국내 소아 뇌정맥혈전증의 임상적, 영상의학적 특징

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Clinical and Radiologic Features of Pediatric Cerebral Venous Thrombosis in Korea

Purpose: Cerebral venous thrombosis (CVT) is a rare cause of pediatric stroke. Our goal was to describe the clinical CVT features among pediatric patients presenting at a tertiary referral center.

Methods: Patient data was retrospectively collected from the charts of all pediatric patients (newborn to 18 years old) who were diagnosed with CVT at Seoul National University Children's Hospital between 2000 and 2016. Magnetic resonance imaging or venography was conducted for diagnostic confirmation. Modified Rankin Scale (mRS) was used to evaluate neurologic outcome.

Results: Twenty patients were diagnosed with CVT during the study period (16 male, 4 female). Median age was 4 years. The most common risk factor was systemic infection (6/20, 30.0%). Twelve patients initially presented with headache or vomiting (12/20, 60.0%). Seizure was in only 3 patients within 48 hours of symptom onset; however, as the clinical course progressed, seizure was the symptom that most frequently led to brain imaging (12/20, 60.0%). Thrombosis in the superior sagittal sinus was frequently associated with intracranial hemorrhage (4/11, 36.4%) and clinical seizure (9/11, 81.8%). Anticoagulation and/or antiplatelet agents were used in 16 patients (16/20, 80%). At the 3-month follow-up, 14 patients (14/20, 70%) had an mRS of 0 or 1, showing that most of these patients had no neurologic impairment.

Conclusion: Seizure and signs of increased intracranial pressure are the most common manifestation of pediatric CVT. However, clinical features are diverse and include age at symptom onset and underlying risk factors. Despite diagnostic delay, neurologic outcome is favorable in most patients.

Key Words: Cerebral venous thrombosis, Pediatrics, Anticoagulation, Outcome

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Introduction

The annual incidence of pediatric stroke is estimated to be 1.3–13/100,000¹⁾. Cerebral venous thrombosis (CVT), an unusual and rare cause of stroke, refers to thrombotic obstruction of the cerebral veins and sinuses that may lead to increased intracranial pressure (IICP) and venous ischemic or hemorrhagic infarction²⁾.

Compared with other adult populations, females under 40 years of age who are pregnant or receiving hormonal contraceptive therapy have a relatively

higher prevalence of CVT³). Genetic or acquired thrombophilia, chronic conditions such as malignancy, and chronic inflammatory diseases are other risk factors⁴). Patients may complain of headache, vomiting, or stroke-like symptoms. However, pediatric CVT has varied risk factors and manifestations^{5,6}). Moreover, annual incidence estimates of pediatric CVT are much lower than among adults: 0.34–0.67/100,000 children⁷). To date, few cases of pediatric CVT have been reported in Korea^{8–10}).

Thus, our goal was to report our clinical experience with pediatric CVT for more than 10 years. This is the first retrospective, descriptive cohort study of pediatric CVT in Korea. We present pediatric CVT patients' clinical and radiologic features throughout their clinical courses, including predisposing factors, treatment, and outcomes.

Materials and Methods

Twenty patients diagnosed with CVT based on magnetic resonance imaging or magnetic resonance venography at Seoul National University Children's Hospital from 2000 to 2016 were included. Above 18 years of age was excluded. We reviewed clinical and radiological data, including risk factors, presenting symptoms and signs, laboratory tests results, involved sites, treatments, and outcomes. Clinical outcome was measured using the modified Rankin Scale (mRS), which was previously developed for assessing global outcomes among stroke patients. The mRS uses a 0–6-point scale (0: no symptoms; 1: minor, non-neurologic symptoms; 2: mild impairment; 3: moderate disability; 4: moderately severe disability; 5: severe disability; 6: death). Patients' neurologic disabilities were evaluated at 3, 6, and 12 months after diagnosis.

Results

1. Demographics

Among the 20 patients whose charts were reviewed, 14 were male (70.0%) and 6 were female (30.0%). Median age at

symptom onset was 4 years (range, 20 days to 17 years). Median duration from symptom onset to diagnosis was 13 days (0–59 days). Identified risk factors were: systemic infection, such as sepsis and meningitis (n=6, 30%); local infection, including otitis media and mastoiditis (n=4, 20.0%); undiagnosed neurologic disease (n=2, 10.0%); IgA nephropathy (n=1, 5.0%); acute lymphoblastic leukemia (n=1, 5.0%); transposition of great artery (n=1, 5.0%); and trauma (n=1, 5.0%). Four patients had no noticeable risk factor (n=4, 20.0%). None of these patients had underlying coagulopathy. Detailed demographics, presenting symptoms, radiologic features, and clinical outcomes are summarized in Table 1.

2. Clinical symptoms and signs

1) Initial presentation

Vomiting or headache, symptoms of IICP, were the most common initial presentation (n=12, 60.0%), followed by fever (n=8, 40.0%), focal neurologic signs (n=3, 15.0%), otalgia (n=3, 15.0%), and seizure (n=2, 10.0%). Among the 3 patients who complained of otalgia, 2 (2/3, 66.7%) also had headache and vomiting at their initial hospital visit.

2) Manifestations throughout the clinical course

Because of the significant delay in diagnosis and the prolonged clinical course, clinical symptoms and signs often changed or accrued throughout the clinical course (Fig. 1). Again, IICP was the most common feature (n=12, 60.0%). However, presenting with seizure was equally prevalent (n=12, 60.0%). Focal neurologic signs (n=8, 40%) were also revealed across the progression of the clinical course and included motor

Fig. 1. Frequency of clinical symptoms and signs at initial presentation and during clinical course. IICP, increased intracranial pressure (e.g., headache, vomiting, and papilledema).

Table 1. Associations Between Infarction, Neurologic Symptoms, and Thrombus Location

	SSS only n=5	SSS+others n=6	TS or Sg n=7	Others* n=2
Infarction, ischemic (n=7)	3	2	1	1
Infarction, hemorrhagic (n=4)	2	2	0	0
Seizure (n=12)	4	5	2	1
Focal neurologic sign (n=8)	2	3	2	1

*Straight sinus or cavernous sinus.

SSS, superior sagittal sinus; TS, transverse sinus; Sg, sigmoid sinus.

weakness (n=5, 25.0%); cranial nerve palsy (n=2, 10.0%); dysarthria (n=2, 10.0%); and numbness (n=1, 5.0%).

3. Laboratory test results

Prothrombin time/activated partial thromboplastin time (n=19), D-dimer (n=10), antithrombin III (n=12), protein C/S (n=13), Lupus anticoagulant (n=9), homocystein (n=3), anticardiolipin antibody IgG/M (n=9), Factor V Leiden gene (n=4), and prothrombin G20210A (n=4) results were available. The results showed that no patient has underlying coagulopathy or vasculitis.

Group B streptococcus (n=1), *Enterococcus faecalis*+*Acinetobacter baumannii* (n=1) were cultured in peripheral blood. Rotavirus (n=1) and enterovirus (n=1) were also found in fecal specimen. No other pathogens were detected in most of the patients.

4. Anatomic location and associated clinical features

The superior sagittal sinus (n=11, 55.0%) and transverse sinus (n=11, 55.0%) were the most predominant sites of thrombosis (Fig. 2A-C). Concurrent involvement of the superior sagittal and transverse sinus was also detected in 5 patients (25%). Superior

sagittal sinus involvement was more frequently associated with infarction (9/11, 81.8%) and seizure (9/11, 81.8%) compared with transverse sinus or sigmoid sinus (infarction: 1/7, 0%; seizure: 2/7, 28.6%). Hemorrhagic infarction was found only in patients with superior sagittal sinus involvement (4/11, 36.4%) (Table 2).

5. Treatment and outcome

Of these 20 patients, 16 (80.0%) were administered at least one anticoagulant or antiplatelet agent. Median total treatment duration was 5.1 months (range, 1 day to 18.1 months). Median specific treatment durations were: 11 days with heparin; 6.7 months with warfarin; and 5.5 months with aspirin.

Fifteen patients (14/20, 70.0%) showed an mRS of 0 or 1, and 6 patients (6/20, 30.0%) had an mRS of 2 or higher at their 3-month follow-up. Two of 20 patients died after their 6-month follow-up (2/20, 10.0%); their underlying predisposing conditions were unidentified. There was no significant change of patients' mRS score at the 12-month follow-up.

Discussion

Although advances in neuroimaging techniques have increa-

Fig. 2. Location of thrombus in cerebral venous sinus among 20 patients (multiple thrombus locations in 1 patient counted separately). B. MRV shows filling defect at superior sagittal sinus (white arrow). C. MRV shows filling defect at transverse sinus (white arrow)

sed CVT diagnostic accuracy, clinical suspicion about diverse clinical features may play a critical role in early diagnosis and treatment. The most frequent risk factors were systemic or localized (i.e. otitis media and mastoiditis) infections, which were present in half of our patients (10/20, 50%). The most frequently presented symptoms were headache and vomiting (12/20, 60%), which could be the results of IICP. Additionally, associated seizure activity increased markedly across these patients' clinical courses. Although this combination of clinical features may not specifically indicate CVT, brain imaging should be considered. Further, CVT should be included in the differential diagnosis when analyzing brain imaging findings.

Several studies have addressed neurological outcome according to the distribution of thrombus and association with

infarction. Deep cerebral venous sinuses tend to cause more severe neurological impairment⁴⁾, and hemorrhagic infarction has also been associated with poor neurological outcome^{11,12)}. Consistent with a previous study¹³⁾, we found that the superior sagittal sinus was most frequently involved, along with transverse or sigmoid sinus. We also noticed that the superior sagittal sinus was more frequently associated with hemorrhagic infarction compared with the transverse or sigmoid sinus. Although 4 out of 5 of our patients with poor neurologic outcome at the 3-month follow-up showed superior sagittal sinus involvement, a large pediatric cohort study recently showed no relationship between neurologic outcome and distribution of thrombus or concomitant hemorrhage¹⁴⁾. Thus, this should be further addressed in future studies of clinical and radiologic features

Table 2. Patient Data

Patient	Sex	Onset age	Risk factor	Initial presentation	Reason for brain imaging	Location of thrombus	Infarction	Treatment	mRS at discharge	mRS at 3 m	mRS at 6 m	mRS at 12 m	Last follow-up
1	M	21 d	sepsis	fever	seizure	SS, TS	No	No	3	3	3	-	spasticity
2	M	1 mo	sepsis	vomiting, fever	seizure	SS	Ischemic, hemorrhagic	LMWH	0	0	0	0	asymptomatic
3	M	1 mo	sepsis	vomiting	seizure	SS, TS, St	Hemorrhagic	LMWH	1	0	0	0	asymptomatic
4	M	2 mo	meningitis	vomiting, fever	fever, vomiting	TS, Sg	No	LMWH+WFR	0	0	0	0	asymptomatic
5	F	3 mo	sepsis	vomiting	seizure	SS, TS	Hemorrhagic	LMWH	3	3	-	-	DD
6	M	3 mo	unknown disease	fever, seizure	seizure, nystagmus	SS, TS	No	LMWH+WFR	4	4	4	6	expired
7	F	8 mo	TGA	seizure	seizure	TS, Sg	No	LMWH+WFR+ASA	0	0	0	0	asymptomatic
8	F	1 yr	trauma	trauma	seizure	SS (diffuse)	Ischemic	LMWH	3	2	2	1	cervical spine instability
9	M	2 yr	unknown disease	L/E weakness	seizure, LOC	Cav	Ischemic	UFH	6	-	-	-	expired
10	M	3 yr	otitis media	otalgia	seizure	Sg	No	LMWH	0	0	-	-	asymptomatic
11	M	4 yr	meningitis	HA, vomiting	symptom aggravation	TS, St	No	LMWH+WFR	0	0	0	0	asymptomatic
12	M	5 yr	none	HA, vomiting	progressive HA	TS, Sg	No	LMWH+WFR	0	0	-	-	asymptomatic
13	F	5 yr	none	ocular pain, behavior change	papilledema	SS	No	No	1	1	1	-	HA
14	M	6 yr	otitis media	otalgia, HA, diplopia	papilledema, left esotropia	TS, Sg	No	Abx	1	1	1	-	HA
15	M	11 yr	otitis media	HA, vomiting	recurrent HA, vomiting	TS, Sg	No	UFH+WFR	1	1	1	1	HA
16	F	11 yr	none	Left hand weakness, facial palsy	Left hand weakness, facial palsy	SS, TS, Sg	Ischemic	ASA	2	1	-	-	HA
17	F	11 yr	IgA nephropathy	HA, seizure	seizure, left hemiparesis	SS	Hemorrhagic	LMWH, ASA	0	0	0	0	asymptomatic
18	M	13 yr	none	fever, dysarthria	dysarthria	Sg	Ischemic	LMWH+WFR	0	0	1	1	tinnitus
19	M	15 yr	ALL	Right arm numbness, dysarthria	seizure	SS, Co	Ischemic	Cessation of L-asparaginase	1	1	1	0	asymptomatic
20	F	17 yr	none	HA	seizure, L/E weakness	SS	Ischemic	LMWH+WFR	1	1	1	1	depression

mRS, modified Rankin Scale; TGA, transposition of great artery; L/E, lower extremity; HA, headache; LOC, loss of consciousness; SS, superior sagittal sinus; TS, transverse sinus; St, straight sinus; Sg, sigmoid sinus; Cav, cavernous sinus; Co, cortical vein; LMWH, low molecular weighted heparin; WFR, warfarin; ASA, aspirin; UFH, unfractionated heparin; DD, developmental delay.

that predict neurological outcome.

The European Pediatric Neurology Society and the French Society for Pediatric Neurology have both recommended using anticoagulation therapy in acute phase CVT in neonates and children in the absence of any contraindication¹⁵⁾. Many studies have supported the use of anticoagulants in children as safe¹⁵⁻¹⁸⁾. Among the 15 patients we treated with anticoagulants (15/20, 75%), 11 had no or mild symptoms (11/15, 73.3%) at their 3-month follow-up. Although we could not directly compare treated and untreated groups, this profile of favorable neurological outcomes may have resulted from our active use of anticoagulation treatment. Since favorable outcomes have also been reported in many previous studies in which anticoagulation treatments were used, anticoagulation treatment should be considered in acute phase pediatric CVT in the absence of contraindication.

We reviewed 20 patients to develop this first Korean descriptive report of pediatric CVT. Although diverse clinical manifestations and underlying conditions may cause diagnostic delay, more than two thirds of our patients had good clinical outcomes and none had an adverse reaction to anticoagulant therapy. Further large, prospective research is needed to investigate the prognostic role of early anticoagulant treatment in CVT.

요약

목적: 뇌정맥혈전증(CVT)은 소아 뇌졸중의 드문 원인이며 다양한 임상양상과 임상양의 인식 부족으로 인해 진단 지연이 흔히 있을 수 있다. 본 연구에서는 단일 3차 어린이병원에 내원한 소아 뇌정맥혈전증 환자들의 임상적 특징에 대해 기술하고자 한다.

방법: 2000년부터 2016년까지 자기공명영상 또는 자기공명정맥조영술로 진단된 18세 이하 소아 뇌정맥혈전증 환자의 임상양상, 혈전이 생긴 부위, 치료, 결과 등에 대한 의무기록 자료를 후향적으로 분석하였다. 퇴원 시와 퇴원 후 3, 6, 12개월에 modified Rankin Scale (mRS) 을 사용하여 신경학적 예후를 평가하였다.

결과: 연구기간 동안 20명의 환자가 뇌정맥혈전증으로 진단되었다. 20명 중 14명은 남자 (14/20, 70%), 6명은 여자 (6/20, 30.0%) 였고 중간값 나이는 4세였다(생후 20일-17세). 가장 흔한 위험요인은 전신 감염이었고(6/2, 30.0%) 12명의 환자가 첫 증상으로 두통과 구토를 보였다(12/20, 60.0%). 처음 증상이 시작되고 48시간 동안 3명의 환자만이 경련을 보였으나 경과가 진행되면서 뇌영상을 찍게 되는 가장 흔한 원인은 경련이었다(12/20, 60.0%). 증상 발생 후 진단 시까지 걸린 시간은 중간값으로 13일이었다(0-59일). 위시상정맥굴에 혈전이 발생하였을 경우 뇌내출혈 (4/11, 36.4%)과 임상적 경련 (9/11, 81.8%)이 흔히 연관되었으며 항 혈전제 또는 항혈소판제 치료는 16명 (16/20, 80%)의 환자에서 투여되었다. 진단 후 3개월째 추적관찰에서

14명 환자 (14/20, 70%)의 mRS 는 0 또는 1 이었고, 이는 3분의 2 이상의 환자에서 신경학적 장애가 없었다는 것을 보여주었다.

결론: 경련과 뇌압상승 징후가 소아 뇌정맥혈전증에서 가장 흔한 임상 양상이었으나 진단 시 나이와 기저요인들을 포함한 임상적 특징들은 다양하였다. 진단 지연이 있음에도 불구하고 대부분의 환자에서 신경학적 예후는 양호하였다.

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