimated to between 0.4 to 0.7 per 100,000 of all children per year according to previous studies (7-9). Up to now, the incidence of CVST in cSLE is still unknown. The reports on CVST in cSLE are anecdotal (10). Little is known about its clinical characteristics, response to treatment and long-term outcome. An exploration of the epidemiology and characteristics of CVST in cSLE is necessary to define clinical figures of this disease.

In current study, we analysed a single-centre case of cSLE presenting with CVST in a paediatric tertiary hospital (National centre) in China. We evaluated the demographic and clinical manifestations of these patients, aiming to better define the characteristics of CVST in cSLE.

Patients and methods

Patients

Patients admitted to Beijing Children's Hospital from January 2006 to December 2019 were screened by reviewing their medical records. All patients were diagnosed as SLE according to 1997 American College of Rheumatology (ACR) revised classification criteria. Patients with CVST, diagnosed based on the patients' clinical features and magnetic resonance venography (MRV) according to diagnostic criteria, and at least one neurologist's confirmation, were included in the present study.

Methods

The demographic information (age, gender), clinical manifestation, treatment, duration of the disease and outcome were captured. The laboratory investigations included blood count, D dimer, autoimmune and vasculitis markers (antinuclear antibody, anti-double stranded DNA, extractable nuclear antigen antibody, antineutrophil cytoplasmic antibody, C-reactive protein, and C3, C4, urine protein et al.) were collected. The results of cerebral spinal fluid (CSF) and cranial magnetic resonance imaging (MRI) with MRV, including the evidence of venous sinus thrombosis, were collected.

Outcome was evaluated by modified Rankin Scale (mRS) on discharge and at 1, 3, 6, 12 months after discharge. The outcome was categorised into poor (mRS >2) and good (mRS ≤2) (11).

Because the study was based on a review of medical records that had been obtained for clinical purposes, the requirement for written informed consent was waived.

Statistical analyses

The statistical package SPSS (v. 25.0; SPSS Inc., Chicago, IL) was used for the statistical analyses. Categorical variables are shown as frequencies and percentages. Continuous variables are presented as the mean ± standard deviation. $p<0.05$ was defined as statistically significant.

Results

A total of 1395 cSLE were reviewed. Of these patients, 27 cases had thrombosis, accounting for 1.94% of all the patients, with 5 patients (0.36%) having CVST. All (100%) of the 5 patients with CVST were female with mean age of 12.98±1.43 years. The median duration from diagnosis of SLE to CVST was 13 days (10 days before to 2 months after diagnosis). The demographic and clinical features of the CVST patients with cSLE are presented in Table I. The presenting symptoms and signs included persistent headache in 80% (4/5) patients, nausea and/or vomiting in 40% (2/5) patients, dizzi-

Table I. Demographic and clinical features of CSVT patients with cSLE.

Parameter	Value (frequency%)
Age	12.98±1.43 years
Gender	
Female	5 (100%)
Male	0
CVST as initial feature of cSLE	2 (40%)
Clinical features of CVST	
Persistent headache	4 (80%)
Nausea/vomiting	2 (40%)
Dizziness	1 (20%)
None	1 (20%)
Number of sinuses involved	
1 sinus	0
2 sinuses	4 (80%)
3 sinuses	1 (20%)
Site of CVST occlusion	11
Superior sagittal sinus	2 (18%)
Transverse sinuses	5 (45%)
Sigmoid sinuses	3 (27%)
Inferior sagittal sinus	0
Straight sinus	1 (9%)
Cavernous sinuses	0
Thrombosis site except CVST	
Renal vein	1
Inferior cava vein	1
Internal jugular vein	1
Outcome	
Good	5
Poor	0

ness in 20% (1/5) patient. Patient 2 did not have any symptoms of CVST. She was admitted to the hospital for pain in renal area, and was found having renal vein and inferior cava vein thrombosis. After MRI and MRV screen, she was diagnosed as CVST. Three patients (patient 1, 3 and 5) had CVST only. Two patients (patient 2 and 4) had more than one thrombotic localisation. Patient 2 had renal vein and inferior cava vein thrombosis. Patient 4 had Internal jugular vein thrombosis. In two cases (patient 4 and 5), CVST occurred as an initial manifestation. both of them came to the hospital for headache and vomiting, and were admitted to the hospital with the diagnosis of SLE. With MRV images, we found that all patients suffered from more than one sinus thrombosis. In total, 11 sinuses were involved in 5 patients. Thrombosis in the transverse sinus was the most common site (5/11, 45%), followed by sigmoid sinus (3/11, 27%). Thrombosis in the superior sagittal sinus (2/11, 18%) and straight sinus (1/11, 9%) was also identified.

Haematologic disorder, neurologic disorder, and lupus nephritis was diagnosed in four, three and two patients, respectively. The SLE disease activity index (SLEDAI) at diagnosis SLE was 12±5, while at the time of CVST was 11±3. Table II summarises the clinical manifestation of all the patients.

The laboratory results of all the patients are summarised in Table III. Routine blood tests showed that the WBC levels ranged from 2.52 to 13.89×10^9/L. The haemoglobin levels ranged from 113 to 141 g/L. The platelet levels ranged from 50 to 158×10^9/L. Three patients had thrombocytopenia. The value of CRP ranged from 8 to 78 mg/L. The value of ESR ranged from 6 to 92mm/h. Elevations in CRP and ESR were found in patient 1 though patient 3. Only patient 4 who had multiple thrombosis including renal vein infarction was positive for urine protein (1.65 g every 24 h). The urine blood qualitative test was positive, ranging from 2+ to 3+ in 3 cases. The D-dimer was elevated in all of 5 cases, ranging from 0.30 to 19.91ng/mL. ANA was positive with high titres in 5 cases (100%), patient 2 and patient 4 had positive anti-double-strand DNA (anti-dsDNA) antibodies. The C3 and C4 levels were decreased, with average level of 0.84±0.42g/L and 0.35±0.05 g/L respectively. Among the 5 cases, only patient 4 was positive for ACL and anti-β2GP-I IgM. The patient had internal jugular vein, sigmoid and transverse sinuses thrombosis. The other 4 cases were negative for LA, ACL and anti-β2GPI. All patients underwent lumbar puncture. The protein level in cerebrospinal fluid (CSF) was as high as 2084mg/L in patient 1, with normal glucose and chloride levels. WBC in CSF of the patient was as high as 714×10^6/L, with 75% of monocyte. While CSF pathogen test (including bacterial, virus and fugi) was negative. The level of D-dimer of the patient was as high as 19.91ng/mL. Biochemical analyses and WBCs were normal in the other four patients. Myelin basic protein (MBP) was normal in all the five patients. All the patients underwent testing to identify congenital or acquired thrombophilia defects. Protein C, protein S and antithrombin III were normal.

All patients received glucocorticoid (GC) combined with immunosuppressant treatment. Three patients (patient 1, 2 and 4) were treated with cyclophosphamide (CTX). The other 2 patients were treated with cyclosporine. All the 5 patients were treated with pulse methylprednisolone therapy for 3 to 5 days at the beginning of diagnosis.

All the five patients were treated with subcutaneous low molecular weight heparin in the acute phase after their thrombosis, followed by long-term oral warfarin, patient 4 was switched to rivaroxaban after LMWH treatment. Patient 2, who had renal infarction and CVST, had combined therapy with aspirin and oral warfarin.

The follow-up time of the 5 patients ranged from 5 months to 25 months, with five patients attending the 1-month and 3-month visit, four patients attending the 6-month visit, and two patients attending the 1-year and 2-year visits. All the 5 patients had mRs scores of 0–1 at the follow up visits. CVST was recovered in 23 days in patient 1. Over the 2 years of visits, her disease was stable with no reoccurrence of the thrombosis, nor any neurologic symptoms. The thromboses in the other 4 patients reduced in size.

Discussion

Cerebral venous sinus thrombosis is a rare manifestation of SLE, especially in cSLE. In this study, we described clinical characteristics, laboratory results, radiological findings, and outcomes of 5 CVST patients with cSLE in a single-centre cohort. In the current cohort, the incidence of CVST was about 0.36% among the cSLE patients, which is similar to a report in adult SLE (5).

All the patients were female. The high incidence rate of CVST in female is similar to the findings in the studies on adults SLE, which may be explained by that both CVST and SLE affected females more frequently. The higher incidence rate in female in our cohort may be because of the small sample size.

In the cohort of the present study, the median duration from diagnosis of SLE to CVST was 13 days. It looks that CVST occurs early in the disease course. Many patients had active dis-

Table II. Systemic manifestations of SLE patients with CVST.

Patient number	1	2	3	4	5
Gender	Female	Female	Female	Female	Female
ACR criteria	M, A, N, I, P	M, O, K, H, P	O, P, H, p	N, H, I, P	K, N, H, P
Age of CVST	14y6m	14y2m	13y1m	12y10d	11y17d
Duration from diagnosis of SLE to CVST (days)	13	30	60	10 before SLE	0
SLEDAI on diagnosis of SLE	19	11	4	13	11
SLEDAI on diagnosis of CVST	6	14	10	13	11
Chief complaint of CVST	Headache	pain in renal area	Headache, Nausea vomiting	Headache, dizziness	Headache, Nausea vomiting
Site of CVST occlusion	Transverse sinuses; Superior sagittal sinus	Transverse sinuses; Sigmoid sinuses	Transverse sinuses, Superior sagittal sinus	Transverse sinuses; Sigmoid sinuses	Transverse sinuses; Sigmoid sinuses
Treatment	GC+CTX	GC+CTX	GC+CSA	GC+CTX/MMF	GC+CSA
Anticoagulation	LMWH	LMWH+aspirin	LMWH	LMWH /Rivaroxaban	LMWH
Outcome	Good (CVST recovered)	Good (thrombosis reduces)	Good (thrombosis reduces)	Good (thrombosis reduces)	Good (thrombosis reduces)

ACR criteria: M: malar rash; A: non-erosive arthritis; H: haemocytopenia, K: kidney disease, N: neurological involvement; I: immunologic disorder; O: oral ulcers; P: positive ANA; p: pleuritis or pericarditis,
Treatment: GC: glucocorticoid; CTX: cyclophosphamide; MMF: mycophenolate mofetil. CSA: cyclosporine; LMWH: low molecular weight heparin.

Table III. The laboratory results of CVST patients.

Patient number	1	2	3	4	5
WBC ($\times 10^9$/l)	4.67	13.89	12.43	2.52	5.46
Hb (g/l)	113	121	141	120	135
PLT ($\times 10^9$/l)	158	50	96	143	88
CRP (mg/l)	78	73	11	8	8
Urine protein	Neg	2+(1648mg/24h)	Neg	Neg	Neg
Urine blood	2+	3+(RBC 100-200/HPF)	2+	(-)	(-)
D-dimer (ng/ml)	19.911	1.897	0.796	0.479	0.301
Fib (g/L)	3.73	4.72	3.85	2.09	1.87
ESR (mm/h)	48	92	12	9	6
C3 (g/l)	1.54	0.83	0.77	0.39	0.7
C4 (g/l)	0.29	0.32	0.34	0.39	0.4
ANA	1:1280	1:160	1:1280	1:2560	1:40
dsDNA	Neg	1:10	Neg	1:640	Neg
anti-protein C/S, Antithrombin III	Normal	Normal	Normal	Normal	Normal
ACL	Neg	Neg	Neg	Positive	Neg
LAC	Neg	Neg	Neg	Neg	Neg
β2 GP1 IgM	Neg	Neg	Neg	Positive	Neg

WBC: white blood cell; Hb: haemoglobin; PLT: platelet; Neg: negative; CRP: C-reactive protein; Fib: fibrinogen; ESR: erythrocyte sedimentation rate; ANA: antinuclear antibody; ACL: anticardiolipin antibody: LAC: lupus anti-coagulant; β2 GP1 IgM: anti-β_2-glycoprotein I antibody; HPF: high power field; Neg: negative.

ease at diagnosis of SLE. The active vasculitis could lead to increased venous pressure, decreased capillary perfusion pressure, and increased cerebral blood volume (4). As a result, CVST may occur. Therefore, we recommend to monitor the manifestations of CVST intensively for newly diagnosed SLE patients with active disease or high SLEDAI score.

The main neurologic manifestations of CVST in cSLE in our study were similar to those reported in adults. The clinical manifestations of CSVT were non-specific. Headache was the most common complaint at the admission of the patients in our study. Neurologic involvement, that can also manifest as headache, occurs in approximately 50% of cSLE. Migraine headache may also occur and may be a sign of central nervous system involvement of SLE (12). The diagnosis of isolated CVST in cSLE remains a particular challenge. While most lupus headaches are chronic and are not accompanied by increased intracranial pressure or other neurological signs. Severe, persistent headache raised the index of suspicion to the possibility of CVST and is an indication for radiologic evaluation (13). Besides headaches, about half of patients developed other neurological symptoms as seizures, papilledema, and hemiparesis indicating the location of thrombosis. Early detection is critical for suspicion or differential diagnosis. The clinical findings of CVST also vary depending on the veins or sinuses obstructed. In our study, in contract to the symptoms of other patients, one patient did not have any neurologic symptom, but had renal pain with renal infarction. It is possible that multiple vascular injuries and active SLE are risk factors for CVST. Vasculitis due to endothelial cell injury mediated by immune-complex deposition is proposed

to lead to CVST in SLE (14). Two patients had more than one thrombotic localisation in this report, which indicates multiple vascular injuries happened in these patients. Regarding the location of thrombosis, the transverse and sigmoid sinuses were involved most frequently in our patients, sagittal sinus was in the third place, which is consistent with the report in other study (6). In our cases, all the patients had more than one sinus involvement, which was higher than the report in adults SLE (5, 6). In two cases, CVST was the initial presentation of SLE. It is important to identify SLE at the diagnosis of CVST, as this may alter treatment strategies and the outcome.

As mentioned before, in SLE, the thrombosis might be caused by active vasculitis. The SLEDAI in SLE patients with CVST were high. These patients also had high titre of ANA, hypocomplementemia, and increased ESR and D dimer, which means most patients had active disease at the onset of CVST. Most of the patients in our study had thrombocytopenia that could be the result of depletion of platelets and autoantibody damage. As is the case in adults, CSVT in children is often multifactorial in aetiology. The common factors include infection, positive antiphospholipid antibodies (APLs), D-dimer, etc. (13). Analysis of the CSF through lumbar puncture is almost always non-specific but it is necessary to differentiate infections. It is observed in a large cohort that infections could be risk factors for arterial or venous thromboses in patients with SLE (15). All of our patients underwent lumbar puncture. According to a report in adults, the existence of APLs may be another cause of CVST in SLE. LA and anticardiolipin antibodies are present in about 40% of SLE patients with CVST (16). However, in our cases, only one patient had positive ACL and anti-β2GPI, which emphasises SLE-related vasculitis as the underlying mechanism in most CVST. It is notable that only patient 2 in our group had nephrotic grade proteinuria, while this patient had multiple location thrombosis including renal vein and inferior cava vein. It was reported that patients with nephrotic syndrome was prone to have thrombosis, because of hypercoagulable state subsequent to membranous disease due to loss of antithrombotic factors (17). It is known that D-dimer (DD) levels correlate with deep vein thrombosis (18) It has been reported that DD concentration, especially in headache patients, may be a factor to predict CVST and an indicator for further diagnostic procedures (19). In the present study, DD were elevated in all cases and was as high as 19.91ng/ml in one case. DD might be an indicator for CVST, although elevation of DD is not rare in SLE. It was reported that multiple venous sinus involvement was more common in the elevated DD group (20). In the present study, all 5 SLE patients with CVST also had multiple sinus thrombosis. Antithrombin III, protein C, and protein S deficiencies are relatively common predisposing conditions to the development of CVST (22). In our patients, the results of these tests were normal in all 5 patients. When CVST is suspected, a radiology study is a useful tool to confirm the diagnosis (23). Filling defects in MRV and/or CT angiography in the venous phase is quite sensitive for the diagnosis of CVST (24). The optimal technique for establishing the diagnosis in children is MRI with MRV. MRI is the most widely used technique and diagnosis requires visualisation of the thrombus within the vessel in combination with absent flow on MR-venography (25) In this study, all the patients underwent MRV screen, and the diagnosis of CVST was determined by imaging as well as clinical manifestations.

CVST is a rare but severe disease. Early diagnosis and treatment are the key to a favorable prognosis. Anticoagulant therapy with LMWH is recommended for all CVST diagnosed patients with cSLE. Following clinical improvement, oral anticoagulation with warfarin for 3–6 months is recommended (26). In our study, the underlying cause of CVST was SLE. The current study showed that these cases had high SLE activity and rapid disease progress. They were given glucocorticoids (GC) combined with immunosuppressant treatment, and received pulse methylprednisolone therapy right after diagnosis of SLE, with a good outcome. In our study, All five patients with CVST were treated with immunosuppressants because of the severity and complication of the SLE. In accordance with the guidelines, publications and based on our experience, three patients (patient 1, 2 and 4) were treated with cyclophosphamide (CTX) for SLE with neurologic disorder, renal involvement, and/or antiphospholipid syndrome (27, 28). The other 2 patients were treated with cyclosporine for SLE with lupus thrombocytopenia (29).

In children, CSVT-specific mortality is less than 10%, but neurologic deficits are present at the time of discharge or follow-up examination in 17% to 79% of survivors (13). All the patients in the present study achieved a good outcome, which could be attributed to the early diagnosis and treatment.

There were several limitations of our study. Because CVST is a rare complication of SLE, our study is limited by its small size. Since it is a single-centre study, we could not know the exact prevalence of CVST in cSLE. A longer follow-up time would provide more data on the prognosis of the CVST in cSLE.

Conclusions

In conclusion, CVST was found in 0.36% of cSLE patients. Headache was the most frequent symptom. The transverse sinus was the most frequent location of thrombus, followed by the sigmoid sinus. The patient outcomes were favourable overall. CVST, a rare but severe complication, should be suspected in cSLE patients with headache. Lumbar puncture and MRV are necessary for differential diagnosis and establishing a diagnosis of CVST. Early diagnosis and more intensive therapy for SLE, combined with anticoagulation therapy, could significantly improve the prognosis of CVST in cSLE.

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