

Cerebral venous sinus thrombosis: an analyses of 47 patients

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Abstract. – OBJECTIVE: Cerebral venous sinus thrombosis (CVST) is an extremely rare disease and its early treatment is important for decreasing the morbidity and mortality. In present study, it was investigated to clinical and etiological factors, localization features, treatment, and prognosis of patients with CVST.

PATIENTS AND METHODS: The study group included CVST cases who were followed up between January 2008 and June 2010. Demographical, clinical, radiological, etiological and prognostic characteristics of 47 patients with CVST were retrospectively investigated.

RESULTS: Presentation complaints of the patients were as follows in order: acute and/or sub-acute headache (80.8%), impaired consciousness (25.5%), ear complaints (21.3%), paresis (19.1%) and epileptic seizures (14.9%). Chronic daily headache without any signs of neurological deficit was found in 10.6% of cases. Neurologic examinations of 40.4% of the CSVT patients were found to be normal. The most frequently found etiological factors were as follows: MTHFR gene mutation (25.5%), local infections due to chronic otitis complications (21.3%), puerperium (17%), pregnancy (12.8%), lupus anticoagulant positivity (12.8%). The sigmoid sinus was found to be involved in 35 patients (74.5%), the transverse sinus in 29 (61.7%) and superior sagittal sinus in 21 (44.7%). Impaired consciousness ($p = 0.046$), hemorrhagic infarct ($p = 0.017$), acute onset ($p = 0.026$), and presence of hemiparesis ($p = 0.019$) were found to be associated with increased mortality.

CONCLUSIONS: New onset sub-acute or chronic headache may be the only neurologic complaint of CVST patients. Early diagnosis and anticoagulant treatment may decrease mortality and/or morbidity rates related with CVST in these patients.

Key Words:

Cerebral venous sinus thrombosis, Etiology, Headache, Radiological evaluation, Prognosis.

usually present with one or more of the clinical conditions related to increased intracranial pressure such as headache, acute or sub-acute neurologic deficits, seizures and impaired consciousness. Less frequently cases may present only with chronic headache. When CVST is the suspected diagnosis, magnetic resonance venography (MRV) may be a useful tool to confirm the diagnosis^{2,3}. CVST is a condition that may result with death. However, early anticoagulant therapy may lead to dramatic clinical improvement. Many causes are thought responsible for etiology. Pregnancy, puerperium, use of oral contraceptives, coagulopathies, intracranial infections, cranial tumors, penetrating head injuries, malignancies, dehydration, inflammatory bowel disease, connective tissue disorders such as systemic lupus erythematosus (SLE), Behcet's disease, sarcoidosis, nephrotic syndrome, parenteral infusions and various medications were found to be related with the etiology. The real etiological factors cannot be determined in 20-25% of the cases^{1,4}. Factors indicative of poor prognosis are advanced age, progressive deterioration of consciousness, diffuse cerebral venous system involvement, significant intracranial pressure increase, being secondary to malignancy, co-morbid hemorrhagic infarcts, complications such as resistant epileptic seizures and pulmonary embolism^{5,6}.

CVST is a rare disease and its early treatment may show dramatic improvements. Therefore, in this study the demographical, clinical, and etiological factors, localization characteristics, and prognoses of the 47 patients with CVST were retrospectively analyzed.

Materials and Methods

Demographical, clinical, radiological, etiological and prognostic characteristics of 47 patients with CVST were retrospectively evaluated. CVST diagnosis was confirmed by Multi-Slice

Introduction

Cerebral venous sinus thrombosis (CVST) is a rare cerebrovascular disease that particularly affects young and middle aged women¹. Patients

Computed Tomography Angiography (MSCTA) and/or MRV. Determination of complete or partial filling defect of at least one sinus at MSCTA and/or MRV was accepted as a sufficient finding for the diagnosis of CVST.

Following assessments were performed for all cases in order to identify the etiology: Biochemical and molecular tests: C-reactive protein (CRP), erythrocyte sedimentation rate, hemogram, protein C, protein S, antithrombin III, homocysteine, anti-nuclear antibody (ANA), antiphospholipid and/or anticardiolipin antibodies, factor V Leiden mutation, prothrombin gene mutation, plasminogen activator inhibitor (PAI) gene mutation, methylene tetrahydrofolate (MTHF) gene mutation, lupus anticoagulant, PT and aPTT. Additionally, relevant evaluations were done for the patients with malignancies.

Serological tests: Anti-HIV, VDRL, borrelia and toxoplasma antibodies were evaluated for required cases.

Consultations: Patergy test, ophthalmology and dermatology consultations were done when the suspected diagnosis was Behcet's disease. Internal medicine consultations were done when the suspected diagnoses were connective tissue or hematologic disorders. Cases with primary ear complaints were assessed and treated by a otolaryngologist. Cerebro spinal fluid (CSF) evaluation and culture was done for required patients.

Patients were divided into three groups as acute, sub-acute and chronic onset according to their presentation times and clinical progresses. Acute, sub-acute and chronic onsets were defined as admission within 48 hours of first complaint, between 48 hours and 30 days, and more than 30 days of onset of first complaint⁷.

Statistical Analysis

The data were analyzed by using Statistical Package for the Social Sciences version 11.5 (SPSS 11.5 for Windows, Chicago, IL, USA). Frequencies of etiological, radiological and clinical data were given in terms of percentages. In order to assess the relationship of age, gender, type of onset or clinical/radiological findings with prognosis Fisher's exact test was used. Statistical significance level was accepted as $p < 0.05$.

Results

A total of 31 (66%) female and 16 (34%) males were included into the study. Mean age of

the total group was 30.2 ± 11.7 (range: 5-65) years. When the patients grouped according to the onset of the complaints: 9 (19.1%) cases were included into acute onset, 23 (48.9%) cases into the sub-acute onset, and 15 (31.9%) cases into the chronic onset groups. Primary complaints of the cases were acute and/or sub-acute headache (80.8%), impaired consciousness (25.5%), local complaints related to ears (21.3%) such as impaired hearing, ear discharge and ear pain, weakness (19.1%), dizziness (19.1%), epileptic seizures (14.9%), dysphasia (4.3%), impaired vision (4.3%) and diplopia (4.3%). In 10.6% of our cases, the only complaint was chronic daily headache without any sign of neurological deficit. Neurologic examination of the cases revealed impaired consciousness (25.5%), hemi-paresis and/or mono-paresis (19.1%), dysphasia (4.3%), papillary edema (38.3%), impaired vision (4.3%), and diplopia (4.3%). Neurologic examination was found as normal in 40.4% of the CVTS patients. Etiological risk factors of CVST patients are shown in Table I. There was more than one risk factor in 27.7% of the cases. On the other hand, in 17% of the cases the cause of CVST could not be determined.

Venous thromboses at jugular vein, sigmoid sinus, transverse sinus, sinus rectus, confluence sinus, superior sagittal sinus were assessed by MRV and/or MSCTA. Venous involvement was found at single area in 36.2% of the patients, at two localizations in 40.4% and at more than two localizations in 23.2% of the cases. We found thrombosis at sigmoid sinus in 74.5% of patients, at transverse sinus in 61.7%, at superior sagittal sinus in 44.7%, at jugular vein in 17%, at sinus rectus in 8.5%, at confluence sinus in 6.4% of our patients. In brain CT and/or MR imaging, hemorrhagic infarct, non-hemorrhagic infarct, cerebral abscesses, and cholesteatoma were found in 38.2%, 2.1%, 6.4%, and 6.4% of the cases, respectively. Treatment with low molecular weight heparin (LMWH) was initiated immediately after CVST diagnosis. Following the LMWH treatment, anti-coagulation therapy was continued by warfarin. Antiepileptic treatment was given to 14.9% of the cases and anti-edema treatment (20% mannitol) was given to 25.5%. Discharged cases were put on warfarin treatment for an average of 6 months. Patients with CVST caused by otitis media and mastoiditis (21.3%) were surgically treated by otolaryngologist. In addition to, a wide spectrum antibiotic treatment was given in these patients. Rate of recovery without any

Table I. Etiological risk factors in respect to frequency for our patients with cerebral venous sinus thrombosis (n = 47).

Risk factors	N	%
MTHF gene mutation	12	25.5
Local infections (chronic otitis media, mastoiditis etc)	10	21.3
Puerperium	8	17
Pregnancy	6	12.8
Lupus antibody positivity	6	12.8
Use of oral contraceptives	5	10.6
PAI gene mutation	5	10.6
Factor V Leiden gene mutation	4	8.5
Protein S deficiency	4	8.5
Hyperhomocysteinemia	3	6.4
Malignancy	3	6.4
SLE	2	4.3
Prothrombin G20210A gene mutation	2	4.3
Protein C deficiency	2	4.3
Antithrombin III deficiency	2	4.3
Antiphospholipid antibody positivity	2	4.3
Behcet's disease	1	2.1
Sepsis	1	2.1

deficit was 85.1%, and 6.4% of the patients recovered with sequel. However, 8.5% of patients died. Three of the 10 patients with acute onset were resulted with death. Impaired consciousness ($p = 0.046$), hemorrhagic infarct ($p = 0.017$), acute onset ($p = 0.026$), and presence of hemiparesis ($p = 0.019$) were found to be associated with increased mortality (Table II).

Discussion

Clinical characteristics, type of onset, radiological, etiological features and prognosis of the CVTS, if not treated early, may vary according to the involved localizations⁸. As previously stated, headache can be the sole clinical manifestation of CVST, but in over 90% of cases it has been associated with focal signs (neurological deficits or

seizures) and signs of intracranial hypertension (subacute encephalopathy, papilledema)⁹. Headache was the most common reason of admission of patients in our study. Interestingly in 10.6% of our cases, chronic daily headache was the sole complaint. Neurological examinations of these cases were normal. Headache of CVST cases may be acute onset, sub-acute with progressive establishment in several days or may be chronic with intermittent onset¹⁰. Usually it is unilateral and throbbing¹⁰. In a study with 200 CVST cases about the localization of headache, only occipital and neck region localization was reported to be associated with sigmoid sinus thrombosis¹¹. Most of our cases with headache (80.8%) had acute/sub-acute onset headache that not localized at any region of the head and was throbbing type. In a previous study, it was reported that impaired consciousness was 22% patients

Table II. Factors affecting mortality in patients with cerebral venous thrombosis.

		Mortality (+) n (%) *	Mortality (-) n (%) *	p^{**}
Impaired consciousness	Yes	3 (25.0)	9 (75.0)	0.046
	No	1 (2.9)	34 (97.1)	
Hemiparesis	Yes	3 (33.3)	6 (66.7)	0.019
	No	1 (2.6)	37 (97.4)	
Hemorrhage	Yes	4 (28.6)	10 (71.4)	0.017
	No	0 (0)	29 (100.0)	
Onset	Acute	3 (12.5)	7 (87.5)	0.026
	Subacute-chronic	1 (0)	36 (100)	

*Percentage of rows, **with Fisher's Exact test.

with CVST⁴. Second most frequent neurologic complaint was impaired consciousness in 25.5% of our cases^{4,8}. Symptoms and signs of otitis complications are high frequent when compared with other studies^{1,4,7,8}. In 21.3% of our cases; fever, ear discharge, ear pain, tenderness at mastoid area and hearing loss were found as otitis complication. Therefore, the presence of offensive otorrhea and headache with intermittent fevers should alert the clinician to the possibility of underlying local infections^{12,13}. Other frequent presentation symptoms were dizziness, weakness of upper and lower extremities, epileptic seizure, disartria, diplopia and decrease of vision^{1,4,7,8}. In a case with diffuse hemorrhagic infarct and brain edema, status epilepticus was developed following resistant focal epileptic seizure. This case was resulted with clinical deterioration and unfortunately death despite antiepileptic treatment. As the most common neurological finding, it was found to impaired consciousness, papilledema, and hemiparesis in our patients with CVST. These findings were similar to previous studies^{1,4,7}. Interestingly, focal neurologic deficit was not determined in 40.4% of our cases.

There are several etiological factors and predisposing factors leading to development of CVST's. Most common risk factors are pregnancy, puerperium, genetic or acquired prothrombotic conditions, local (chronic otitis media, mastoiditis, cerebral abscess and chronic sinusitis) and systemic infections. Approximately in 15% of the cases the cause may not be identified^{4,8}. In a significant proportion of cases two or more etiological risk factors may be determined. After CVST diagnosis pregnancy, puerperium, central nervous system, otologic and rhinologic infections, hematologic diseases, malignancies, lupus anticoagulant, anticardiolipin antibodies, protein S and C deficiencies, antithrombin 3 deficiency, prothrombin G20210A, PAI-1, MTHFR and factor V Leiden gene mutations are assessed to identify the risk factors^{14,15}. Pregnancy, puerperium and use of oral contraceptives are common risk factors determined usually in young women¹⁶. In our study 80.9% of the cases were below 40 years of age and 66% of the cases were women. In pregnancy and puerperium weight gain, immobilization, physiological changes in coagulation system, venous stasis due to pelvic and leg vein pressure and hypercoagulability may cause CVST. In our study, pregnancy, puerperium and use of oral contraceptives were three major risk factors for CVST in women^{4,16-18}. Ad-

ditionally, gene mutations known to cause thrombophilia may increase the risk of CVST in pregnancy and puerperium period^{16,17}. In one of our six pregnant cases protein C and antithrombin 3 deficiencies were found together. One of the eight cases with puerperium had antithrombin 3 deficiency, one had MTHFR gene mutation and one had increased homocysteine. Prothrombotic states, either genetically imposed or acquired, represent a large component of the etiology and play an important role in the development of CVST. Antithrombin III, protein C, and protein S deficiencies, MTHFR, and factor V Leiden gene mutations among genetic thrombophilias are relatively common predisposing conditions to the development of CVST^{4,5}. Also, PAI-1 gene mutation was formerly proposed as an independent risk factor for CVST¹⁹. In this study, in order of frequency, MTHFR gene mutation, lupus anticoagulant positivity, PAI-1 gene mutation, factor V Leiden gene mutation, and protein S deficiencies were found as thrombophilic risk factors. Also, although CVST due to local infections in adults has become rare in developed countries, it still remains a serious problem in countries that insufficiently used antibiotic treatment¹³. In this study, local infections such as otitis and mastoiditis were high frequent (22%) predisposing factors for CVST, when compared with other studies^{1,4,7,8,18}. This condition can be associated with low socio-economic status of patients in southeast region. Cases having more than one risk factor formed 27.7% of all our patients. We were unable to demonstrate any known etiological factor or any risk factor in 17% of our cases. In a case with colon cancer homozygous MTHFR gene mutation and mutation at homozygous PAI-1 gene (4G/5G) were found.

Because of the various clinical presentations, neuroimaging is very important for the diagnosis of CVST. Brain CT, brain MR imaging, MRV, MSCTA and DSA are common imaging methods used for the diagnosis. Filling defects in MRV and/or CT angiography in venous phase is quite sensitive for the diagnosis of CVST. Brain CT angiography has advantages over MR venography for non-cooperated^{14,20}. Additionally, sometimes open venous sinuses may appear in CT angiography despite flow decrease in MRV. Involvement of more than one sinus was present in 63.8% of our patients²⁰. In previously many studies, it has been reported in patients with SVST that superior sagittal sinus is the most commonly affected sinus, followed by the transverse si-

nus^{4,11}. However, some studies have demonstrated that transverse sinus is the most commonly affected sinus, followed by the superior sagittal sinus^{7,21}. Likewise, according to frequency, thromboses were found sigmoid sinus, transverse sinus, and superior sagittal sinus in our study. Since etiology of CVST in 21.3% of our cases was chronic otitis, the most frequent affected sinuses were seen at sigmoid and transverse sinuses. Brain CT/MR imagines may show hemorrhagic or less frequently non-hemorrhagic venous infarcts in CVST²². In our study, hemorrhagic infarct, brain abscess at the neighborhood of involved sinus, cholesteatoma and non-hemorrhagic cortical infarct were seen in 38.3%, 6.4%, 6.4% and 2.1% of cases, respectively.

Anticoagulant therapy with LMWH is recommended for all CVST diagnosed patients if chronic otitis media or mastoiditis is not in etiology even in presence of hemorrhagic infarct. Following clinical improvement oral anticoagulation with warfarin for 3-6 months is recommended. For the cases that cause chronic thrombophilia anticoagulation may be given for long term²³. In our study all cases except for who had CVST due to local infections received LMWH treatment followed by oral anticoagulation. Antiepileptic treatment was given to 14.9% of the cases due to epileptic seizures and anti-edema treatment was given to 25.5% due to impairment consciousness and brain edema. The diagnosis of mastoiditis and otitis media in association with CVST is important because septic cerebral thrombophlebitis requires a prolonged course of antibiotics and consideration of surgical treatment, whereas nonseptic CVST

is generally treated with anticoagulants alone^{12,13}. In this study, patients with CVST caused by otitis media and mastoiditis were surgically treated from a otolaryngologist. In addition, a wide spectrum antibiotic therapy was continued in these patients. In recent studies, it has been reported that used modern neuroimaging technics such as MRV and MSCTA and LMWH administration associated with much lower mortality rates (8-14%) and significant better outcome^{8,14,23,24}. A meta-analysis of 19 studies conducted by Dentali et al²⁵ have demonstrated that the mortality rate was about 5.6%. Rate of cases who recovered without any deficits was 85.1% in our report and, 6.4% of the patients recovered with sequel such as hemiparesis, visual field defects, speech defects. In this study, 8.5% of our cases were resulted with mortality. Advanced age, progressive deterioration of consciousness, diffuse cerebral venous system involvement, significant intracranial pressure increase, being secondary to malignancy, accompaniment of hemorrhagic infarcts, complications such as resistant epileptic seizures and pulmonary embolism have been reported as related with poor prognosis^{5,6,8,26}. In our study diffuse hemorrhagic infarct, initial presentation with impaired consciousness, presence of hemiparesis, and acute onset were found to be correlated with poor prognosis (sequel or death). Also, status epilepticus followed secondary generalized seizure in one of our cases presented with unconsciousness and focal epileptic seizure. Patient was dead due to diffuse hemorrhagic infarct and brain edema despite seizures were controlled.

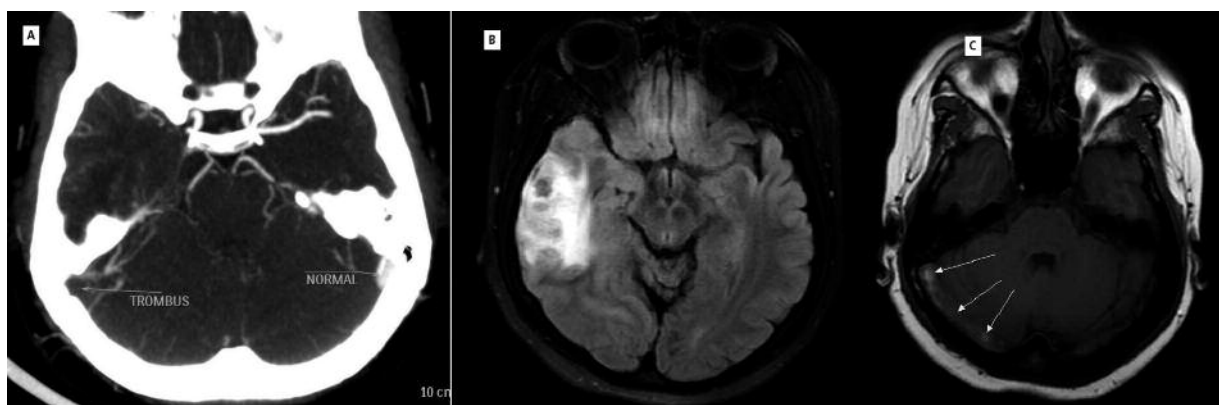


Figure 1. Brain CT angiography of a female patient presented with acute headache and weakness at left side showed filling defect compatible with thrombus at right transverse sinus at venous phase **(A)**, local hypointense fields in hyperintense lesion compatible with hemorrhagic infarct at fat suppressed axial FLAIR MR imaging **(B)** and hyperintense image compatible with thrombus at right transverse sinus at axial T1A MR section.

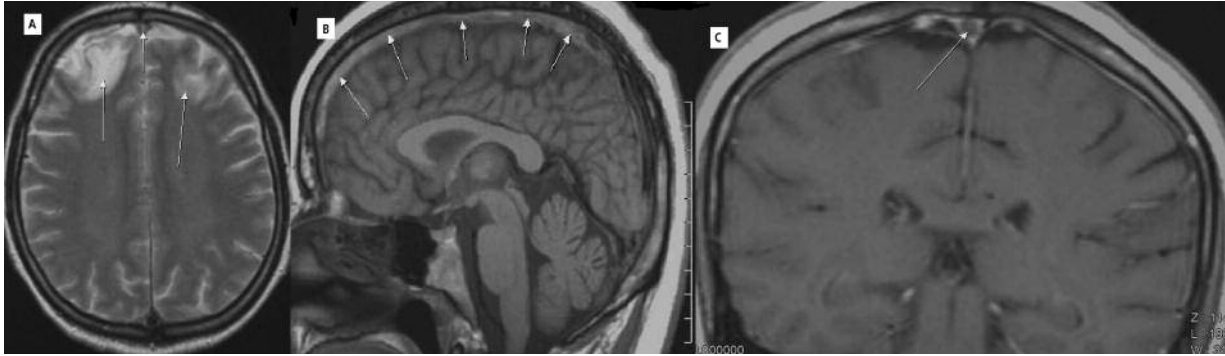


Figure 2. Axial T2A brain MRI section of a 37 years old male patient presented with acute headache and epileptic seizure showed hyperintense venous infarct fields at bilateral frontal area (A), sagittal T1A image showed hyperintense lesion compatible with thrombus and contrast enhanced coronal T1A MR section showed filling defect compatible with thrombus at superior sagittal sinus (B-C).

In conclusion, various clinical conditions may be seen in CVST. Treatment can be delayed in particular cases which has no focal neurological finding. For cases with newly onset and resistant headache that becomes chronic progressive, MRV should be performed by considering the characteristic of the patient even neurological examination is normal. The establishment of CVST diagnosis and the initiation of anticoagulant therapy are important for the recovery of the patient without any sequel and to reduce in the mortality. Consequently, because of patients with diffuse hemorrhagic infarct, initial presentation with impaired consciousness, presence of hemiparesis, and acute onset associated with poor prognosis, these patients should be closely followed.

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